The missing link between autoimmune diseases and microchimerism

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Abstract

BACKGROUND
Autoimmune diseases (AIDs) are characterized by being more common in females, but the cause is still unclear. Among the hypotheses explaining the reason, fetal microchimerism (Mc) involvement theory is the most convincing, but it is unclear how microchimerism cells impair recipients, and there is a significant missing link. The incidence of chronic graft-versus-host disease (cGVHD) after bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT), which is the basis of the microchimerism theory of AIDs, also has a gender bias due to the combination of donor and recipient, but the cause is unknown. It is assumed that bone marrow cells (BMC) attacking allogeneic somatic cells (Soc) is the common cause of cGVHD and AIDs, and combining both genders gives gender bias. It is thought that examining which combination matches the actual gender bias and incidence of cGVHD and AIDs will validate the microchimerism etiology theory of AIDs.

METHODS
The onset probability (OnP) is the sum of the encounter probabilities (EnP) of all combinations of BMC and allogeneic Soc caused by microchimerism. EnP is expressed as the product of the existence probability (ExP) of BMC and allogeneic Soc. ExP is expressed as the product of probabilities by factors such as the Mc pathway and cell aging involved in the existence of each cell. OnP was calculated for each gender combination of BMC and Soc to verify whether it matched the actual gender bias and incidence of cGVHD and AIDs.

RESULTS
The combination of female BMC attacking male Soc, a unidirectional heterosexual relationship, best matched the actual gender bias and incidence of cGVHD and AIDs.

CONCLUSIONS
The author hypothesized that the cause of AIDs is the same as cGVHD after BMT, and encounters between BMC and Soc in an allogeneic relationship brought about by microchimerism determine gender bias and incidence, and simulated the encounter probability for each gender combination. As a result, it was found that assuming that female BMC attacks male Soc can best explain the gender bias and incidence of cGVHD and AIDs. Furthermore, it is speculated that the target factor was H-Y antigen and the effector cell was H-Y antigen-specific long-lived memory plasma cells, and the author considered the missing link between AIDs and Mc.

Introduction

Since Hashimoto reported chronic thyroiditis (Hashimoto's disease) in 1912 (Hashimoto, 1912), many AIDs have been discovered. The estimated prevalence of overall AIDs is 4.5% worldwide (Hayter et al., 2012). They form a large and diverse group of diseases, ranging from AIDs that cannot be questioned by anyone (so-called classic AIDs) to those with unclear autoimmune reactions (chronic inflammatory syndromes) (Herrero-Cervera et al., 2022). It is no exaggeration to say that the quest to elucidate the etiology of AIDs has driven the development of immunology. However, many etiological hypotheses have been proposed for 110 years since the discovery of Hashimoto's disease, but there is still no definitive one. There are three common phenotypes of classical AIDs: (1) Chronic inflammatory disease. (2) Tissue damage caused by autoreactive molecules (autoantibodies) or cells (autoreactive T cells). (3) It is overwhelmingly common in adult females. Chronic inflammation is fundamental and essential to the pathogenesis of AIDs. Autoantibodies are a characteristic finding that constitutes a means for diagnosing AIDs, and AIDs can be divided into the following four types from the standpoint of autoantibodies. 1) AIDs with pathogenic autoantibodies. 2) AIDs with only nonpathogenic autoantibodies. 3) AIDs without autoantibodies. 4) Special type with autoantibodies but no AIDs. Gender bias, which is more prevalent in adult females, is also a prominent feature of AIDs, and at least the etiological hypothesis that fails to explain the overwhelming female dominance seen in classic AIDs is incomplete, which means that something is missing or wrong. However, some cases of AIDs have no gender bias in young people or are slightly more prominent in males (Fig. 1). It should be verified whether the AIDs etiological hypothesis can include not only typical cases but also exceptional diseases.

As hypotheses to explain this gender bias, there are sex hormone or sex chromosome involvement theory. However, it is difficult to explain for AIDs, which is common in young people. There is a report that the presence or absence of pregnancy history was the only influence on the onset in multivariate analysis in primary biliary cirrhosis with a female-to-male ratio of 9:1 (Parikh-Patel et al., 2002). Approximately 8% of females after pregnancy develop postpartum autoimmune thyroiditis (Stagnaro-Green et al., 2004). These findings suggest that pregnancy is intensely involved in developing female-dominant AIDs. Nelson et al. focused on natural microchimerism (Mc) as an etiology of systemic sclerosis (SSc) because of the similar phenotypes of SSc and chronic graft-versus-host-disease (cGVHD) after BMT (Nelson et al., 1998). Mc is the state in which another individual's cells are mixed in small amounts. Mammals exchange each other's cells between the mother and the fetus through the placenta. In the case of stem cells, they can be established over several decades (Bianchi et al., 1996). It is not a rare occurrence, but it happens frequently and can be said to be the fate of mammals. The Mc caused by pregnancy is called natural Mc, while that caused by medical procedures such as blood transfusion and organ transplantation is called artificial Mc (Shrivastava et al., 2019). Male cells were detected in 59% of SSc females in the blood (25% in controls) (Nelson et al., 1998). Since then, fetal-derived Mc (FMc) cells and mother-derived Mc (MMc) cells have been detected with various AIDs (Nelson et al., 2012). Nelson et al.

suggest that the involvement of Mc in AIDs may be due to the relationship of HLA between Mc and the host. However, there is no clear explanation for the mechanisms underlying AIDs development and the female predominance, etc., indicating the presence of a missing link between AIDs and Mc. The author speculated that the Mc hypothesis has the highest possibility of explaining the female predominance among the many AIDs etiology theories and that the gender of Mc cells and host cells, which are in an allogeneic relationship, determines the gender bias of AIDs.

Even in cGVHD, which is said to be the phenocopy of AIDs (Murray et al., 2018), there is a gender bias that the combination of female donor and male recipient (F→M) has the highest incidence rate of cGVHD. At first glance, the female BMC seems to be attacking the male Soc, but it also develops in other combinations (Remberger et al., 2002; Randolph et al., 2004; Kim et al., 2016). After BMT, various AIDs develop, and cGVHD may be a type of AIDs rather than a phenocopy of AIDs. If AIDs and cGVHD consider Mc as a common etiology, the cell clusters brought in by BMT may also cause AIDs. Although the cell types transferred by natural Mc are diverse, BMT, which destroys the recipient's bone marrow during pretreatment, has few factors involved and is very suitable for pathogenesis analysis among artificial Mc. Potential target cells for artificial Mc would be organ somatic cells or tissue-specific stem cells. If the tissue-specific stem cells are target cells, the tissue can not be repaired, and the tissue seems to be depleted. However, no such observation has been reported, so the target cells are probably the recipient somatic cells. Possible effector cells in BM administered with BMT include cytokines, mature blood cells, long-lived memory T and B cells, hematopoietic stem cells (HSC), and stromal cells (such as mesenchymal stem cells (MSC) and fibroblasts) (Morrison et al., 2014; Khodadadi et al., 2019). Since cGVHD and AIDs are chronic inflammatory diseases, short-lived cytokines and mature blood cells cannot be considered as effector cells. Therefore, the factors involved in the pathogenesis of cGVHD may be somatic cells (Soc) as target cells, long-lived bone marrow cells (LLBMC) (long-lived memory T and B cells, HSC, MSC and fibroblasts) and mature blood cells differentiated from HSC as effector cells. The cell types considered for the cause of AIDs and cGVHD can be simplified to two allogeneic-related LLBMC and Soc. It is highly likely that the gender combination of LLBMC and Soc causes gender bias in AIDs and cGVHD. Therefore, it can be inferred that the encounter probability of allogeneic LLBMC versus Soc correlates with disease incidence and gender bias.

Mc cells have been detected at damaged sites of maternal tissue and are thought to play an active role in tissue repair (Mahmood et al., 2014). It has been reported that Soc is replaced by Mc cells in damaged organs of AIDs (Nelson et al., 2012). The recipient Soc is thought to contain Mc-derived maternal and sibling cells. Among LLBMC, it is MSC that can repair tissue. Therefore, it is necessary to consider not only recipient Soc but also chimeric Soc as target cells. When the target cells are recipient Soc, the relative number of recipient Soc to the effector factor is much larger than the chimeric Soc replaced by MSC, so the effect is thought to be diluted and attenuated, and it is necessary to consider the dilution effect. In natural Mc, not only between mother and fetus but also the stem cells of the older brother and sister may be transmitted to the younger brother and sister through the mother's body. In the case of multiple births, the influx occurs in the uterus via the placenta as well as via the mother (this route cannot be ignored in laboratory animals where multiple births are the basis). In addition, the stem cells of grandmother, uncle, and aunt will also be transmitted to the fetus through the mother. However, LLBMC are not totipotent stem cells and have a lifespan, so the chain of Mc effects through the pregnant females will not last long. Since the onset of AIDs is rare in people over the age of 80 years old (Hayter et al., 2012), it is thought that LLBMC has a healthy lifespan (Pritz et al., 2015), and its activity and number as effector factors decline with aging. Therefore, it is necessary to consider the difference in the effect of receiving aged maternal LLBMC or young fetal LLBMC.

From the above, in the all gender combination of LLBMC and Soc that have an allogeneic relationship, the product of the existence probability (ExP) of each cell is the encounter probability (EnP), and the sum of EnP is the onset probability (OnP) and examined which combination could explain the gender bias and incidence of AIDs and cGVHD. As a result, it turned out that assuming that female LLBMC is attacking male Soc can explain almost of the gender bias and incidence of AIDs and cGVHD. This time, a part of the missing link between Mc and AIDs was clarified in this study, but the effector cell or factor of female LLBMC and the target factor of male Soc remain unknown. The author would like to discuss the possible molecules and mechanisms and present hypothesis.

Methods

Allogeneic relationship of effector/target cells The following six combinations of effector/target gender can be considered for LLBMC and Soc in the allogeneic relationship. As an assumption of the gender combination of effector/target in LLBMC and Soc that have an allogeneic relationship, (1) female LLBMC is attacking male Soc (♀→♂). (2) Male LLBMC is attacking female Soc (♂ →♀). (3) Both sexes are attacking in both directions (♀⇄♂). (4) Attacking between female (♀→♀) (5) Attacking between male (♂→♂) (6) LLBMC is attacking all of allogeneic Soc regardless of gender (all LLBMC→all Soc).

Existence probability (ExP) of each cell Five parameters and coefficients are considered for natural Mc and six for artificial Mc as factors that determine the existence of each cell, and the product is ExP (Fig. 2, 3). The range of effective Mc is up to the mother, older siblings, and children; the grandmother's Mc was excluded as they were considered advanced in age. The ExP of the self LLBMC is set to 1.0, the ExP of chimeric LLBMC transferred and established between mother and child is set to 0.1, and the ExP of chimeric LLBMC received from older sibling via mother is 0.1x0.1 (Mc parameter). For both natural Mc and artificial Mc, it is assumed that adult females become pregnant at 30 years old, with one male and one female, and there are no pregnancies under 20 years old. The probability of pregnancy of adult females who have experienced pregnancy is 1.0, and the probability of pregnancy of individual adult females is assumed to be 0.5 (pregnancy coefficient). The probability of having a mother is 1.0, and the probability of having older siblings is assumed to be 0.5 (sibling coefficient). If there are siblings, there is one older brother and one older sister (there is no age difference between them), and the age difference between the older siblings and the subject is two years, and cases of multiple births are not included. The dilution effect due to diffusion is 1.0 when the target is chimeric Soc and 0.1 when the target is recipient Soc (dilution coefficient). Since the onset age of AIDs is up to the 60s, and there are few in the 70s to 80s (Hayter et al., 2012), the healthy lifespan of stem cells, including MSC, is 80 years old. The functional decline (reduction of number) is 1/80 per year, and the LLBMC activity is expressed as 1-age/80 (1.0 at 0 years old and 0 at 80 years old) (aging parameter). The target age for natural Mc is from 10 to 80 years

old. For artificial Mc, both donor and recipient are 30 years old. Since the artificial Mc by sibling-sibling and parent-child BMT causes a combination of syngeneic relationships between chimeric cells, the ExP of allogeneic cells between chimeric cells of different ages is 1.0, and the ExP between the same age is 0.5 (syngeneic coefficient).

Encounter probability (EnP) The product of ExP between each cell is EnP, and the sum of EnP between all cells is the OnP of the individual. In six combinations of effector/target cells, natural Mc simulates OnP for each gender and age, and artificial Mc simulates OnP for each gender combination of donor and recipient. In natural Mc, an example of a 30-year-old female with female effector/male target (♀→♂) is shown in Fig. 2. In artificial Mc, an example of female effector/female target (♀→♀) and male donor/female recipient (M→F) is shown in Fig. 3.

Matching phenotypes The following six characteristics of AIDs and cGVHD to be collated were verified. 1) In adult AIDs, many female-dominant diseases are highly prevalent. 2) There is also AIDs, which is more common in middle-aged and elderly males, but the prevalence is low. 3) In young AIDs, diseases with a female/male ratio of 1 or less are predominant, and there are a few diseases with a slightly higher female ratio (Fig. 1). 4) The incidence of cGVHD is highest in gender mismatch from female donor to male recipient (F→M). 5) cGVHD also develops in other combinations (Randolph et al., 2004; Gahrton et al., 2005; Kim et al., 2016). 6) The risk of developing cGVHD according to the donor's pregnancy history is significantly higher for parous females than for male donors. It tends to be lower for nulliparous females than parous females, but the difference is insignificant (Loren et al., 2006). (There is also a report that it is as low in nulliparous females as in male donors (Kollman et al., 2001).)

Results

Natural Mc The incidence frequency of natural Mc in all combinations, males gradually decreased from 10 years old to peak with age to 0 at 80 years old, and females decreased from 10 to 20 years old, then increased at the age of 30 at the age of pregnancy and then decreased gradually. The aging changes in females were consistent with the observation that AIDs increases after pregnancy. The male-to-female ratio in youth was slightly male-dominant in ♀→♂, and strongly male-dominant in ♂→♀ and ♀⇄♂, and the same frequency in all LLBMC→all Soc. In adults, female predominance was strong in ♀→♂ and ♀→♀, and mild female predominant in ♀⇄♂ and all LLBMC→all Soc (Fig. 4, Table S1, S2). Only ♂→♂ became dominant in middle-aged and elderly males, but they were male-dominated at all ages (Fig. 4E). From the above, in natural Mc, ♀→♂ best matched the gender bias of AIDs, followed by all LLBMC→ all Soc. However, no combination could explain all the phenotypes, including the middle-aged and elderly male-dominated AIDs.

Artificial Mc Only ♀→♂ matched the observation that the onset of cGVHD is highest in the case of F→M (Fig. 5A, Table S3). In addition, ♀→♂ and ♀→♀ matched the observation that the incidence of cGVHD of parous donors tended to be higher than that of nulliparous donors and significantly higher than that of male donors (Fig. 5B, Tables S4, S5). There was no significant difference in natural Mc and artificial Mc results if each probability coefficient and parameter was $0 \leqq p \leqq 1.0$. From the above, the simulation of ♀→♂ between unidirectional heterosexuals best matched the actual gender bias and incidence of AIDs and cGVHD. That is, it is considered that the female LLBMC is attacking the male somatic cell.

Discussion

Gender bias

AID and GVHD When AIDs are divided into four groups according to gender and age of onset, there is a group that is overwhelmingly common in young adults to middle-aged females and has a high prevalence. These are the groups into which the most significant amount of research and medical resources have been invested and can be considered classical AIDs (group 1). In the young age group, diseases with a female/male ratio of 1 or less are the central diseases, and there are a few with a slightly higher female ratio. There is no female-dominant disease like group 1. This group has a not-so-low prevalence rate, with Coeliac disease at the top (group 2). In addition, there is a group of middle-aged to older adults with a distinct male predominance but a lower prevalence (group 3). Group 3 AIDs includes IgG4-related disease (IgG4-RD), which has recently attracted attention (Fig. 1) (Inoue et al., 2015).

In cGVHD, the combination of female donor and male recipient has the highest incidence rate, but other combinations also develop (Remberger et al., 2002; Randolph et al., 2004; Kim et al., 2016). In addition, the risk of cGVHD was high in the case of older female donors (Friedrich et al., 2018; Zhan, 2020) and parous donors (Kollman et al., 2001; Loren et al., 2006). Both AIDs and cGVHD strongly suggest that pregnancy is involved in the onset. GVHD that occurs within 100 days after BMT was classified as acute GVHD (aGVHD), and what occurs after that is cGVHD, but recently it has been classified by phenotype. It is because there are aGVHD that occurs even after 100 days and cGVHD that occurs even within 100 days. aGVHD develops in 35–50% of patients after HSCT (Jacobsohn et al., 2007), primarily affecting the skin, gastrointestinal tract, and liver, and lesions with a strong inflammatory component, according to a Th1/Th17-driven process. Since aGVDH can be prevented by transplantation of T cell-depleted grafts, donor cytotoxic T cell is the main cause (Blazar et al., 2012). The lifespan of lymphocytes is about two weeks (Coassin et al., 1957), and it is thought that donor mature T cells or donor HSC-derived T cells are involved. Recently, it has been found that there is an overlap syndrome in which cGVHD and aGVHD co-occur (Vigorito et al., 2009). In BMT, in which the recipient HSCs are depleted by pretreatment, the lymphocytes responsible for aGVHD and cGVHD are derived from the same donor, and it is unlikely that the same cells exhibit different phenotypes simultaneously. Therefore, the primary etiology, particularly effector cells, of aGVHD and cGVHD are considered to be different. cGVHD develops in 30-70% of patients after HSCT (Jagasia et al., 2015) and damages a broader range of organs, mainly on the same skin, gastrointestinal tract, and liver as aGVHD. The lesions exhibit autoimmune and fibrotic features (Blazar et al., 2012). 50% of patients who were able to prolong life after the onset of aGVHD develop cGVHD, and most cGVHD has aGVHD as a precursor, so aGVHD is considered to be the risk factor of cGVHD (Jacobsohn, 2007). cGVHD is not preventable by T cell-depleting therapy (Pavletic et al., 2005) and is a Th2-dominant reaction in which B cell dysregulation results in the emergence of autoreactive B cells and autoantibody production (Blazar et al., 2012; Kuzmina, 2015). Antinuclear and anti-dsDNA antibodies appear in more than 50% of cGVHD, so

cGVHD is considered a phenocopy of AIDs (Murray et al., 2018). However, there is no correlation between autoantibodies and the activity and severity of cGVHD (Kuzmina et al., 2015), and pathogenic autoantibodies have not been identified. Not only does cGVHD mimic SSc, but the development of many typical AIDs with autoantibodies one month to 4.5 years after BMT has been reported (Yanir et al., 2018). Both cGVHD, which develops three months to several years after BMT (Murray et al., 2018), and post-BMT AIDs (pBMT-AIDs) are triggered by BMT and have similar onset times. cGVHD is not just a phenocopy of AIDs and may have the same etiology. Therefore, gender bias in cGVHD and AIDs may be due to the same etiology. It is thought that cGVHD that develops after BMT, which ablates the recipient's bone marrow as a pretreatment, occurs between BMC and Soc, which are allogeneic relationships. Therefore, the etiology of AIDs may also be due to BMC and Soc in an allogeneic relationship brought about by natural Mc.

X chromosome and sex hormone When the etiological hypotheses of AIDs cannot clearly and directly explain gender bias, the sex hormone and sex chromosome involvement theories are constantly relied on. When considering the gender bias of AIDs, we cannot but pay attention to the sex chromosomes, especially the X chromosome. Therefore, Turner's syndrome (TS) and Klinefelter's syndrome (KS) caused by sex chromosome nondisjunction are suitable research subjects. The karyotype of TS is mainly 45, XO, which is X monosomy, and 46, X, i(Xq), which lacks the short arm of the X chromosome, and KS is 47, XXY (Gravholt et al., 2019; Groth et al., 2013). The incidence rate of AIDs in KS males is higher than in general males, indicating a risk comparable to that in general females (Seminog et al., 2020). In addition, the prevalence of KS was higher in SLE males than in general males (Scofield et al., 2008). From gene-dose theory, the incidence of AIDs in TS females was expected to be about the same as that of XY males, but the actual risk is twice that of the general females and 3.9 times higher in male-dominant AIDs (Jørgensen et al., 2010). Usually, one X chromosome of XX females is inactivated (i.e., X chromosome inactivation, XCI) except for the PAR region at the tip of the short arm, so the gene dosage on the X chromosome is the same for XX females, XO females, XY males, and XXY males. However, some genes escape XCI, resulting in an imbalance in the amount of the X gene. There is a theory that XCI escape is the cause of the increase in AIDs in KS (Navarro-Cobos et al., 2020), but this cannot be applied to TS. There is also a theory that the lack of PAR region is the cause of the increase in AIDs in TS (Jørgensen et al., 2010), but this cannot be applied to KS. There are many reports that among the sex hormones, estrogen and progesterone promote autoimmunity, while androgen works protectively, which is the basis for the female predominance of AIDs (Ngo et al., 2014). Insufficient secretion of female hormones is observed in TS and male hormones in KS (Gravholt et al., 2019; Groth et al., 2013). The cause of the increase in AIDs in KS can be explained by male hormone insufficiency, but the sex hormone theory collapses due to the presence of TS. From the above, the X chromosome and sex hormones cannot explain the gender bias of AIDs. Recently, it has been reported that the intestinal microbiota is involved in developing AIDs by affecting sex hormones (Markle et al., 2013). However, while it may modulate the pathogenesis, it is unlikely to be the primary cause of gender bias. It seems that the etiology hypothesis of AIDs needs to be able to explain gender bias without relying on X chromosomes and sex hormones.

Although TS and KS seem to have nothing in common regarding the increased incidence of AIDs, the phenotype common to both is hypogonadism (Gravholt et al., 2019; Groth et al., 2013). In fact, castration in male non-obese diabetes mice, a model of human autoimmune diabetes, significantly increases the prevalence of the disease (Fitzpatrick et al., 1991), and 4 to 30% of females with premature ovarian insufficiency (POI) who show estrogen deficiency have AIDs coexistence (Kirshenbaum et al., 2019). In addition, a prospective study of POI patients without AIDs and X-chromosome abnormalities found 40.4% to develop AIDs (Grossmann et al., 2019). From the above facts, it is clear that AIDs development is accelerated by genital dysgenesis, defect and disease in both sexes, regardless of sex chromosomes or sex hormones. It is suggested that the reproductive organs may secrete some humoral factor other than sex hormones that suppresses the development of AIDs.

Trigger of AID

Destruction Vaccines, wounds, drug disorders, infections, etc., are considered to be triggers for AIDs. There are cases where AIDs develop after vaccination. Usually, an adjuvant is added to the vaccine to enhance its efficacy. The effect of adjuvant is said to be that the released cell contents by damaging the cells activate the immune system. Post-vaccine AIDs are thought to be due to this adjuvant's action rather than the vaccine itself (Wraith et al., 2003). Lens-induced uveitis and sympathetic ophthalmia (OA) develop after lens and eyeball damage due to trauma and surgery. Usually, the eye has an immune privilege and is protected from the immune system. However, it is said that the lens and eyeball proteins leaked by injury are exposed to the immune system, and autoimmune uveitis develops (Nche et al., 2020). Anti-mitochondrial antibody (AMA) specific for PBC have been detected after acute liver failure due to an overdose of acetaminophen, but they are transient and do not cause PBC (Leung et al., 2007). Acetaminophen-induced liver injury shows necrosis (Arnaiz et al., 1995), and there is no gender difference in the positive rate of AMA (Leung et al., 2007).

Many reports show that AIDs develops after bacterial, fungal, and viral infections. Molecular mimicry, endothelial cell damage, and superantigens have been proposed to explain the relationship between infectious pathogens and AIDs (Sener et al., 2012). Recently, the hypothesis that pyroptosis (immune cells and some somatic cells) (Magna et al., 2015) and NETosis (neutrophil) (Brinkmann et al., 2004; Darrah et al., 2013) as cell death for pathogen clearance is the etiology of AIDs has also been proposed. In addition, Pender et al. hypothesize that EBvirus-infected B cells and dysfunctional $CD8^{+}$T cells cause autoimmunity (Pender, 2003). However, many reports show a rather male-dominated bias in infectious diseases (Bernin et al., 2014), and none of the hypotheses seem to explain the female dominance of AIDs beyond male-dominated infectious diseases. As mentioned above, the development of many typical AIDs with autoantibodies after BMT has been reported (Yanir et al., 2018). The immunosuppressed state after BMT becomes a battle against infectious diseases. The infection after BMT may be the trigger of pBMT-AIDs. Most cases of cGVHD have aGVHD as a precursor. cGVHD may not be a phenocopy of AIDs, but pBMT-AIDs triggered by aGVHD. The underlying mechanism of occurrence of cGVHD and pBMT-AIDs is the same, and the sites of trigger damage likely determine both phenotypes. Just as infections have a favorable age and organ depending on the pathogen, most AIDs also have a favorable age and organ. Among those showing multiple AIDs in the same organ and tissue, many have almost the same age of onset. For example, UC and CD involving the gastrointestinal tract are most common at ages 20-29, PBC and PSC involving the bile ducts are 30-49, and MS and GBS involving the myelin sheath are 30-45 years old (Hayter et al., 2012). Pathogen-infected cells exhibit cytolysis and inflammatory cell content release (i.e., pyroptosis) (Fink et al., 2005).The favorable age of infection determines the onset age of AIDs, and the site

and range of infection and the host's response to the released autoantigens determine the phenotype of AIDs. Infection is only a trigger, and there seems to be a factor determining gender bias of AIDs in the next step following the trigger. The common event for various triggers of the onset of AIDs and autoantibody production would be cell destruction and release of cell contents.

Regeneration Neurons in the central nervous system and myocardium are tissues with an extremely low prevalence of organ-specific AIDs. However they occupy a considerable volume in the human body and trigger infectious diseases are not uncommon. Multiple sclerosis (MS) is representative of the AIDs of the cranial nervous system, but it is a disease of the myelin sheath (Dobson et al., 2019). Guillain-Barre syndrome (GBS) has not only a demyelinating type but also an axonal type, but it is a peripheral neuropathy (Hughes et al., 2005). Autoimmune encephalitis (AE) includes Hashimoto's encephalopathy (HE), autoimmune disseminated encephalomyelitis (ADEM), limbic encephalitis (LE), etc. HE is a disease that is concurrent with Hashimoto's disease, and ADEM is a demyelinating disease (Tenembaum et al., 2007). LE has a low prevalence rate of 2.0/100,000 and is mainly associated with tumors (Dubey et al., 2018; Anderson et al., 2008). There are few cases of AE where purely neurons primarily cause inflammation. Autoimmune myocarditis (AMC) includes dilated cardiomyopathy (DCM), giant cell myocarditis (GCM), eosinophilic myocarditis (EM), etc. DCM is to the extent that autoimmune mechanisms are considered as one of the causes (McKenna et al., 2017), while GCM and EM are mainly secondary to collagen disease (Bracamonte-Baran et al., 2017), and the prevalence is also low (Brambatti et al., 2017; Cooper Jr, 2009). The brain has immune privilege, and the immune system in the brain is suppressed, so it was thought that no immune response would occur, but recent research has shown that it is subject to immune surveillance (Ransohoff et al., 2012). The prevalence of MS, an AID of the myelin sheath in the central nerve, is not low at 58.3/100,000. The myocardium is not an immune privilege tissue, and the low prevalence of AIDs in neurons and myocardium are unlikely to be due to a suppressive immune system. The myelin sheath has a robust regenerative capacity (Franklin et al., 2017), and peripheral nerves have some regenerative capacity, whereas neurons in the central nervous system do not (Mahar et al., 2018). Myocardium also has little regenerative capacity (Uygur et al., 2016). Cell regeneration may be necessary for the onset of AIDs. The lack of regenerative capacity in two major organs, which are extremely important for the survival of animals, may be due to the more significant disadvantages than the benefits associated with regeneration. From the above, it is considered that the development of AIDs requires cell destruction and regeneration.

Mesenchymal stem cells MSC is a self-renewing multipotent stem cells that can differentiate not only into mesoderm but also into ectoderm and endoderm. MSC promotes anti-inflammatory effects and tolerance induction by cooperating with immune cells at the inflammatory site (Aggarwal, 2005) and is involved in cell repair and regeneration (Fu et al., 2019). MSC can also be differentiated into pancreatic β cells (Li et al., 2013), and there is a report that pancreatic β cells are replaced by chimeric cells in type 1 DM (Nelson et al., 2007). Recipient Soc was likely replaced with chimeric Soc by the chimeric MSC. In neurons and myocardium, where there is little regeneration, regenerative replacement by male chimeric MSC rarely occurs, so it is predicted that the incidence of AIDs will be low in females. In fact, GBS and DCM are male-dominated (Hayter et al., 2012). Bone marrow-derived MSC can also be differentiated into fibroblast and plays an vital role in wound healing and skin repair (Tanaka et al., 2022). Fibrotic lesions in SSc result from excessive extracellular matrix synthesis by locally abnormally activated fibroblasts (Usategui et al., 2011). Therefore, the target cells of systemic AIDs (i.e., collagen or connective tissue disease), such as SSc and SLE, would be fibrocytes differentiated and replaced by bone marrow MSC. MSC has no expression of HLA class II, and the expression of HLA class I is low, so it is immune-privileged, and the risk of rejection is low (Lee et al., 2017). Therefore, male MSC is unlikely to be attacked by female LLBMC. In addition, MSC has not only tissue repair ability but also immunosuppressive and anti-inflammatory effects, so it is used for transplant treatment of GVHD and AIDs, and a certain alleviation effect is recognized (Gao et al., 2016). However, in this simulation, it is inferred that the transplantation of male MSCs to a female patient may cause the development of AIDs. In fact, there is a report that no significant difference in an MSC transplantation trial of 192 GVHD patients was observed in the clinical outcome compared to controls, and there is also a report of exacerbation of Crohn's disease and recurrence of SLE (Gao et al., 2016).

In the simulation, the assumption that chimeric Soc replaced tissue Soc by chimeric MSC and female LLBMC attacked male Soc matched well with the gender bias and incidence rates of cGVHD and AIDs except for group 3, where adult males dominate. What gives AIDs and cGVHD gender bias is the combination of gender in effector cells and target cells. This result is considered to support the Mc cause theory of AIDs strongly. However, what has been clarified this time is only a part of the missing link from Mc to AIDs, and which cells among female LLBMC are effector cells and what is the target factor of male Soc remain a mystery.

Target factor

From the result that female LLBMC is attacking male Soc, it is most likely that females are exposed and sensitized to male cell-specific molecules. In the case of human females, who are internally fertilizing species and placental mammals, the only opportunities for sensitization would be male pregnancy or sperm. GVHD that develops after major HLA-matched BMT (or HSCT) is thought to be caused by minor HA (mHA) mismatch. In addition, there are many reports that H-Y antigen (H-Y Ag) in mHA is the cause of the highest incidence of cGVHD in the combination of female donor/male recipient（Randolph et al., 2004; Miklos et al., 2005; Stem et al., 2008). mHA is a major HLA-presented peptide recognized as non-self by alloimmunity (Linscheid et al., 2013). H-Y Ag encoded by six genes on the Y chromosome, which exhibits an amino acid sequence different from the peptide derived from the X homologous gene, is a molecule specific to male cells presented by HLA class I or HLA class II and is recognized as non-self by female B, T cells (Popli, 2014). There are no male Soc-specific proteins among the autoantigens detected to date. H-Y Ag is the only molecule expressed explicitly in male Soc, and the molecule of male Soc that female LLBMC can target is H-Y Ag.

Effector factor

Anti-H-Y antibody (H-Y Ab) H–Y Ab was positive in 7.8% of healthy males and 41.4~49% of healthy females (Miklos et al., 2005; Nakasone et al., 2016). Nakasone et al. measured six types of H–Y Ab in 136 F→M HSCT patients, detected at least one in 57% three months after HSCT, and developed cGVHD in 61%, suggesting a significant correlation between the presence of H–Y Ab and the incidence of cGVHD. Since H–Y Ab are detected three months or more after HSCT, they note that it coincides with the onset of cGVHD, although the association with aGVHD is low (Nakasone et al., 2015). Miklos et al. also measured five types of H–Y Ab and detected H–Y Ab four months after HSCT, with 52% in F→M and 8.7% in M→M, and observed that the

incidence of cGVHD was significantly higher in H–Y Ab-positive patients compared to negative patients. However, there was no correlation with aGVHD (Miklos et al., 2005). Sahaf et al. detected B cells (DBY-2-B cells) expressing DBY-2 (one of the H-Y Ag) specific BCR in 28 F→M HSCT patients by FACS and found that 16 patients (57%) were positive. 15 (94%) of 16 DBY-2-B cells positive and 5 (42%) of 12 DBY-2-B cells negative developed cGVHD, suggesting that H-Y Ag-specific B cells are involved in the development of cGVHD (Sahaf et al., 2013). Mismatch of mHA (HA-1, CD30) other than H-Y antigen between donor and recipient was a risk factor for the development of aGVHD after HSCT but was not associated with cGVHD (Gallardo et al., 2001; Grumet et al., 2001). The above suggested that the H-Y Ab is involved in the bias of cGVHD incidence due to the gender combination of donor/recipient. However, Nakasone et al. found that the H-Y Ab of female donors and male recipients after HSCT had a low matching rate of corresponding antigens, suggesting that it is produced de novo by naive B cells (derived from chimeric HSC?) sensitized by H-Y Ag (Nakasone et al., 2016).

Long-lived memory plasma cells (LLMPC) As mentioned above, the development of many typical AIDs with autoantibodies after BMT has been reported (Yanir et al., 2018). Observation of before and after the onset of pBMT-AIDs within the reset immune environment of the recipient, achieved through strong pretreatment in BMT, provides crucial insights into the development of AIDs. After BMT, the patient has severe immunosuppression due to immunosuppressants, including steroids. In addition, it has been observed that highly suppressive Treg subsets are increased in patients receiving methylprednisolone, commonly used during transplantation (Seissler et al., 2012). Since pBMT-AIDs develops in a robust immunosuppressive state in which Treg functions well after BMT, the effector cells of pBMT-AIDs are thought to be resistant to immunosuppressants and Treg.

The effector factor that can recognize the H-Y Ag presented on the HLA class I of male Soc is probably H-Y Ab, H-Y Ag-specific BCR, and H-Y Ag-specific TCR. There is a report that antibodies can also bind to antigens on HLA molecules (Jin et al., 2014). As mentioned above, the effector cells in BMC are LLBMC (HSC, MSC, long-lived memory T, B cells), excluding mature lymphocytes. H-Y Ag-specific long-lived memory plasma cells (H-Y-LLMPC) and H-Y Ag-specific long-lived memory T cells (H-Y-LLMTC) hold these factors. Both LLMPC and LLMTC are present in the bone marrow. As mentioned above, the etiology of cGVHD is thought to be primarily in cells of the B cell lineage. LLMPC exists not only in the bone marrow, which is the central niche but also in inflammatory tissues and is maintained by supporting inflammatory cells (Hiepe et al., 2011; Khodadadi et al., 2019). Maternal Mc cells have been detected in bone marrow and organs in SSc patient who has not been detected four times in peripheral blood (Lambert et al., 2004). LLMPC is a non-proliferative cell that has a lifespan of several months to decades and secretes highly-affinity class-switched antibodies in the bone marrow (Khodadadi et al., 2019). Compared to aGVHD, cGVHD is less responsive to immunosuppressants, including steroids (Berger et al., 2008), and AIDs also have a limited effect on immunosuppressants (Wang et al., 2015). Even B cell depletion therapy has a certain effect on cGVHD and AIDs, but it is limited（Cutler et al., 2006; Tony et al., 2011). LLMPC is resistant to steroids, immunosuppressants, cytotoxic agents, radiation, and B cell depletion therapy (Hiepe et al., 2011). LLMPC maintenance does not require T cell involvement (Khodadadi et al., 2019), so there may be no Treg suppression. Administration of CD20 monoclonal antibody to mice successfully depleted B cells and memory B cells but did not affect LLMPC with less expression of CD20 and immunoglobulin levels (DiLillo et al., 2008). By continuously secreting pathogenic antibodies, LLMPC may support the chronic inflammatory process of AIDs and contribute to symptom flares (Hiepe et al., 2011). Based on the above, the effector cells of cGVHD and AIDs are highly likely to be H-Y-LLMPC. In Females, target cells are male Soc replaced by male chimeric MSC, and effector cells are female H-Y-LLMPC from self or maternal Mc. In males, target cells are own male Soc, and effector cells are female chimeric H-Y-LLMPC.

Is H–Y Ab a pathogenic antibody? This simulation is performed on the premise that cGVHD and AIDs are based on the same Mc mechanism, and a solution was obtained that could explain the gender bias of both. However, a contradiction occurs if cGVHD and AIDs are based on the direct action of H-Y-specific B and T cells. Because there have been no reports that the H-Y Ab shows antibody transfer AIDs, that the H-Y gene mutation shows phenocopy of AIDs, and that the H–Y Ab is a pathogenic autoantibody for AIDs. The fetus and placenta retain immune privilege. Immune privilege refers to the state of organs and tissues protected from the immune system, including not only the fetus and placenta but also the central nervous system, the anterior chamber of the eye, hair follicles, testes, stem cells and cancer cells. As a way to acquire this state, there is a passive form due to the low or no presentation of HLA molecules and active regulation by suppressing the immune response to the target antigen (Ichiryu et al., 2013). H-Y Ag-specific $CD8^{+}$T cells were detected during male pregnancies (Lissauer et al., 2012). The H-Y antibody positive rate in patients with secondary recurrent miscarriage was significantly higher than in controls, and the male birth rate of positive females was low (Nielsen, 2010). It seems to be true that the H–Y Ab is a pathogenic antibody. However, most male fetal pregnancies continue due to the functioning of the immune tolerance systems that protect the fetus, such as the scarcity of HLA class I expression on placental trophoblasts (Petroff, 2005), the elevation of Treg in maternal blood (Kahn et al., 2010), and the production of anti-idiotype antibodies (Naz et al., 1994), etc. As mentioned above, nearly 50% of female donors carry H-Y Ab (Miklos et al., 2005; Nakasone et al., 2016), and mHA mismatches other than H-Y Ag are involved in early aGVHD onset after HSCT (Gallardo et al., 2001; Grumet et al., 2001), H-Y Ab does not appear until three to four months at the onset of cGVHD (Miklos et al., 2005; Nakasone et al., 2015), and there is little similarity in H-Y Ab between female donor and male recipient (Nakasone et al., 2016). The most frequently expressed H-Y Ab in male recipients after F→M HSCT was DBY-Ab (Miklos et al., 2005), but not only DBY-Ab but also other H-Y Ab did not correlate with the presence or absence of individual antibodies and the incidence of cGVHD (Nakasone et al., 2016). These facts may indicate that H-Y Ab is not only suppressed by H-Y Ab specific anti-idiotype antibodies but also the production of H-Y Ab that is an autoantibody for male recipients is strongly suppressed. In contrast, only H-Y Ab that is an anti-non-self Ag antibody escapes suppression. In other words, H-Y Ab, H-Y specific B cells or LLMPC from female donors are transferred to male recipients, but a robust immune tolerance system may suppress their expression. As a result, no H-Y Ab can recognize the male recipient H-Y Ag, but how can H-Y Ab exhibit pathogenicity and develop cGVHD? Since B cell depletion therapy for AIDs exerts a certain effect without affecting the blood autoantibody concentration, it is believed that B cells are involved in the pathogenesis of AIDs not only in autoantibody production but also in antibody-independent functions such as antigen presentation, cytokine production, and immune regulation (Finnegan et al., 2012). However, as mentioned above, pBMT-AIDs with autoantibodies develops in a situation where Treg is increased after BMT (Seissler et al., 2012), so it is possible

that LLMPC resistant to B cell depletion therapy and Treg, not B cells, are involved in the development of AIDs with antibody-independent functions. Furthermore, the fact that there was a significant correlation between the H–Y Ab positive rate and the incidence of cGVHD (Nakasone et al., 2015) suggests that the H–Y Ab may have a non-directly impaired effect. H-Y Ag as a target molecule and H–Y Ab as an effector factor seem to be a missing link between Mc and AIDs. However, it does not seem to be explained by a simple antigen-antibody reaction, and it is necessary to review the findings in AIDs research further.

Autoantibody and autoantigen

AIDs and autoantibodies Hayter et al. reviewed 81 AIDs, of which 45 (56%) had well-defined autoantigens, and among the 51 autoantigens, 28 (55%) were classified as highly pathogenic. They also found that only 8 of 36 tissue-specific AIDs with well-defined autoantigens showed antibody transfer disease, and only 19 showed phenocopy due to mutations in autoantigen genes. Based on these results, Hayter et al. recommend that the presence of phenocopy hereditary disease in a single autoantigenic AID should be added to the diagnostic criteria of AIDs (Hayter et al., 2012). Based on the existence of pathogenic autoantibodies and experiments on the reproduction of phenocopy using autoantigen genes, it is likely that some autoantibodies are clearly involved in the phenotype of AIDs. Indeed, the prevalence of AIDs with well-defined autoantigens is high (Fig. 1), but it cannot be ignored that 44% of AIDs do not have well-defined autoantigens. Autoantibodies have not been identified even in diseases thought to develop by an autoimmune mechanism after apparent trigger, such as aforementioned autoimmune uveitis (Nche et al., 2020). In addition, autoantibodies were also detected in 62% of cGVHD, which is considered to be a phenocopy of AIDs. However, there was no correlation between autoantibodies and cGVHD activity or severity (Kuzmina et al., 2015), and no pathogenic autoantibodies have been identified. Males after vasectomy have seen the appearance of autoantibodies at a high rate, but AIDs has not developed (Mathews et al., 1976). Anti-mitochondrial antibodies have been detected after acetaminophen liver injury, but no PBC occurred (Leung et al., 2007). B cell depletion therapy for AIDs has a certain effect without affecting the blood autoantibody concentration (Finnegan et al., 2012). Cincinelli et al. found that antinuclear antibody was detected at a high rate of 18.1% in the general population, with a significantly lower female predominance than connective tissue diseases. They concluded that autoantibody production alone cannot explain the pathology and pathogenesis of AIDs. (Cincinelli et al., 2018). Although autoantibodies are inseparable from AIDs, there is no denying the possibility that pathogenic autoantibodies are not directly related to the pathogenesis of AIDs, act as mere secondary modifiers, increasing the prevalence by intensifying the symptoms and contributing to the improvement of the diagnostic rate.

Features of autoantigens As a feature of this well-defined autoantigens, 80% is tissue-specific, 57.8% has a membrane-binding protein, 33.3% has a repeat domain, and 35.6% has a coiled-coil sequence, which is higher than the proportion in the human proteome. It has been shown that autoantigens are not a random selection (Hayter et al., 2012). There is a hypothesis that autoantibodies are caused by molecular mimicry of the pathogen protein epitope (Sener et al., 2012). Regarding tissue-specific and membrane-binding proteins, there is a possibility that positive selective pressure is exerted on pathogen proteins because proteins that are more likely to be bound by host autoantibodies are more advantageous for pathogens to mimic. However, since housekeeping proteins have more varieties than tissue-specific proteins and are more advantageous for mimicking, selecting of tissue-specific proteins may depend on host-side factors. In addition, membrane-binding proteins are often glycosylated by post-translational modification (Stanley, 2011), and the immunogenicity of glycated proteins increases (Bednarska et al., 2017). However, the enhancement of immunogenicity is not directly related to the enhancement of affinity with antibodies, that is, antigenicity. The selection of membrane-bound proteins may be due to a factor on the host side that it is easy to produce antibodies rather than the result of being mimicked. Repeat domains such as tetratricopeptide repeat (TPR), ankyrin repeat, and leucine-rich repeat provide flexible binding to multiple binding partners and are involved in cell cycle regulation, transcriptional regulation, protein transport, protein folding support, etc. The target binding affinity of these domains is equivalent to those of antibodies, and their binding properties have been exploited to create high-affinity binders as an alternative to antibodies (Björklund et al., 2006). The coiled-coil sequence is also involved in protein-to-protein interactions (Strauss et al., 2008). The selection of repeat domains and coiled-coil sequences is also likely due to intrinsic necessity rather than extrinsic chance due to molecular mimicry. These facts suggest that some protein may mediate autoantibody formation.

anti-sperm antibody (ASA)

ASA and H–Y Ab Females are sensitized not only by male pregnancies but also by sperm male-specific antigens, including H-Y Ag. Spermatogenesis begins after puberty, so sperm are absent during the fetal period (Dohle et al., 2003). Therefore, it is after puberty that females are sensitized by sperm. When the barrier of an immune-privileged organ is destroyed by trauma, surgery, inflammation, etc., sequestered antigens exposed to the immune system induce an immune response (Rajabi et al., 2018). The exposed antigen has a strong immunogenicity because immune tolerance is not established. Testis also develops autoimmune orchitis when the blood-testis barrier is disrupted (Pelletier et al., 1992). The specificity of the testis is that it presents antigens outside the barrier in the form of sperm. Of the 27 infertile females who habitually had vaginal intercourse during menstruation, 22.2% were positive for ASA, significantly higher than the 3.3% positive among 30 infertile females without that habit (Wang et al., 2013). It suggests that sensitization by sperm may be enhanced in conditions such as menstruation in which the protective response of the mucosal epithelium of the female reproductive tract is declining. Many testis-specific antigens (TSA) are also expressed in cancer cells and belong to cancer-testis antigen (CTA). CTA with strong immunogenicity is used as a target for cancer immunotherapy. Sperm express sperm-specific antigens (SSA) that are part of the TSA and cause the production of ASA. ASA is detected by an indirect immunofluorescent antibody method using sperm or an indirect immunobead method, but SSA and H-Y antigens cannot be distinguished. However, ELISA or microarray can detect H–Y Ab using recombinant H-Y protein. Eighteen sperm-associated antigens (SPAG1~18) have been identified by two-dimensional electrophoresis of sperm membrane proteins and immunoblotting with ASA-positive seminal plasma in unexplained infertile males (Bohring et al., 2001). SPAG1, 6, 8, 15 and 17 are mainly expressed in the testis; others are ubiquitous,but none are specifically expressed exclusively in male Soc (Silina et al., 2011). SPAG does not contain H-Y antigen (Bohring et al., 2001). As mentioned above, 7.8% of healthy males are H–Y Ab positive (Miklos et al., 2005). Even if H–Y Ab exist in males, they may not be pathogenic. ASA is formed in 50% of men (2% in control) due to continued sperm absorption by epididymal or ejaculatory duct obstruction,

and is still detectable 20 years after vasectomy. ASA-induced infertility is common after vasovasostomy (Sotolongo, 1982). ASA is detected in 72.1% of females with unexplained infertility. ASA is regarded as a cause of infertility as a sperm immobilization antibody (Chamley et al.,2007) and can be said to be a pathogenic antibody. The corresponding antigen of ASA detected in females is unknown, but it is presumed mainly SPAG or H-Y Ag. Tung et al. detected ASA in 90% of prepubertal males and females by immunofluorescence. Although it decreased to 60% after that, it persisted throughout life, suggesting that ASA may be due to molecular mimicry (Tung et al., 1976). However, maternal SSA-specific LLMPC sensitized by sperm or male pregnancies may have been transferred as Mc cells.

ASA and autoantibodies Autoantibodies other than ASA are also produced after vasectomy. Lucas et al. detected ASA at 64%, antinuclear Ab at 78%, antithyroglobulin Ab at 12% after vasectomy, and autoantibodies that respond to various tissue antigens by indirect immunofluorescence method are detected with a weak but significant difference (Lucas et al., 1978). Mathews et al. also found increases in antinuclear Ab, anti-smooth muscle Ab, antimitochondrial Ab, etc., after vasectomy, but no significant increase in AIDs (Mathews et al., 1976). Vasectomy may be a trigger for autoantibody production other than ASA. Baker et al. detected anti-microsome antibodies in 11.8% of 102 infertile males with ASA-positive who had not undergone vasectomy, a significant difference compared with 4.3% of 277 infertile males with ASA-negative, suggesting effects of genetic predisposition of sperm in autoimmunity (Baker et al., 1985). Soares et al. detected ASA in 40% of 35 men with SLE (Soares et al., 2007). D'Cruz et al. detected ASA in 15.2% of 33 SLE patients, antinuclear antibodies in 17.2%, anti-DNA antibodies in 27.6%, and anti-dsDNA antibodies in 6.9% of 29 ASA-positive patients excluding SLE (D'Cruz et al., 1994). SSA, including H-Y Ag, induces ASA in many males and females regardless of age and is likely to be related not only to the production of other autoantibodies but also to the development of AIDs.

Apoptosis and necrosis

AIDs and mitophagy Previously, apoptosis has been considered as cell death of tissue damage caused by the direct action of autoreactive T cells and pathogenic autoantibodies in AIDs. However, it is said that apoptotic cells that arise in autoimmune reactions usually do not induce inflammation and are even anti-inflammatory (Muñoz et al., 2010). In recent years, mitophagy, the autophagy of mitochondria, has attracted attention and the elucidation of its mechanism is progressing (Pickles et al., 2018). The dysfunction of mitochondria plays an vital role in the pathogenesis of SLE (Yang et al., 2020). Autophagy inhibitors improve SLE, RA, and MS (Wu et al., 2017). When acteoside, a mitophagy inhibitor with anti-inflammatory and neuroprotective properties, was administered to experimental autoimmune encephalomyelitis (EAE) model mice, it inhibited excessive neuronal mitophagy and reduced the progression and exacerbation of EAE (Li et al., 2020). A study using cultured bile duct epithelial cells of PBC indicated that autophagy may mediate the aging process of the bile duct epithelium and be involved in the pathogenesis of bile duct lesions (Sasaki et al., 2010). Mitophagy may be involved in the development and progression of AIDs. Xia et al. demonstrated that the oncolytic measles virus infects lung cancer cells, inducing mitophagy and suppressing apoptosis through decreased cytochrome C release, which favors viral replication, and ultimately, cancer cells undergo necrosis due to ATP depletion (Xia et al., 2014). It indicates that the final form of mitoptosis due to excessive mitophagy may be necrosis, not apoptosis.

AIDs and necrosis Autoimmune lymphoproliferative syndrome (ALPS), which is caused by defective genes for proteins involved in apoptosis such as Fas, Fas ligand, and caspase10, etc., develops AIDs with autoantibody production (Shah et al., 2014). Fas and FasL gene-mutated lpr and gld mice develop autoantibody production, SLE-like AIDs, and glomerulonephritis (Rieux-Laucat et al., 2003). At least antibody production may not require an apoptotic body. Knockout mice of MFG-E8 protein, which is involved in the recognition of phosphatidylserine, which is an eat-me signal of apoptotic cells, produce anti-dsDNA antibodies and anti-nuclear antibodies and develop glomerulonephritis (Hanayama et al., 2004). It is suggested that impaired clearance of apoptotic cells is involved in the onset of AIDs. However, the fact that antibodies were produced despite impaired clearance also means that the clearance process of apoptotic cells may not be involved in antibody production. Apoptotic cells, which are not cleared in the environment of phagocytes that have lost their phagocytic ability, cause secondary necrosis, the cell membrane collapses and release the contents. Accumulation of non-phagocytosed apoptotic cells in the germinal centers of the lymph nodes of some SLE patients has been observed, and it has been pointed out that apoptotic cells due to lack of clearance and their secondary necrosis may be one of the etiologies of SLE (Gaipl et al., 2006). Therefore, in the MFG-E8 knockout mouse, it is not the accumulated apoptotic body but the cellular contents released by secondary necrosis that promote autoantibody production.

Among paraneoplastic AIDs, there is ovarian teratoma-associated anti-NMDA receptor antibodies encephalitis (NMDAR encephalitis)（Acién et al., 2014). Teratoma is a tumor containing all three blastodermic layers. When it contains a receptor on the nerve cell membrane of the brain tissue, it produces an antibody that binds to the receptor and develops a central nervous system disorder. Even though there is no problem with the cranial nerves, the pathogenic autoantibodies can damage them remotely. The cell death of the tumor shows the swelling of organelles due to ATP depletion and the release of inflammatory cell contents due to the destruction of cell membranes (i.e., oncosis) (Fink et al., 2005), which is similar to necrosis in terms of destruction of cell membranes. Since surgical removal of the teratoma cures encephalitis, cutting off the source of autoantigens appears to prevent the persistence of autoimmune disorders. This fact may mean that a device that provides antigens by necrosis is necessary for the inflammation to persist even in usual AIDs. The effects of recently developed photoimmunotherapy against cancer are said to be due not only to the immunogenic cell death (necrosis) of cancer cells caused by near-infrared light, but also to the activation of multiclonal immune responses by the released cancer cell contents. (Kobayashi et al., 2019). As mentioned earlier, the infection considered to be a trigger for AIDs leads to pyroptosis, which is characterized by cytolysis and the release of inflammatory cellular contents (Fink et al., 2005). From the above, there is no involvement of pathogenic autoantibodies and associated apoptosis in the etiology and autoantibody production of AIDs, and another mechanism involving mitophagy-induced necrosis (i.e., mitoptosis) and continuous supply of autoantigens may be hidden. Is it possible that the result of the reaction between male Soc presenting H-Y antigen and female H-Y-LLMPC targeting it can be necrosis instead of apoptosis?

Antibody production against endogenous antigens

Endogenous antigens and exogenous antigens In order for B cells to produce anti-A antibodies against tissue-

specific autoantigen A, the action of effector $CD4^+$T cells activated by antigen A is usually required. For naive $CD4^+$T cells that have escaped negative selection against antigen A to be activated and differentiate into antigen A-specific effector $CD4^+$T cells, antigen A presented on the HLA class II molecules of dendritic cells (DC) is necessary. Exogenous antigens are usually presented by HLA class II molecules, and autoantigens, which are endogenous proteins, are presented by HLA class I. DC can also present endogenous antigens by HLA class II molecules by cross-presentation, but organ-specific proteins, which account for 80% of autoantigens (Hayter et al., 2012), are not expressed in DC without the expression of AIRE protein found in medullary thymic epithelial cells (mTEC). In order to present endogenous antigen A by HLA class II, DC must be internalized it as exogenous antigens.

Immune complex (IC) and complement Complement is activated mainly by binding to the Fc portion of antibodies of IC and causes cell and tissue damage as an opsonin, chemotactic factor, membrane invasion complex, and chemical mediator-releasing factor (Sarma et al., 2011). All humans with C1q deficiency develop severe SLE, and C1q-deficient mice also exhibit an SLE-like phenotype (Nagata et al., 2010), so the complement is thought to be working defensively against tissue damage caused by autoimmunity. However, the lack of processing process of IC due to the opsonizing effect of complement did not enhance the pathology of SLE but rather caused SLE to develop spontaneously de novo, suggesting that IC is not only the result of AIDs but also the cause of AIDs onset or autoantibody production.

Fcγ receptor (FcγR) The *FCGR* gene, which codes Fcγ receptors (FcγR), is identified as a disease-susceptibility gene in many AIDs（Takai, 2005; Li et al., 2014). APC takes up extracellular substances using receptors on the cell membrane. It is the Fc receptor (FcR) and complement receptor (CR) that are involved in the uptake of opsonized antigens by antibodies and complements (Allen et al., 1996). FcγR is involved in the phagocytosis of antigens captured by IgG and antigen presentation and is expressed on the membranes of various hematopoietic cells (Takai, 2005). FcγR has activating subtypes (FcγRIa, IIa, IIc, III a, IIIb) and an inhibitory subtype (FcγRIIb) in cell function through intracellular signal molecules, and it is said that the balance between these subtypes regulates immune responses. However, many unclear points exist, such as the development of AIDs and autoantibody production. FcγRIa, IIa, IIb, IIIa are expressed in DC. FcγRs are not expressed on T cells, and only FcγRIIb is expressed in B cells (Takai, 2005; Bournazos et al., 2020). A study of FcγRIIa polymorphisms has shown a strong correlation with etiology, onset, and increase of susceptibility of several AIDs, particularly SLE and RA. Furthermore, human FcγRIIa transgenic mice (no FcγRIIa expression in mice) showed the onset of RA and SLE with antinuclear antibodies, suggesting that FcγRIIa plays a vital role in the activation of inflammation and antibody production in AIDs. (Tan Sardjono et al., 2003). FcγRIIb is suppressive to autoantibody production, but like other FcγRs, it is involved in IC phagocytosis and antigen presentation (Takai, 2005). Therefore, DC can internalize and present autoantigen A in the form of IC using FcγR Ia, IIa, IIb, and IIIa, and autoantigen A-specific B cells can do so using FcγRIIb or BCR. AIDs with *FCGR 1A, 2A, 2B,* and *3A* as disease susceptibility genes include SLE, RA, MS, SjS, ITP, GBS, MPA, WG, UC, TA, and KD (Tsuchiya et al., 2003; Takai, 2005; Bergmann et al., 2010; Carmona et al., 2014; Li et al., 2014).

FcγR and HLA classII HLA allele is the most common disease-susceptibility gene of AIDs, and among them, the HLA class II allele is considered to be AIDs susceptibility HLA (Jones et al., 2006; Matzaraki et al., 2017). However, it is still unclear how the HLA allele, especially the class II allele, is involved in developing AIDs. Is HLA class II, which presents exogenous antigens, more susceptible to AIDs than HLA class I, which is the target of autoimmunity? Some attempts have been made to understand the disease susceptibility of HLA class II based on the idea that pathogen peptides presented on HLA class II of APC activate naive $CD4^+$T cells through molecular mimicry with autoantigens (Sener et al., 2012). However, as mentioned above, it is difficult to explain all autoantibody production by molecular mimicry. There are also attempts to explain cell damage caused by autoantibodies by aberrant HLA class II expression in diseased tissue (Hanafusa et al., 1983). However, this has not been demonstrated in many AIDs. Many AIDs with disease susceptibility to the HLA class II allele have autoantibodies. In contrast, AIDs with only class I tend not to have well-defined autoantibodies (Amur et al., 2012) (Fig. 1). These findings suggest that HLA class II molecules in AIDs increase susceptibility by being involved in autoantibody production, while HLA class I molecules that present autoantigen may not be directly involved in the development of disease after trigger. Among the above AIDs that have the *FCGR* gene as a disease-susceptibility gene, only KD, which do not have autoantibodies, are not susceptible to HLA class II allele (Tsuchiya et al., 2003; Lin et al., 2009; Stassen et al., 2009; Bergmann et al., 2010; Amur et al., 2012; Terao et al., 2014; Blum et al., 2018). If IC uptake by FcγR and antigen presentation by HLA class II are not independent events but a series of antigen priming and presentation process events, the possibility that the process is involved in autoantibody production arises. That is, IgG antibodies bound to endogenous protein A released from necrotic cells are captured by FcγR on immature DC, internalized, processed, and presented as antigen A by HLA class II molecules. The naive $CD4^+$T cells that recognize it differentiate into effector $CD4^+$T cells and activate antigen A-specific B cells which take in antigen A with FcγR or BCR and presented it by HLA class II molecules. However, at least until an anti-A antibody is produced, the IgG antibody that binds to antigen A is not an anti-A antibody, and some protein will mediate between the antigen A and the IgG antibody, but is it possible?

Aging of effector cells and target cells

Immunosenescence is said to not only increase cancer and infectious diseases due to a decline in normal immune responses but also enhance chronic inflammation and autoimmune responses (Pawelec, 2018). This fact may be related to middle-aged onset AIDs, but they are rare to develop in older age. The number of MPC, which is a candidate for effector cell, decreases in the blood and bone marrow with age, and blood antibodies corresponding to some antigen-specific bone marrow MPC also decreases (Pritz et al., 2015). MSC, a candidate for stem cells that provide target cells, also decreases in quantity and regenerative capacity with age, suggesting a relationship with individual aging (Liu et al., 2020). Simulation assumes that both effector cells and target cells decline linearly with age. Males have no influx of new Mc cells after birth, and the Mc cells environment is determined at birth. Male target cells are self-Soc, so aging will have little impact. Female H-Y-LLMPC from mother, aunt, and older sister through mother as effector cells will likely decline in function after birth. As autoantibodies are produced after vasectomy, T and B cells derived from female chimeric HSC may become sensitized to autologous sperm after puberty, but this is unlikely to affect prevalence. As a result of the interaction, the incidence of AIDs in males will decline with age. In females, effector cells will decline from birth, but antigen-specific LLMPC increases after puberty due to sensitization by SSA and gradually declines after middle age. The

chimeric male MSC as a target cell from the uncle and older brother through the mother at birth will decline with age, but it will increase rapidly due to male pregnancy, and then it will decline. As a result of the interaction, the onset of AIDs in females may increase gradually from puberty, increase further after male pregnancy, and gradually decrease after middle age. These predictions are confirmed in the ♀→♂ simulation and are also consistent with the actual AIDs prevalence (Hayter et al., 2012) and the observation of GD (Stagnaro-Green et al., 2004), which increases after pregnancy and MS (Sandyk, 1993), which increases after puberty. In addition, these also match the fact that AIDs onset is the most at 40 to 49 years old, but considering the prevalence, 20 to 29 years old is the most (Hayter et al., 2012).

Therapy and reaction

As mentioned above, steroids, immunosuppressants, and molecular-targeted drugs against lymphocytes have a certain effect on AIDs, but their effects are limited (Wang et al., 2015), so they are not curative drugs. An interesting finding is that zinc (Zn), and autophagy inhibitors have therapeutic effects on AIDs. The blood Zn concentration was significantly lower in patients with AIDs (Sanna et al., 2018) and patients with psoriasis (Lei et al., 2019). A patient with oral lichen planus improved after administration of zinc acetate. Administration of Zn to experimental autoimmune encephalomyelitis (EAE) model mice significantly improved symptoms (Straubel et al., 2018). Zn is thought to stabilize Treg without suppressing the immune system (Rosenkranz et al., 2016; Maywald et al., 2018). Zn deficiency induces mitophagy of porcine oocytes and increases reactive oxygen species, causing meiotic abnormalities (Lai et al., 2023). As mentioned above, autophagy inhibitors improve SLE, RA, and MS (Wu et al., 2017), and mitophagy inhibitors reduce the progression and exacerbation of EAE (Li et al., 2020). It is possible that enhancement of mitophagy is involved in the development of AIDs, and the effect of Zn on AIDs is mediated through inhibition of mitophagy.

Summary of the phenome of AIDs

Based on the results of this simulation, the author will summarize the phenome of AIDs that may connect the missing link from Mc to AIDs. The assumption that female LLBMC attacks male Soc could explain the gender bias and prevalence of AIDs in adults and youth. In females, the male Soc replaced by chimeric male MSC is attacked by own or chimeric female LLBMC, and in males, the own male Soc is attacked by chimeric female LLBMC. H-Y Ag is likely to be the target factor of male Soc. It is highly possible that female H-Y Ag-specific LLMPC is the effector celll. However, it is unlikely that H–Y Ab is involved in developing AIDs as a pathogenic autoantibody. Destruction and regeneration of cells, mainly by infection, are necessary as triggers for the onset of AIDs. The sensitive organ and the favorable age of the pathogen determine that of the AIDs. Autoantibody production and maintenance of AIDs inflammation require autoantigen release by necrosis, not apoptotic cells. The autoantigen selection is not random and may be mediated by some protein. It is suggested that phagocytosis and antigen presentation of IC containing autoantigens by FcγR and HLA class II may be involved in autoantibody production. Moreover, the antibodies that form IC are not antibodies against autoantigens, and some protein may mediate them. ASA, including anti-H-Y antibody, which is found in many males and females regardless of age, is likely to be related to not only other autoantibody production but also the development of AIDs. There is no involvement of sex hormones or sex chromosomes in the gender bias of AIDs. However, it may be releasing humoral factors that downregulate the development of AIDs from the gonads. Immunosuppressants and B cell depletion therapy for AIDs have certain effects but are limited. The onset of AIDs may be related to the enhancement of mitophagy. Zn have a certain effect on AIDs, and the effect of Zn may be mediated by suppression of mitophagy. Are there any factors or mechanisms that can satisfy these phenome of AIDs? The author would like to present hypothesis below.

Eri15/Spag1/Xt-mir axis

The author would like to present the exosome and Eri15/Spag1/Xt-mir axis as the mechanism to cause necrosis of male Soc with H-Y Ag as a target. Hayashida et al. reported that maternal mitochondrial DNA inheritance (MMI) is established through the exclusion of sperm mitochondrial DNA due to tthe ransport of the endogenous retroviral integrase 15 kD (Eri15) by the egg cytosol Spag1-2 via the SPAG1-1 protein on the sperm mitochondria outer membrane during fertilization (Hayashida et al., 2005, 2008). In addition, it was proved that hybrid male sterility (HMS) occurs due to mitophagy by malfunction of the MMI system, which is suppressed in the testes (Hayashida et al., 2009). Furthermore, it was suggested that the Eri15/Spag1 axis is suppressed by micro RNA (Xt-mir) on the X chromosome, mainly expressed in the testis (Hayashida, 2022). It has been observed that miR506, which targets Spag1-2, is overexpressed in the bile duct epithelium of PBC (Banales et al., 2012). There is a possibility that negative feedbach is working against excessive mitophagy by the HMS system in PBC.

As mentioned above, SPAG1 was discovered as one of the target proteins of ASA in unexplained infertile males (Bohring, 2001). SPAG1-1 is expressed in the mitochondrial outer membrane of sperm and glycosylated by post-translational modification in the epididymis (Hayashida et al., 2005), so it has a high immunogenicity. SPAG1-2, a splicing variant of SPAG1-1, is widely expressed in the cytoplasm of organs other than sperm and provides a platform for quaternary protein folding of proteins via the TPR domain involved in protein-protein interaction as a member of the co-chaperone R2SP complex (SPAG1, PIH1D2, RUVB1/2) (Maurizy et al., 2018). Both Spag1-1 and Spag1-2 are also expressed in cancer cells and stem cells, suggesting involvement in the Warburg effect by programmed mitophagy (mitochondrial quantity control) (Hayashida, 2022). Spag1-1 is a sperm-specific antigen and belongs to the cancer-testis antigen. Zeng et al. detected differentially methylated regions (DMRs) in ACPA (anti-citrullinated protein antibodies, RA-specific autoantibodies that correlate with disease severity)-related and RA-related epigenome-wide association studies (EWAS) in RA patients. They compared these DMRs-related protein-coding genes with the 295 associated genes in the RA-associated GWAS, identifying four genes that are duplicated in all. SPAG1 was included in these four genes (Zeng et al., 2021). It is suggested that SPAG1 may be involved in the onset and progression of RA. In orbital fibroblasts of Active Graves ophthalmopathy (GO), the SPAG1 gene was detected among hypermethylated genes compared to inactive GO (Virakul et al., 2021). Furthermore, 72 genes differentially expressed in fibroblasts of skin lesions of SSc compared to healthy people were detected, among which the SPAG1 gene was recognized (Zhou et al., 2005). The involvement of SPAG1 in fibroproliferative AIDs is suggested. Eri15 is an integrase that exists as a multimer in the cytoplasm not only in the ovaries but also in the testes and most somatic cells in mice. Eri15 is an integrase adapted to the mitochondria matrix environment, which is activated by Mn and Mg and suppressed

by Zn. Eri15 is conversely suppressed by truncating the Zn binding site required for regular integrase activity (Hayashida et al., 2008). As mentioned above, the onset of AIDs may be associated with increased mitophagy. The therapeutic effects of Zn on AIDs (Maywald et al., 2018) may be due to the suppression of mitophagy via Eri15. Mn promotes mitophagy and induces mitochondrial dysfunction (Zhang et al., 2016) (the effect of Mn on AIDs is unknown), and its effect on mitophagy may also be via Eri15.

Exosome and BCR

The exosome is a small vesicle surrounded by a lipid bilayer membrane, containing proteins, lipids, mRNAs, and microRNAs. It is released outside the cell and has attracted attention recently as an intercellular information transmission medium (Raposo et al., 2013). The Eri15/SPAG1 axis is used to avoid apoptosis by mitophagy during division in stem cells and cancer cells, so it is presumed to be an anti-apoptosis system (Hayashida, 2022). MPC does not divide, but its differentiation and maintenance require autophagy and anti-apoptosis molecules (Khodadadi et al., 2019). MPC may express Spag1-1 protein to utilize Eri15/SPAG1 axis as an anti-apoptotic system. Cytosolic proteins remain within the exosomes, and proteins derived from the plasma membrane are retained in the vesicle membrane (Chen et al., 2018). SPAG1 protein (isoform unknown) has been detected in the exosome secreted by ovarian cancer cells (Liang et al., 2013). If MPC expresses Spag1-1 protein, it is likely that it is contained in the exosome. It is said that exosome has a target cell. TCR/CD3 complex and BCR are detected on the surface of exosomes secreted from human T and B cells. It suggests transmitting specific signals to target cells with appropriate MHC/peptide combinations (Blanchard et al., 2002; Rialland et al., 2006). There is a report that antibody can bind to the antigen on the HLA class II molecule (Jin et al., 2014), so BCR may also be able to bind to antigen on the HLA class I molecule. H-Y Ag-specific MPC produces and releases an exosome with H-Y Ag-specific BCR on the surface and contains SPAG1-1 protein inside. The exosome binds to the H-Y Ag on the HLA class I molecule of the male Soc in which Spag1-2 protein and Eri15 protein are expressed. HLA class I molecules are internalized and recycled by endocytosis (Chiu et al., 1999). The exosome is internalized with the HLA class I molecule. As mentioned above, male MSC is unlikely to be a target because HLA class I expression is low on MSC (Lee et al., 2017). As a result, the Spag1-1 protein is incorporated into the mitochondrial outer membrane in the male Soc. The MMI system works, and the mitochondria that have lost their action potentials are processed by mitophagy. If it becomes excessive, necrosis will come as a result of mitoptosis. At the same time, SPAG1-1 will also bind SPAG1-2 expressed in the cytosol of the target Soc.

Autoantibody

Affinity of SPAG1 to autoantigen As mentioned above, autoantigen selection may be mediated by some protein , and sperm-specific antigen (SSA) induces not only ASA but also other autoantibodies production (Lucas et al., 1978). There may be a molecule that promotes autoantibody production in SSA, including SPAG. Molecular chaperones are most likely common molecules interacting with many autoantigen proteins to support protein folding. In addition, the membrane-binding protein, common among autoantigens, needs a molecular chaperone to be transported to the cell membrane after translation. Heat shock protein (HSP) is a typical molecular chaperone. It is a housekeeping protein well-preserved from bacteria to humans and works in all cells. HSP reacts efficiently with co-chaperones assistance (Graham et al., 2019). As mentioned above, SPAG1-2, as a member of R2SP, binds to HSP via the TPR domain of SPAG1-2 to form a multi-chaperone complex and is involved in protein complex assembly (Maurizy et al., 2018). Repeat domains, including the TPR domain, and coiled-coil domains which are common in autoantigens, are involved in protein-protein interactions. The TPR domain also has DNA and RNA binding activity (D'Andrea et al., 2003; Björklund et al., 2006). Four of the five epitopes detected in SLE and autoimmune hepatitis were in the coiled-coil domain (Chih-Hao et al., 1992). The affinity between the TPR and coiled-coil domain is high (Jabet et al., 2000). The target binding affinity of the TPR domain is strong and equivalent to antibodies (Björklund et al., 2006). Hayashida et al. detected the bait protein and Eri15 in a combined molecular weight band by conventional Western blotting using SDS, DTT, and heat treatment of immunoprecipitated proteins from the recombinant Spag1-1 specific region and mouse ovarian lysates. It was suggested that Spag1 shows a robust affinity depending on the partner molecule (Hayashida et al., 2008). HSP does not have a repeat domain and captures the substrate proteins by closing the lid using ATP energy, and protein/HSP complexes released from dead cells are captured by HSP receptors on DC (Sun et al., 2012; Zininga et al., 2018). Similarly, endogenous proteins with a strong affinity for Spag1-2 may be released outside the cell as endogenous antigen/Spag1-2 complex.

Production of autoantibody As mentioned above, SPAG1-1, which was found as one of the target antigens of ASA in infertile men, has high immunogenicity, but its epitope is unknown. Human SPAG1-1 shares 365 aa on the N-terminal with SPAG1-2 and has a SPAG1-1 specific sequence of 51 aa at the C-terminal, but the homology of the specific sequence and common part is low (Hayashida, 2022). It is difficult to think that the epitope of anti-SPAG1 antibody exists in SPAG1-2, a housekeeping protein, so the epitope likely exists in the SPAG1-1 specific sequence. Antibodies may not usually be produced against SPAG1-1, a sequestered antigen expressed in immune-privileged stem cells and testis (Hayashida, 2022). However, in females, antibodies will be produced due to exposure to the immune system by sperm. Unlike anti-H-Y antibodies that affect the maintenance of pregnancy, antibodies against SPAG1-1 on sperm, which are not formed in the fetus, are considered to have sufficient function as an antibody. Among the many proteins or protein complexes released from male Soc that have necrosis due to the influx of SPAG1-1 protein by the exosome, the anti-SPAG1-1 antibody produced by SPAG1-1 specific LLMPC (SPAG1-1-LLMPC) binds to SPAG1-1 of the autoantigen A/SPAG1-2/SPAG1-1 complex. This immune complex is phagocytosed by DC via the FcγR and is presented by HLA class II or HLA class I by cross-presentation. Autoantigen A-specific B cells capture and internalize the autoantigen A/SPAG1-2/SPAG1-1/anti-SPAG1-1 antibody complex with BCR or FcγR and present the antigen with HLA class II molecules (Autoantigen A and SPAG1-2 are not antigen-antibody bindings, so the autoantigen A epitope is empty). Usually, when DC presents a complex with only autoantigen A through priming, autoantigen A-specific naive $CD4^{+}$T cells are not activated by autoantigen A-specific Tregs, and autoantibodies are not produced. As mentioned above, this possibility is low because AID with autoantibody developed after BMT, where Treg is increasing (Seissler et al., 2012). Based on the observation that many autoantigen epitopes were located in the coiled-coil region (Dohlman et al., 1993), the epitopes of the autoantigens may be cryptic and not recognized by Treg. However, it is difficult that all epitopes of many autoantigens are assumed to be cryptic. It has been observed that misfolded proteins are presented in HLA class II molecules (Jin et al., 2014). The binding between SPAG1-2 and SPAG1-1 is a strong affinity between TPR domains, and in the case of SPAG1-2 and a client protein with strong affinity, it may be primed as a complex peptide (or protein) in APC and presented on the

HLA class II molecule. SPAG1-1 specific naive $CD4^+$T cells recognize SPAG1-1 epitope and are activated by DC presenting a complex peptide containing two epitopes of autoantigen A and SPAG1-1 (Unlike endogenous antigens such as autoantigen A and SPAG1-2, SPAG1-1 is an exogenous protein and is usually not suppressed by Treg). SPAG1-1 specific effector $CD4^+$T cells bind to the complex peptide SPAG1-1 epitope presented by autoantigen A-specific B cells, which activates B cells to produce autoantibody A (i.e., helper T cell bypass). Since SPAG1-2 as a chaperone forms a complex with many autoantigens, many autoantibodies are produced (similar to epitope spreading?) (Krishna et al., 2016). After necrosis of target cells, the released SPAG1-1 stimulates SPAG1-1-LLMPCs to maintain antibody production and new SPAG1-1-LLMPCs will also be differentiated. The above autoantibody production is not due to immune abnormalities but is an extension of the normal immune response.

Chaperones that capture many autoantigens include not only HSP, SPAG1, and P1H1D1/2 but also RPAP3 and DNAAF2, which are members of R2SP-like co-chaperone complexes such as R2TP and R2SD (Maurizy et al., 2018). It is unknown whether P1H1D1/2, RPAP3, and DNAAF2 have an isoform also expressed in sperm like SPAG1, induce antibody production, and can uptake client protein into DC via antibodies. HSP can be uptaked by HSP receptors of APC without antibodies (Zininga et al., 2018). However, ADP is easily dissociated in the priming process, and the lip opens, and it will not be presented as an autoantigen A/HSP complex. Smith et al. detected 506 client proteins by immunoprecipitation of human bronchial epithelial cell lysates with SPAG1-2 antibody (Smith et al., 2022). Among them, four autoantigen genes (*SSB, TRIM21, SNRPD2, VIM*) (Hayter et al., 2012) are recognized, but it will be necessary to search with various tissue cells hereafter. Among the many endogenous proteins that are clients of SPAG1-2, those with an extreme affinity with SPAG1-2 may become autoantigens. In addition, the tissue-specific proteins, which account for 80% of the autoantigens (Hayter et al., 2012), are thought to have evolved into more advanced protein complexes to perform tissue-specific functions compared to the primitive housekeeping proteins. It has been reported that tissue-specific combination formation of transcriptional coregulator complexes is essential for tissue-specific transcriptional regulation (Yokoyama et al., 2014). R2SP complex also has the R2TP complex and R2SD complex, which share some of their constituent proteins. The evolution and diversity of protein complexes under limited genes leads to tissue-specific responses, and chaperone, which supports the quaternary structure, is thought to have coevolved as a complex. HSP, which is evolutionarily well conserved from single-celled organisms and is ubiquitous in all tissues (Zininga et al., 2018), has poor substrate protein selectivity (Stebbing et al., 2004) and cannot explain the selectivity of tissue-specific proteins in AID.

The individual is likely sensitized by both SPAG1-1 and H-Y Ag by sperm. Sperm appears unique because they can present SPAG1-1 and H-Y Ag to females as antigens and transmit acquired immunity to offspring with chimeric LLMPC through pregnancy. Furthermore, SPAG1-1 differs from other SPAG proteins in that it is not only immunogenic because it is expressed in immune-privileged testis and stem cells, but it is also incorporated into the mitochondrial outer membrane to induce necrosis, and the antibody binds to SPAG1-2 bound to many autoantigens to promote the production of autoantibodies. The SPAG1 protein is a unique molecule in that the initiation and persistence of inflammation in AIDs and the production of autoantibodies are inseparable. As mentioned above, the SPAG1 gene has been detected in new disease susceptibility tests such as GWAS and EWAS in RA, GO, and SSc, but no reports show the relationship between H-Y Ag genes and AIDs. Females do not have H-Y Ag genes, and male Mc cells resulting from male pregnancy are few in the blood, so they will not affect polymorphism detection. In males, the maternal chimeric H-Y-LLMPC mainly acts as effector cells, so the polymorphism of the individual's H-Y Ag genes does not seem to be involved in disease susceptibility.

Gender bias of cancer and lifespan

In many cancers, the incidence rate of females is lower than that of males, and there is also gender bias, but the cause is unclear (Dorak et al., 2012). In thyroid cancer, Mc cells are less in the blood and increase in cancer tissue, and Mc cells with hematopoietic differentiation may destroy tumors. There are many reports that Mc is suppressive against cancer (Fugazzola et al., 2012). In leukemia patients, F→M HSCT has a higher graft-versus-leukemia effect independent of GVHD development than other combinations, suggesting the involvement of H-Y Ag (Randolph et al., 2004). As mentioned above, Spag1-1 and Spag1-2 are expressed in both stem cells and cancer cells (cancer stem cells?), suggesting their involvement in the Warburg effect by mitochondrial quantity control (Hayashida, 2022). If malignant transformation occurs in stem cells, including MSC, chimeric male MSC will also become malignant with the same probability as own stem cells. There is also a report that MSC transplantation in patients with hematologic malignancies increases recurrence (Gao et al., 2016), suggesting that MSC may be involved not only in its malignant transformation but also in cancer repair. mHA is also expressed on tumor cells (Bonnet et al., 1999). If the individual has female H-Y-LLMPC, necrosis due to self-destruction of cancer cells will cause LLMPC to migrate, and H-Y Ag-expressing cancer cells will cause necrosis by the SPAG1-1/H-Y-LLMPC/exosome axis. In this case, females have not only chimeric H-Y-LLMPC from their mother but also their own H-Y-LLMPC through sperm sensitization after puberty, whereas males have only chimeric H-Y-LLMPCs from their mother. In addition, in males, all the cells surrounding the cancer express the H-Y antigen, so the SPAG1-1/H-Y-LLMPC/exosome axis effect will be diluted. For this reason, the incidence of cancer in females will be relatively lower than in males. Generally, females tend to have a longer lifespan than males, which may be affected by the difference in cancer incidence due to SPAG1-1/H-Y-LLMPC/exosome axis.

Gonad dysgenesis and Xt-mir

Three out of eight Xt-mir targeting mouse Spag1-2 mRNA 3'UTR are also expressed in the ovary (Song et al., 2009). These Xt-mir are likely contained in exosomes released from testes and ovaries. The increase in AIDs in Turner's syndrome (Jørgensen et al., 2010), POI (Grossmann et al., 2019), and Klinefelter's syndrome (Seminog et al., 2020) mentioned above may be due to decreased release of Xt-mir-containing exosomes and inability to suppress Eri15/SPAG1 axis by common gonadal development disorders.

Autoantibody and prevalence

In this simulation, by seeking the optimal combination of LLBMC and Soc in an allogeneic relationship, it was finally pointed out that autoantibodies may not be directly involved in developing AIDs. This result is consistent with the fact that autoantibody production is not essential for AIDs. The only thing that was difficult to explain in the simulation was the existence of adult male-dominant AIDs. Most of the middle-aged and elderly male-dominant AIDs have a low prevalence (Fig. 1). AIDs with a high prevalence of more than 10 per 100,000

population were 21 (47%) of 45 AIDs with pathogenic molecular target, while 7 (26%) of 27 AIDs without pathogenic molecular target. However, not all AIDs with pathogenic molecular targets have a high prevalence (Fig. 1). That is, the presence of autoantibodies is a necessary condition for an increase in the prevalence of AIDs, but it is not a sufficient condition, and factors other than the mere presence or absence of autoantibodies are presumed to be involved. For example, the prevalence of triggering infections may be affected. Acquisition of autoantibodies may be determined by the strength of autoantigen and SPAG1-2 affinities, and autoantibody hazards may be determined by the affinities with binding autoantigens, the sites of autoantigen expression in cells, and the functions involved. The degree of pathologic modification by autoantibodies may affect the rate of consultation at medical institutions and the rate of diagnosis, which may be reflected in the difference in prevalence. Mc is such a common event, and Mc cells are observed even in asymptomatic healthy females, so it is thought that it cannot be considered a cause of cGVHD and AIDs (Tyndall et al., 2008). However, various individual factors other than those mentioned above are involved in the pathway from Mc to the onset of AIDs. Ultimately, the ratio of male MSC, female H-Y-LLMPC, and female SPAG1-1-LLMPC in the bone marrow will decide the onset of AIDs.

The fact that adult male-dominant AIDs and AIDs without well-defined autoantigens show a low prevalence may be explained by the presence or absence of pathogenic autoantibodies. A female-dominant chronic inflammatory group develops in the adult population where the Eri15/SPAG1/H-Y-LLMPC/male MSC axis is working by the same trigger in the same organ. Acquisition of chimeric female SPAG1-1-LLMPC in this population would be the same in both males and females because they are maternally derived. Males without chimeric female SPAG1-1-LLMPC do not produce autoantibodies. Females without chimeric female SPAG1-1-LLMPC are divided into those who produce autoantibodies and those who do not, depending on the presence or absence of their own SPAG1-1-LLMPC acquired by sperm sensitization after puberty. As a result, the rate of females in the group without autoantibodies will not be overwhelmingly higher than in the group with autoantibodies. If the autoantibodies were not pathogenic, they would all show the same phenotype and be diagnosed with the same disease, and the antibody retention rate in males would be lower than in females. If autoantibodies are pathogenic (although cytotoxic T cells may also be involved), the phenotypes of autoantibody-possession and non-possession patients will be completely different so that will be recognized as different disease groups. Moreover, it is predicted that the prevalence rate and female/male ratio of autoantibody-non-possession groups are lower than that of autoantibody-possession groups. Sjogren's syndrome (SjS) and Mikulicz's disease (MD), Hashimoto's disease (HD) and Riedel's thyroiditis (RT), RA and adult Still's disease (ASD), SLE and discoid lupus erythematosus (DLE), and SSc and CREST syndrome (CREST) are possible AIDs suggestive of the above two related groups.

These disease pairs are close to the onset age, with the latter tends to be higher (Fig. 1). The apoptosis image by autoimmune response is expected to be detected in the tissues of the autoantibody-possession group but is rarely observed in the autoantibody-non-possession group. In fact, there are reports that apoptosis is significantly less in MD tissues than in SjS (Tsubota et al., 2000; Yamamoto et al., 2005). MD and RT are classified as IgG4RD. IgG4RD is characterized by compression symptoms due to fibrosis and the accumulation of IgG4-holding plasma cells. It is a chronic inflammatory disease common in middle-aged and older adults and responds well to steroid and B cell depletion therapy but does not have defined autoantibodies (Stone et al., 2020). IgG4 is thought to have an anti-inflammatory effect and is produced as a response to inflammatory stimuli (Maslinska et al., 2022). Due to the absence of pathogenic autoantibodies, the disease activity is weak and the onset of subjective symptoms is delayed. It may develop in middle-aged and older adults who cause compression symptoms due to the fibrosis and infiltration of reactive mature B cells as the terminal image of chronic inflammation. The reason why the effect of steroid and B cell depletion therapy is more robust than regular AIDs is probably because they act on accumulated mature B cells rather than LLMPC and weaken compression symptoms. IgG4RD may be looking at the terminal image of non-autoantibody-bearing AIDs without SPAG1-1-LLMPC.

Inflammatory field

In the model presented here, three types of cells, male MSC, female H-Y-LLMPC, and female SPAG1-1-LLMPC, are required to develop AIDs. As chimeric cells, males require female H-Y-LLMPC and female SPAG1-1-LLMPC, while females require male MSC. Males can use their own H-Y antigen or SPAG1-1-sensitized male LLMPC, but chimeric male MSC is essential for females. Necrosis as a trigger is necessary to induce the migration of LLMPC to the inflammatory field, and especially for females, it is also necessary to replace male Soc with male MSC. Male MSC and female H-Y-LLMPC are required for inflammation persistence, and SPAG1-1-LLMPC is required for autoantibody production. If the autoantibodies produced are self-reactive, they will be accompanied by apoptosis or dysfunction of target cells. However, it is an incidental reaction and may not necessarily be required to maintain the inflammatory field. As long as the relationship between male Soc and female H-Y-LLMPC continues, even without autoimmune reactions caused by pathogenic autoantibodies, necrosis→release of inflammatory cytokines and chemokines by phagocytic cells that have taken up damage-associated molecular patterns (DAMPs)→LLMPC and MSC migration→regeneration by MSC, supply of Spag1-1 protein by H-Y-LLMPC→necrosis cycle, and the inflammatory field will be established and sustained. The group mentioned above in which autoantibodies appear after acetaminophen liver injury or after vasectomy but do not develop AIDs corresponding to antibodies can be explained by the presence of necrosis and SPAG1-1-LLMPC but the absence of H-Y-LLMPC. AMA in post-acetaminophen liver injury was transient, and there was no gender bias in its detection rate (Leung et al., 2007), supporting the absence of chimeric H-Y-LLMPC. This phenomenon may be related to the high use of acetaminophen leads to plasma cell disorders (Walter et al., 2011). Furthermore, it also means no gender bias in the autoantibody production system. Post-vasectomy males who develop autoantibodies and ASA do not develop AIDs (Mathews et al., 1976) but often present with infertility after vasovasostomy (Sotolongo, 1982). ASA is considered a pathogenic antibody, but H-Y Ag is not included in SPAG detected by seminal plasma of ASA-positive infertile males (Bohring, 2001). For males, SPAG is a sequestered antigen, and antibodies are produced, whereas H-Y Ag is an autoantigen and does not produce antibodies, thus not being included in SSA. These facts indicate that it is SSA that does not contain H-Y Ag, namely SPAG, that induces autoantibody production in males after vasectomy and that only autoantibodies without H-Y Ab do not cause AIDs. NMDAR encephalitis with ovarian teratoma seems to be an AID with pathogenic autoantibodies, but it may not involve H-Y-LLMPC or SPAG1-1-LLMPC. Since neurons rarely express HLA class I molecules (Ichiryu et al., 2013), they do not present receptor antigens or H-Y

antigens. Therefore, the receptor antigen released by necrosis of teratoma is treated as an exogenous antigen for APC, so anti-receptor antibodies are not autoantibodies, and SPAG1-1-LLMPC is not required. Also, even if H-Y-LLMPC exists, it cannot act on neurons, so the chain of necrosis will not occur. These predictions are supported by encephalitis being cured by removing teratoma. In addition, if the anti-receptor-specific LLMPC continuously releases anti-receptor antibodies, the encephalitis will persist, but this does not occur (Acién et al., 2014), suggesting that sustained antigen stimulation may be necessary for the antibody production of LLMPC in vivo. Therefore, NMDAR encephalitis is not strictly AIDs in this model.

De Bari suggests that the effect of molecular-targeted treatment for cytokines, B cells, and osteoclasts in RA is limited, and bone destruction progresses even if the inflammatory findings are in remission, so the suppression of inflammation is not enough to stop the progression of RA, and the mechanism of joint destruction may be detached from inflammation (De Bari, 2015). Immunosuppressive agents, molecular-targeted drugs, and MSC transplantation therapy for AIDs show a certain level of alleviation. However, they are not curative treatments because they act only on the inflammation reaction associated with necrosis and autoimmune reaction due to autoantibodies, but not on the necrosis of male Soc caused by H-Y-LLMPC. It is predicted that if chimeric male MSC in females and chimeric female H-Y-LLMPC in males can be depleted, the chain reaction in the inflammatory field can be broken.

The origin of AIDs

Mammals that enable placental nurture face the problem of microchimerism. Male β cell substitution has been observed in the female pancreas (Nelson, 2007), but there is no problem if Mc cells are compatible Soc between males and females. However, sex hormone-producing cells become endocrine disruptors. Therefore, exosomes targeting the H-Y antigen may eliminate male cells using the Eri15/SPAG1 axis. Female Soc cannot be excluded because it does not have a molecule that recognizes it. However, this system is thought to be immune to selection pressure because females should be protected for the survival of organisms, especially mammals. The reason why six genes that provide the H-Y antigen remain on the Y chromosome maybe because it is beneficial for females to identify male cells. Then, why not directly use H-Y antigen-specific T and B cells for elimination?

When the mother becomes pregnant with a male fetus, the direct reaction is thought to be severely suppressed by the maternal H-Y antigen-specific Treg and anti-H-Y antigen idiotype antibodies so as not to reject the male fetus. Male Mc cells that invade the thymus may activate H-Y Ag-specific Treg, or induced Treg may be generated by contact with H-Y Ag at the periphery. H-Y-LLMPC, generated after escaping a strict immune surveillance system, had to eliminate male Mc cells by harboring spag1-1 protein in immune-privileged exosomes, which seems purposeful. The subsequent autoimmune reaction is considered to be a secondary reaction caused by the fact that the female is presented as an exogenous antigen by the sperm and acquires antibodies because SPAG1-1 is an immune-privileged molecule, and its isoform protein (SPAG1-2) was a chaperone involved in the formation of many protein complexes in somatic cells. Clinical concordance for SSc in monozygotic twins was <5% (Zhou et al., 2005). Monozygotic twins, whose Mc environment is considered to be almost the same, have few simultaneous onset, so postnatal trigger or sperm sensitization may have a ignificant effect. In recent years, AIDs has tended to increase, and changes in environmental factors, including the intestinal flora, are thought to be the cause (Smits et al., 2007; Markle et al., 2013), but from the author's hypothesis, it is speculated that the increase in opportunities for sensitization by sperm antigens in females may be the cause. As placental mammals with internal fertilizing, humans cannot avoid ASA and Mc and may be destined to develop AIDs.

Conclusion

Assuming that cGVHD and AIDs are caused by microchimerism, the author simulated which gender combination of LLBMC and Soc in the allogeneic relationship matches the gender bias and incidence rate. As a result, it was reasonable to assume that female LLBMC is attacking male Soc. In order to elucidate the further missing link connecting AIDs and microchimerism, the author proposed the following hypotheses. After puberty, females acquire H-Y-LLMPC and SPAG1-1-LLMPC by sperm or male pregnancy. During pregnancy, female H-Y-LLMPC, female SPAG1-1-LLMPC, and male MSC are transferred and settled as microchimerism cells from the mother in males and from the mother and older brother through the mother in females. Immune cells such as LLMPC and MSC migrate due to necrosis caused by triggers such as infectious diseases. In females, female Soc that has been eliminated is regenerated by male MSC and replaced with male Soc. Spag1-1 protein-encapsulated exosomes with H-Y-BCR on the surface are released from female H-Y-LLMPC. This exosome is taken up by male Soc presenting H-Y Ag on HLA class I molecules, Spag1-1 protein is integrated into the mitochondrial outer membrane, and at the same time, it binds to autoantigen A/Spag1-2 complex. Eri15 is transported by SPAG1-2 and incorporated into the matrix via Spag1-1 on the mitochondrial outer membrane, destroying mtDNA and causing mitophagy. Cells with excessive mitophagy undergo necrosis from mitoptosis and release cell contents. The anti-Spag1-1 antibody secreted from SPAG1-1-LLMPC binds to the autoantigen A/Spag1-2/SPAG1-1 complex in these. This IC is taken up by FcγR on DC, primed and presented with the HLA classII molecule as a complex peptide. The SPAG1-1 specific naive $CD4^{+}$T cell reacting to the SPAG1-1 epitope of the complex peptide is activated. Autoantigen A-specific B cell takes up IC by BCR or FcγR, presents complex peptide with HLA class II molecule, and is activated by SPAG1-1-specific effector $CD4^{+}$T cell bound to the SPAG1-1 epitope of the complex peptide to produce anti-A antibody. Among these antibodies, those that bind to autoantigens and impair cell function or cause apoptosis become pathogenic autoantibodies and modify the pathology. Mitoptosis by Eri15/SPAG1-2/SPAG1-1 axis and apoptosis by pathogenic autoantibodies promote the migration of MSC and immune cells, including LLMPC, to form an inflammatory field.

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Figure 1. Distribution of autoimmune diseases by age and female/male ratio. red circle; autoantibodies (+)/ pathogenic molecular target (+), orange circle; autoantibodies (+)/pathogenic molecular target (-), green circle; autoantibodies (-)/pathogenic molecular target (-). small circle; 0.1~10 prevalence per 10^5 people, medium circle; 10~100 prevalence per 10^5 people, large circle; >100 prevalence per 10^5 people. Cases with a prevalence of less than 0.1 were excluded. blue character; IgG4-RD. Referring to Hayter et al. 2012, added the following; IgG4-RD (AIP, PSC, RT, MD, TIN) (Kamisawa, 2023; Trivedi et al., 2022; Hennessey, 2011; Yamamoto et al., 2006; Quattrocchio et al., 2016), AS (Mauro et al., 2021), PSV/PFV(Gudjonsson et al., 2007), ASD (Efthimiou et al., 2021), DCM (Rakar et al., 1997), PMR (González-Gay et al., 2017), MGN (Lai et al., 2015), OLP (Lozada-Nur et al., 1997) and IgAN (Donadio et al., 2002).

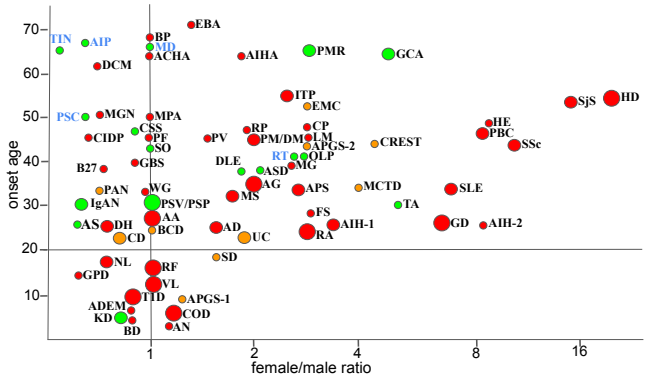

Figure 2. Natural microchimerism: simulation of onset probability. OnP; onset probability, EnP; encounter probability, ExP; existence probability, M; Mc parameter, S; sibling coefficient, P; pregnancy coefficient, A; aging parameter, D; dilution coefficient, LLBMC; long-lived bone marrow cells, Soc; somatic cells, circle; LLBMC (effector), square; somatic cells (target), orange circle (square); own cells, red circle (square); maternal Mc cells, green circle (square); sibling Mc cells, blue circle (square); fetal Mc cells, number in the circle (square); age of cells, circle (square) with +; female cells, circle (square) with arrow; male cells, Sample is a case of a female effector/male target combination in a 30-year-old female.

$$\mathrm{OnP} = \sum_{i=1}^{n} \{ \mathrm{EnP} \}_i = \sum_{i=1}^{n} \{ \mathrm{ExP(LLBMC)} \}_i \times \{ \mathrm{ExP(Soc)} \}_i$$

$$= \sum_{i=1}^{n} \{ \mathrm{M \times S \times P \times A} \}_i \times \{ \mathrm{M \times S \times P \times A \times D} \}_i$$

example (30 female / ♀→♂) LLBMC: 30 60 32 32 0 0; Soc: 30 60 32 32 0 0

i	effector	target	M	S	P	A	M	S	P	A	D
1.	30	32	1.0			x (1 - 30 / 80)	0.1 x 0.1	x 0.5		x (1 - 32 / 80)	x 1.0
2.	30	0	1.0			x (1 - 30 / 80)	0.1		x 0.5	x (1 - 0 / 80)	x 1.0
3.	60	32	0.1			x (1 - 60 / 80)	0.1 x 0.1	x 0.5		x (1 - 32 / 80)	x 1.0
4.	60	0	0.1			x (1 - 60 / 80)	0.1		x 0.5	x (1 - 0 / 80)	x 1.0
5.	32	32	0.1 x 0.1	x 0.5		x (1 - 32 / 80)	0.1 x 0.1	x 0.5		x (1 - 32 / 80)	x 1.0
6.	32	0	0.1 x 0.1	x 0.5		x (1 - 32 / 80)	0.1		x 0.5	x (1 - 0 / 80)	x 1.0
7.	0	32	0.1	x 0.5	x (1 - 0 / 80)		0.1 x 0.1	x 0.5		x (1 - 32 / 80)	x 1.0
8.	0	0	0.1	x 0.5	x (1 - 0 / 80)		0.1		x 0.5	x (1 - 0 / 80)	x 1.0

Figure 3. Artificial microchimerism: simulation of onset probability. OnP; onset probability, EnP; encounter probability, ExP; existence probability, M; Mc parameter, S; sibling coefficient, P; pregnancy coefficient, A; aging parameter, D; dilution coefficient, Sy; syngeneic coefficient, LLBMC; long-lived bone marrow cells, Soc; somatic cells, circle; LLBMC (effector), square; somatic cells (target), orange circle (square); own cells, red circle (square); maternal Mc cells, green circle (square); sibling Mc cells, blue circle (square); fetal Mc cells, number in the circle (square); age of cells, circle (square) with +; female cells, circle (square) with arrow; male cells, Sample is a case of a female effector/female target combination in a male donor/female recipient.

$$\mathrm{OnP} = \sum_{i=1}^{n} \{ \mathrm{EnP} \}_i = \sum_{i=1}^{n} \{ \mathrm{ExP(LLBMC)} \}_i \times \{ \mathrm{ExP(Soc)} \}_i$$

$$= \sum_{i=1}^{n} \{ \mathrm{M \times S \times P \times A} \}_i \times \{ \mathrm{M \times S \times P \times A \times D \times Sy} \}_i$$

example (M→F / ♀→♀) LLBMC: 30 60 32 32; Soc: 30 60 32 32 0 0

i	effector	target	M	S	P	A	M	S	P	A	D	Sy
1.	60	30	0.1			x (1 - 60 / 80)	1.0			x (1 - 30 / 80)	x 0.1	
2.	60	60	0.1			x (1 - 60 / 80)	0.1			x (1 - 60 / 80)		x 0.5
3.	60	32	0.1			x (1 - 60 / 80)	0.1 x 0.1	x 0.5		x (1 - 32 / 80)		
4.	60	0	0.1			x (1 - 60 / 80)	0.1		x 0.5	x (1 - 0 / 80)		
5.	32	30	0.1 x 0.1	x 0.5		x (1 - 32 / 80)	1.0			x (1 - 30 / 80)	x 0.1	
6.	32	60	0.1 x 0.1	x 0.5		x (1 - 32 / 80)	0.1			x (1 - 60 / 80)		
7.	32	32	0.1 x 0.1	x 0.5		x (1 - 32 / 80)	0.1 x 0.1	x 0.5		x (1 - 32 / 80)		x 0.5
8.	32	0	0.1 x 0.1	x 0.5		x (1 - 32 / 80)	0.1		x 0.5	x (1 - 0 / 80)		

Figure 4. Natural microchimerism: Odds of onset probability by gender and age for each combination of effector cells/target cells. A; female effector→male target, B; male effector→female target, C; female⇄male, D; female effector→female) target, E; male effector→male target, F; all LLBMC effector→all Soc target, red line; female, blue line; male.

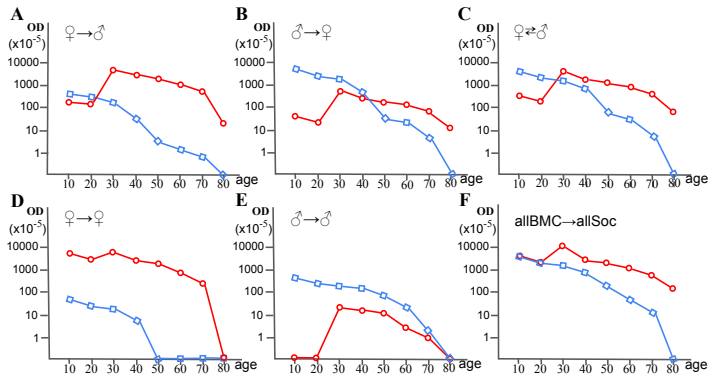

Figure 5. Artificial microchimerism: A; Odds of onset probability by pregnancy history of donor and recipient for each combination of effector cells/target cells. orange bar: female donor/male recipient, yellow bar: female donor/female recipient, green bar: male donor/male recipient, blue bar: male donor/female recipient. B; Odds of onset probability by pregnancy history of the donor for each combination of effector cells/target cells. red bar: parous donor→all, yellow bar: nulliparous donor→all, blue bar: male donor→all

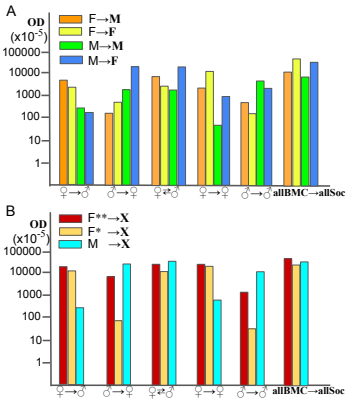

Table S1. Natural microchimerism: Onset probability (OnP), odds and odds ratio by gender and age for each combination of effector cells/target cells. ♀→♂; female effector cells/male target cells.

effector →target		age and gender															
		10		20		30		40		50		60		70		80	
		F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
♀→♂	OnP	0.003949	0.004977	0.002868	0.003233	0.037259	0.001834	0.025767	0.000779	0.016259	0.000069	0.009142	0.000029	0.003838	0.000007	0.000352	0
	odds	0.00396	0.00500	0.00288	0.00324	0.03870	0.00184	0.02645	0.00078	0.01653	0.00007	0.00923	0.00003	0.00385	0.00001	0.00035	0
	odds ratio	396	500	288	324	3870	184	2645	78	1653	7	923	3	385	1	35	0
♂→♀	OnP	0.000602	0.047699	0.000421	0.030993	0.007447	0.017584	0.00501	0.007473	0.003012	0.000659	0.001822	0.000283	0.000969	0.000063	0.000352	0
	odds	0.00060	0.05009	0.00042	0.03198	0.00750	0.01790	0.01790	0.00753	0.00302	0.00066	0.00183	0.00028	0.00097	0.00006	0.00035	0
	odds ratio	10	835	7	533	125	298	84	126	50	11	31	5	16	1	6	0
♀⇄♂	OnP	0.004551	0.052676	0.003289	0.034226	0.044706	0.019418	0.030777	0.008252	0.019271	0.000728	0.010964	0.000312	0.004807	0.00070	0.000704	0
	odds	0.00457	0.05561	0.0030	0.03544	0.04680	0.01980	0.03175	0.00832	0.01965	0.00073	0.01109	0.00031	0.00483	0.00007	0.00070	0
	odds ratio	65	794	47	470	669	283	454	119	281	10	158	4	69	1	10	0
♀→♀	OnP	0.048355	0.000425	0.034200	0.000272	0.056575	0.000150	0.033605	0.000059	0.014916	0	0.008973	0	0.003531	0	0	0
	odds	0.05081	0.00043	0.03541	0.00027	0.05997	0.00015	0.03477	0.00006	0.01514	0	0.00905	0	0.00354	0	0	0
	odds ratio	847	7	590	5	1000	3	580	1	252	0	151	0	59	0	0	0
♂→♂	OnP	0	0.004091	0	0.002991	0.000300	0.002063	0.000208	0.001306	0.000131	0.000722	0.000070	0.000309	0.000025	0.000069	0	0
	odds	0	0.00411	0	0.00300	0.00030	0.00207	0.00021	0.00131	0.00013	0.00072	0.00007	0.00031	0.00003	0.00007	0	0
	odds ratio	0	137	0	100	10	69	7	44	4	24	2	34	1	2	0	0
all LLBMC →all Soc	OnP	0.057192	0.057192	0.037489	0.037489	0.101581	0.021649	0.042714	0.009618	0.035725	0.001450	0.019537	0.000621	0.008363	0.000138	0.001472	0
	odds	0.06066	0.06066	0.03895	0.03895	0.11307	0.02213	0.04462	0.00971	0.03705	0.00145	0.01993	0.00062	0.00843	0.00014	0.00147	0
	odds ratio	433	433	278	278	808	158	319	69	264	10	142	4	60	1	11	0

Table S2. Natural microchimerism: Female to male ratio of onset probability odds by age for each combination of effector cells/target cells. ♀→♂; female effector cells/male target cells.

effector →target	age							
	10	20	30	40	50	60	70	80
♀→♂	0.8	0.9	21.0	33.9	236.1	307.7	385.0	-
♂→♀	0.01	0.01	0.4	2.4	4.6	6.5	16.2	-
⚥→♂	0.08	0.01	2.4	3.8	26.9	35.8	69.0	-
♀→⚥	118.2	131.1	399.8	579.5	-	-	-	-
♂→♂	0	0	0.1	0.2	0.2	0.1	0.4	-
all LLBMC →all Soc	1.0	1.0	5.1	4.6	25.6	32.1	60.2	-

Table S3. Artificial microchimerism: Onset probability (OnP), odds and odds ratio by gender of donor and recipient for each combination of effector cells/target cells. F→M; female donor/male recipient, ♀→♂; female effector cells/male target cells.

effector →target		donor →recipient			
		F→M	M→F	F→F	M→M
♀→♂	OnP	0.046047	0.001484	0.037259	0.001834
	odds	0.04827	0.00149	0.03870	0.00184
	odds ratio	32.4	1.0	26.0	1.2
♂→♀	OnP	0.001484	0.105109	0.007447	0.017584
	odds	0.00149	0.11745	0.00750	0.01790
	odds ratio	1.0	78.8	5.0	12.0
⚥→♂	OnP	0.047531	0.106593	0.044706	0.019418
	odds	0.04990	0.11931	0.04680	0.01980
	odds ratio	2.5	6.0	2.4	1.0
♀→♀	OnP	0.019367	0.003617	0.098580	0.000467
	odds	0.01975	0.00363	0.10936	0.00047
	odds ratio	42.0	7.7	232.7	1.0
♂→♂	OnP	0.003467	0.033280	0.001555	0.041130
	odds	0.00348	0.03443	0.00156	0.04289
	odds ratio	2.2	22.1	1.0	27.5
all LLBMC→all Soc	OnP	0.070365	0.126615	0.143465	0.061015
	odds	0.07569	0.14497	0.16749	0.06498
	odds ratio	1.2	2.2	2.6	1.0

Table S4. Artificial microchimerism: Onset probability (OnP), odds and odds ratio by pregnancy history of donor and recipient for each combination of effector cells/target cells. F*; nulliparous, F**; parous, M; male. F*→M; nulliparous donor/male recipient, ♀→♂; female effector cells/male target cells.

effector →target		donor →recipient								
		F*→M	M→F*	F*→F*	F**→M	M→F**	F**→F**	F*→F**	F**→F*	M→M
♀→♂	OnP	0.042772	0.000084	0.001959	0.049322	0.002884	0.079425	0.067259	0.002259	0.001834
	odds	0.04468	0.00008	0.001959	0.05188	0.00289	0.08628	0.07211	0.00226	0.00184
	odds ratio	559	1	25	649	36	1079	901	28	23
♂ →♀	OnP	0.000084	0.073709	0.000272	0.002884	0.136509	0.075872	0.000572	0.009322	0.017584
	odds	0.00008	0.07957	0.00027	0.00289	0.15809	0.08210	0.00057	0.00941	0.01790
	odds ratio	1	995	3	36	1976	1026	7	118	224
⚥	OnP	0.042856	0.073793	0.002231	0.052206	0.139393	0.155297	0.067831	0.011581	0.019418
	odds	0.04477	0.07967	0.0022	0.05508	0.16197	0.18385	0.07277	0.01172	0.01980
	odds ratio	20	36	1	25	72	82	32	5	9
♀→♀	OnP	0.017967	0.002217	0.060155	0.020767	0.005017	0.139505	0.105923	0.069202	0.000467
	odds	0.01830	0.00222	0.06401	0.02121	0.00504	0.16212	0.11847	0.07435	0.00047
	odds ratio	39	5	136	45	11	345	252	158	1
♂→♂	OnP	0.000192	0.001880	0.000005	0.006742	0.064680	0.005605	0.000305	0.000305	0.041130
	odds	0.00019	0.00188	0.00001	0.00679	0.06915	0.00564	0.00031	0.00031	0.04289
	odds ratio	19	188	1	679	6915	564	31	31	4289
all LLBMC →all Soc	OnP	0.009350	0.061015	0.061015	0.080036	0.192536	0.221886	0.192536	0.079715	0.061015
	odds	0.00944	0.06498	0.06498	0.08700	0.23845	0.28516	0.23845	0.08662	0.06498
	odds ratio	1	7	7	9	25	30	25	9	7

Table S5. Artificial microchimerism: Onset probability (OnP), odds and odds ratio by pregnancy history of the donor for each combination of effector cells/target cells. F*; nulliparous, F**; parous, M; male, X; all (nulliparous, parous and male). F*→X; nulliparous donor/all recipient, ♀→♂; female effector cells/male target cells.

effector →target		donor →recipient		
		F* →X	F**→X	M→X
♀→♂	OnP	0.111990	0.131006	0.004802
	odds	0.12611	0.15076	0.00483
	odds ratio	26	31	1
♂ →♀	OnP	0.000928	0.088078	0.227802
	odds	0.00093	0.09659	0.29500
	odds ratio	1	104	317
⚥	OnP	0.112918	0.219084	0.232604
	odds	0.12729	0.28055	0.30311
	odds ratio	1	2	18
♀→♀	OnP	0.184045	0.229474	0.007701
	odds	0.22556	0.29781	0.00776
	odds ratio	29	38	1
♂→♂	OnP	0.000502	0.012652	0.107690
	odds	0.00050	0.01281	0.12069
	odds ratio	1	31	24
all LLBMC →all Soc	OnP	0.192536	0.381637	0.314566
	odds	0.23845	0.61717	0.45893
	odds ratio	1	3	2

Supplementary information: Abbreviations of autoimmune diseases

AA: alopecia areata
AG (PA): atrophic gastritis (pernicious anamia)
ACHA: acquired hemophilia A
AD: Addison's disease
ADEM: autoimmune disseminated encephalomyelitis
AE: autoimmune encephalitis
AIH-1: autoimmune hepatitis type 1
AIH-2: autoimmune hepatitis type 2
AIHA: autoimmune hemolytic anemia
AIP: autoimmune pancreatitis
ALPS: autoimmune lymphoproliferative syndrome
AMC: autoimmune myocarditis
AN: autoimmune neutropenia
APS: antiphospholipid syndrome

APGS-1: autoimmune polygladular syndrome-1
APGS-2: autoimmune polygladular syndrome-2
AS: ankylosing spondylitis
ASD: adult Still's disease
BCD: Behcet disease
BD: Batten disease
BP: bullous pemphigoid
B27: HLA-B27-associated acute anterior uveitis
CD: Crohn's disease
CIDP: chronic inflammatory demyelinating polyneuropathy
COD: coeliac disease
CP: cicatrical pemphigoid
CREST: CREST syndrome
CSS: Churg-Strauss syndrome
DCM: dilated cardiomyopathy
DH: dermatitis herpetiformis
DLE: discoid lupus erythematosus
EAE: experimental autoimmune encephalomyelitis
EBA: epidermolysis bullosa acquisita
EM: eosinophilic myocarditis
EMC: essential mixed cryoglobulinemia
FS: Felty's syndrome
GBS: Guillain-Barré syndrome
GCA (TA): giant cell arteritis (temporal arteritis)
GCM: giant cell myocarditis
GD: Graves' disease
GO: Graves' ophthalmopathy
GPD: Goodpasture's disease
HD: Hashimoto's autoimmune thyroiditis
HE: Hashimoto's encephalopathy
IgAN: IgA nephropathy
ITP: immune thrombocytopenic purpura
KD: Kawasaki disease
LE: limbic encephalitis
LM: linear morphea
MCTD: mixed connective tissue disease
MD: Mikulicz's disease
MG: myasthenia gravis
MGN: membranous glomerulonephropathy
MPA: microscopic polyangitis
MS: multiple sclerosis
NL: narcolepsy
OLP: oral lichen planus
PAN: polyarteritis nodosa
PBC: primary billiary cirrhosis
PF/PV: pemphigus foliaceus/pemphigus vulgaris
PM/DM: polymyositis/dermatomyositis
PMR: polymyalgia rheumatica
PSC: primary sclerosing cholangitis
PSV/PSP: psoriasis vulgaris/pustular psoriasis
RA: rheumatoid arthritis
RF: rheumatic fever
RP: relapsing polychondritis
RT: Riedel's thyroiditis
SSc: scleroderma
SjS: Sjogren's syndrome
SLE: systemic lupus erythematosus
SO: sympathetic ophthalmia
SD: Still's disease
TA: Takayasu arteritis
TIN: tubulointerstitial nephritis
T1D: diabetes mellitus type I
UC: ulcerative colitis
VL: vitiligo
WG: Wegener's granulomatosis