Title: IL-17 signaling and neuroimmunology: Psoriasis to Autism Spectrum Disorder

Abbreviated title: Neuroimmune IL-17 Axis: Psoriasis and ASD

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Word count: approximately: 3, 900

Number of Figures: 2

Number of Tables: 0

Supplementary Figures: 0

Supplementary Table: 0

Abstract

The IL-17 pathway is involved in diverse diseases, including psoriasis and autism spectrum disorder (ASD). IL-17 inhibitors have shown high efficacy in the treatment of psoriasis, and their indications are expanding to other autoimmune diseases; in ASD, it has been suggested that maternal IL-17 may affect fetal brain development, and existing psoriasis drugs may be applied to ASD interventions. In this paper, we discuss whether IL-17 inhibitors used for psoriasis treatment can be indicated for the prevention and treatment of autism. Further elucidation of the interaction between the immune system and the nervous system is expected to lead to the development of new therapeutic strategies.

Keywords: autism spectrum disorder, drug repositioning, IL-17/IL-17R inhibitors, neuroimmunology

1. Introduction

Rapid advances in our understanding of the interactions between the immune and nervous systems have suggested that common mechanisms may exist between various diseases previously thought to be distinct. In particular, the interleukin-17 (IL-17) pathway has been shown to be involved in the pathogenesis of a wide range of diseases, from autoimmune diseases such as psoriasis to autism spectrum disorders (ASD, Fig. 1)(1). In this review, we will review the latest findings in these diseases, focusing on the IL-17 pathway, and discuss the possibilities and challenges of immunological approaches. In addition, the currently marketed IL-17/IL-17R inhibitors will be described.

2. IL-17 pathway

The IL-17 family consists of six cytokines (IL-17A-F), of which IL-17A and IL-17F have been studied the most. These cytokines bind to the IL-17 receptor family (IL-17RA to RE) and induce inflammatory responses(2). IL-17A/F are mainly produced by Th17 cells, but are also produced by γδ T cells and innate lymphocytes (ILCs)(3). IL-17 signaling activates transcription factors such as NF-κB, MAPK, and C/EBP, which induce the production of inflammatory cytokines, chemokines, and antimicrobial peptides. While this pathway plays an important role in infection defense, excessive activation leads to autoimmune diseases and chronic inflammation(4).

3. Role of IL-17 in psoriasis

Psoriasis is a typical disease in which abnormal activation of the IL-23/IL-17 axis is central to the pathogenesis; IL-17 acts on epidermal keratinocytes and induces the production of chemokines (such as CXCL1, CXCL2, CCL20) and antibacterial peptides (such as β-defensins and S100 proteins). This promotes neutrophil and T cell infiltration and maintains chronic inflammation(5). Cytokine levels such as IL-17A, IL-17F, and IL-22 are elevated in lesional areas of psoriasis, and these induce epidermal keratinocyte hyperproliferation and abnormal differentiation. IL-17 also promotes the production of angiogenic factors, which also contribute to angiogenesis at the lesion site(6).

4. Development and Clinical Application of IL-17/IL-17R inhibitors

With the elucidation of the pathophysiological importance of the IL-17 pathway, several IL-17/IL-17R inhibitors have been developed (Fig. 2). The major drugs currently on the market are as follows.

4.1. secukinumab (trade name: Cosentyx):

- Fully human monoclonal anti-IL-17A antibody
- Indications: Psoriasis vulgaris, psoriatic arthritis, ankylosing spondylitis
- Administration: subcutaneous injection, usually at 4-week intervals(7)

4.2. ixekizumab (trade name: Toltz):

- Humanized anti-IL-17A monoclonal antibody
- Indications: Psoriasis vulgaris, psoriatic arthritis, ankylosing spondylitis
- Administration: subcutaneous injection, usually at 4-week intervals(8)

4.3. brodalumab (trade name: Lumicef):

- Fully human monoclonal anti-IL-17RA antibody
- Indication: Psoriasis vulgaris
- Administration: subcutaneous injection, usually at 2-week intervals(9)

These agents have been used to treat moderate to severe psoriasis, psoriatic arthritis, and ankylosing spondylitis, and have shown high efficacy. Clinical trials have reported PASI 75 (75% improvement in psoriasis symptoms) achievement rates exceeding 80-90%, demonstrating efficacy superior to that of conventional biologic agents (10). The safety profile includes a reported increased risk of upper respiratory tract infection and cutaneous candidiasis, as well as new onset or exacerbation of inflammatory bowel disease (11). For brodalumab in particular, warnings regarding the risk of suicidal ideation and behavior are included in the package insert. The introduction of these agents has greatly expanded the options for psoriasis treatment. However, more needs to be learned about their long-term safety, cost-effectiveness, and optimal use.

5. Role of IL-17 in diseases other than psoriasis

The main indications for IL-17/IL-17R inhibitors other than psoriasis are as follows.

1. Psoriatic Arthritis (PsA): secukinumab and ixekizumab are approved for the treatment of psoriatic arthritis (12). These agents have shown efficacy in improving joint symptoms and inhibiting the progression of structural damage. Psoriatic arthritis is a disease with both cutaneous and joint symptoms, and the use of IL-17 inhibitors has the advantage of improving both symptoms simultaneously.

2. Ankylosing Spondylitis (AS): secukinumab and ixekizumab are also approved for the treatment of ankylosing spondylitis(13). These agents have shown efficacy in reducing inflammation in the spine and improving pain and functional disability. In particular, efficacy has been reported in patients who do not respond to conventional TNF inhibitors.
3. Non-radiographic axial spondyloarthritis (nr-axSpA): Secukinumab is also approved in some countries for the treatment of non-radiographic axial spondyloarthritis(7,14). This condition is considered to be a pre- or early stage of ankylosing spondylitis and is used in patients with no definite radiographic changes.
4. Hidradenitis Suppurativa (HS): Phase III clinical trial of secukinumab and brodalumab for suppurative hidradenitis is currently ongoing(15). It is expected to be a new treatment option for this refractory chronic inflammatory skin disease.
5. Rheumatoid Arthritis (RA): clinical trials of secukinumab for rheumatoid arthritis were conducted but did not show the expected effect and the drug is not currently approved (16). The role of the IL-17 pathway in rheumatoid arthritis continues to be investigated.
6. Crohn's Disease (Crohn's disease): initially expected to benefit from IL-17 inhibitors for Crohn's disease, but secukinumab clinical trials did not show the expected benefit(17). Because of worsening of symptoms in some patients, IL-17 inhibitors are not currently recommended for Crohn's disease patients.
7. Multiple Sclerosis (MS): IL-17 pathway has been implicated in the pathogenesis of multiple sclerosis, and clinical trials of secukinumab are ongoing(18). At this time, the drug has not been approved.

These expanded indications indicate that the IL-17 pathway is involved in a variety of autoimmune and inflammatory diseases. However, it is also becoming clear that inhibition of IL-17 is not necessarily effective in all inflammatory diseases, as in the case of Crohn's disease. This suggests the importance of the different roles of the IL-17 pathway in different diseases and the immunological background of individual patients.

6. Neuroimmunology and ASD

6.1 Maternal Immune Activation (MIA) and ASD

In the field of neuroimmunology, Maternal Immune Activation (MIA) during pregnancy is implicated

in miscarriage rates (19,20) and may affect fetal neurodevelopment and increase the risk of developmental disorders, including ASD (21). Of particular interest is the role of IL-17 (19). In a mouse model, Choi et al. showed that IL-17A produced by maternal Th17 cells crosses the placenta and affects fetal brain development (22). Specifically, MIA activates maternal Th17 cells and increases IL-17A production, which then crosses the placenta and reaches the fetal brain. IL-17 receptor expression in the fetal brain is increased, and IL-17 signaling alters the pattern of neural progenitor cell proliferation and differentiation. The resulting abnormalities in cortical layer formation and neural circuit formation suggest that these changes may lead to autism-like behavioral abnormalities (22).

6.2 Microglia and neuroinflammation

Activation of microglia has also been observed in the brains of autistic patients. Microglia are immune cells in the brain that play an important role in the regulation of synaptic pruning and neuroinflammation (23). In ASD, microglial hyperactivation, synaptic pruning failure, and persistent neuroinflammation have been observed, which may lead to abnormal neuronal circuit formation and dysfunction IL-17 is known to promote microglial activation and induce the production of proinflammatory cytokines (24). Thus, abnormalities in the IL-17 pathway may contribute to neuroinflammation in ASD (25,26).

6.3 Autoantibodies and ASD

Autoantibodies against fetal brain proteins have been detected in mothers of some ASD children. It has been suggested that these autoantibodies may cross the placenta and affect fetal brain development (27). Targeted proteins include NMDA receptors and GABA alpha receptors, etc. Since IL-17 promotes B cell activation and autoantibody production, it is possible that abnormalities in the IL-17 pathway are also involved in autoantibody production (28).

6.4 Gut Microbiota and Brain-Gut Correlation

In autistic patients, “dysbiosis” has been reported, which leads to increased intestinal permeability ("leaky gut") and may trigger a systemic inflammatory response (29). This inflammatory response may affect brain development and function; IL-17 is also involved in the regulation of intestinal barrier function, and abnormalities in the IL-17 pathway may contribute to changes in the intestinal microbiota and increased intestinal permeability (30).

6.5 Potential Applications of IL-17 Inhibitors for ASD Prevention

Since the involvement of the IL-17 pathway in the development of ASD has been suggested, it is theoretically possible that IL-17/IL-17R inhibitors could be applied to the prevention of ASD (drug repositioning). Drug repositioning is a research approach to discover new drug effects from existing drugs whose safety and pharmacokinetics in the human body have already been confirmed by actual results, and to put them to practical use. The greatest advantages of drug repositioning are the "certainty" that the drug has already been marketed and its safety and pharmacokinetics have been confirmed at the clinical level, and the "low cost" of using existing data that have already been accumulated.

Potential applications of IL-17/IL-17R inhibitors include identifying high-risk pregnant women, such as those with a family history of ASD, a history of autoimmune disease, and pregnant women at high risk of infection, and measuring IL-17 levels early to mid-term pregnancy and cytokine profiling of the placenta and amniotic fluid (31). Administration should be started at low doses for a short period of time in the second trimester of pregnancy, when fetal brain development is active, and careful monitoring of fetal growth status, maternal immune status, and postnatal neurodevelopment should be conducted.

6.6 Issues and Ethical Considerations

Safety concerns include effects on fetal immune system development and increased risk of maternal infection (1). Considering the diversity (spectrum) of ASD, it is difficult to prevent all cases with a single method. There is a need to fully discuss the pros and cons of intervening in the fetus and considering ASD as a condition that should be prevented (32). The development of the immune system is complex and the long-term impact of early intervention is currently unknown. Commercially available IL-17/IL-17R inhibitors have insufficient safety data for use in pregnant women and are not recommended for use during pregnancy. The application of this signaling pathway for ASD prevention will require new formulation development and rigorous clinical trials in the future.

7. Future Research Directions

A multifaceted approach is needed to further elucidate the link between the IL-17 pathway and neurodevelopmental disorders and to develop new therapeutic and preventive strategies. First, it is

essential to verify long-term safety and efficacy using animal models, especially to evaluate in detail the impact of interventions during fetal and early developmental stages. At the same time, comprehensive biomarkers, including factors other than IL-17, must be developed. This would enable early prediction of disease risk and monitoring of treatment efficacy.

Detailed elucidation of gene-environment interactions is also essential. Since complex genetic and environmental factors are involved in the pathogenesis of ASD, understanding these interactions may lead to the development of more personalized prevention and treatment strategies. The development of new drugs targeting the IL-17 pathway, especially formulations that minimize fetal effects, is also an important issue. Improvement of existing IL-17/IL-17R inhibitors and development of agents with new mechanisms of action are expected to provide safer and more effective treatment options.

Elucidating the relationship between subtype (subtype) classification of ASD and the IL-17 pathway is also an important research topic. given the diversity of ASD, clarifying the involvement of the IL-17 pathway for specific subtypes may allow for more precise therapeutic approaches. IL-17/IL-17R inhibitors Follow-up studies are needed to assess long-term safety and efficacy. In particular, it is important to evaluate the long-term effects and risk of rare side effects of existing drugs used in the treatment of autoimmune diseases through large cohort studies and post-marketing surveillance. Through these multifaceted research approaches, the link between the IL-17 pathway and neurodevelopmental disorders will be further elucidated, leading to the development of new treatment and prevention strategies(29) .

8. Conclusion

The IL-17 pathway may be involved in the pathogenesis of a wide range of diseases from autoimmune diseases such as psoriasis to ASD; IL-17/IL-17R inhibitors have shown high efficacy in the treatment of psoriasis and their clinical application is steadily progressing. On the other hand, with regard to ASD, an association between maternal IL-17 production and fetal neurodevelopment has been suggested, and theoretically, IL-17 inhibitors could be a possible prophylactic approach. Clinical application of this hypothesis will require overcoming many challenges, including safety, efficacy, and ethical issues. In particular, careful consideration must be given to interventions during the fetal period and early developmental stages.

Future research will further our understanding of the interaction between the immune and nervous systems and lead to the development of new therapeutic and preventive strategies; studies centered on

the IL-17 pathway are expected to play an important role in exploring the interface between immunology and neuroscience and to promote an integrated understanding of these fields. The development and clinical application of IL-17/IL-17R inhibitors is a good example of how the results of basic research have been translated into actual therapies, and close collaboration between the two will continue to be important. At the same time, the long-term safety, cost-effectiveness, and optimal use of these drugs require continuous evaluation and further accumulation of evidence (33,34) .

Advances in IL-17 pathway research have great potential for elucidating the pathogenesis of autoimmune and psychiatric disorders (e.g., ASD and schizophrenia) and developing novel therapies. It is hoped that further research will provide more effective and safer treatment options for patients.

Availability of data and materials

The datasets, which were used and/or analyzed in the current study, are available from the corresponding author on reasonable request.

Author Contributions

TS designed the study and wrote the initial draft of the manuscript. AK and TS revised the manuscript. Final approval of the manuscript was obtained from all authors.

Acknowledgements

We are grateful to Sara Kamiya, Koki Higuchi and Kenyu Nakamura for valuable discussions and critical reading of this manuscript.

Funding Information

This work was supported by Grants-in-Aid for Scientific Research C (KAKENHI Nos. 19K08065, 22K07611), and Grant-in-Aid for Scientific Research on Innovative Areas “Multiscale Brain” (No. 19H05201) from The Ministry of Education, Culture, Sports, Science and Technology MEXT Japan. T.S. was also supported by the Foundation for Advanced Medical Research, the Naito Foundation, the Takeda Science Foundation, the Kawano Masanori Memorial Public Interest Incorporated Foundation for Promotion of Pediatrics, the Taiju Life Social Welfare Foundation, the Life Science Foundation of Japan, the Nakatomi Foundation, the Mishima Kaiun Memorial Foundation, the Kanehara Ichiro Memorial Foundation for Medical Science and Medical Care, the Foundation for Pharmaceutical Research. Part of this work was supported by the NIBB Collaborative Research Program and Advanced Animal Model Support (16H06276) of Grant-in-Aid for Scientific Research on Innovative Areas to T.S.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Ethics statement

Not applicable.

Figures

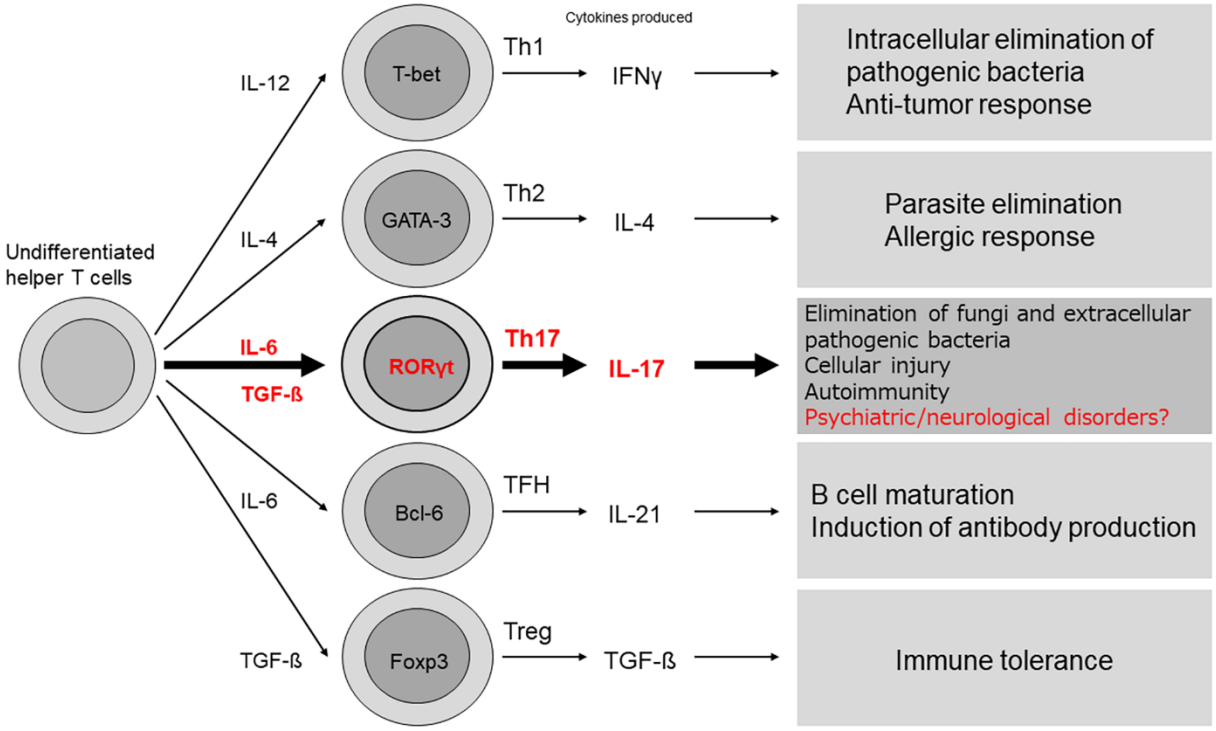

Fig 1. Differentiation of Th17 cells. Th17 cells are induced to differentiate from naive T cells by co-stimulation with IL-6 and TGF-β. Expression of the transcriptional regulator retinoic acid receptor-related orphan nuclear receptor gamma t (RORγt) is essential for Th17 cell differentiation. This figure is modified from Ivanov et al, 2006 (35).

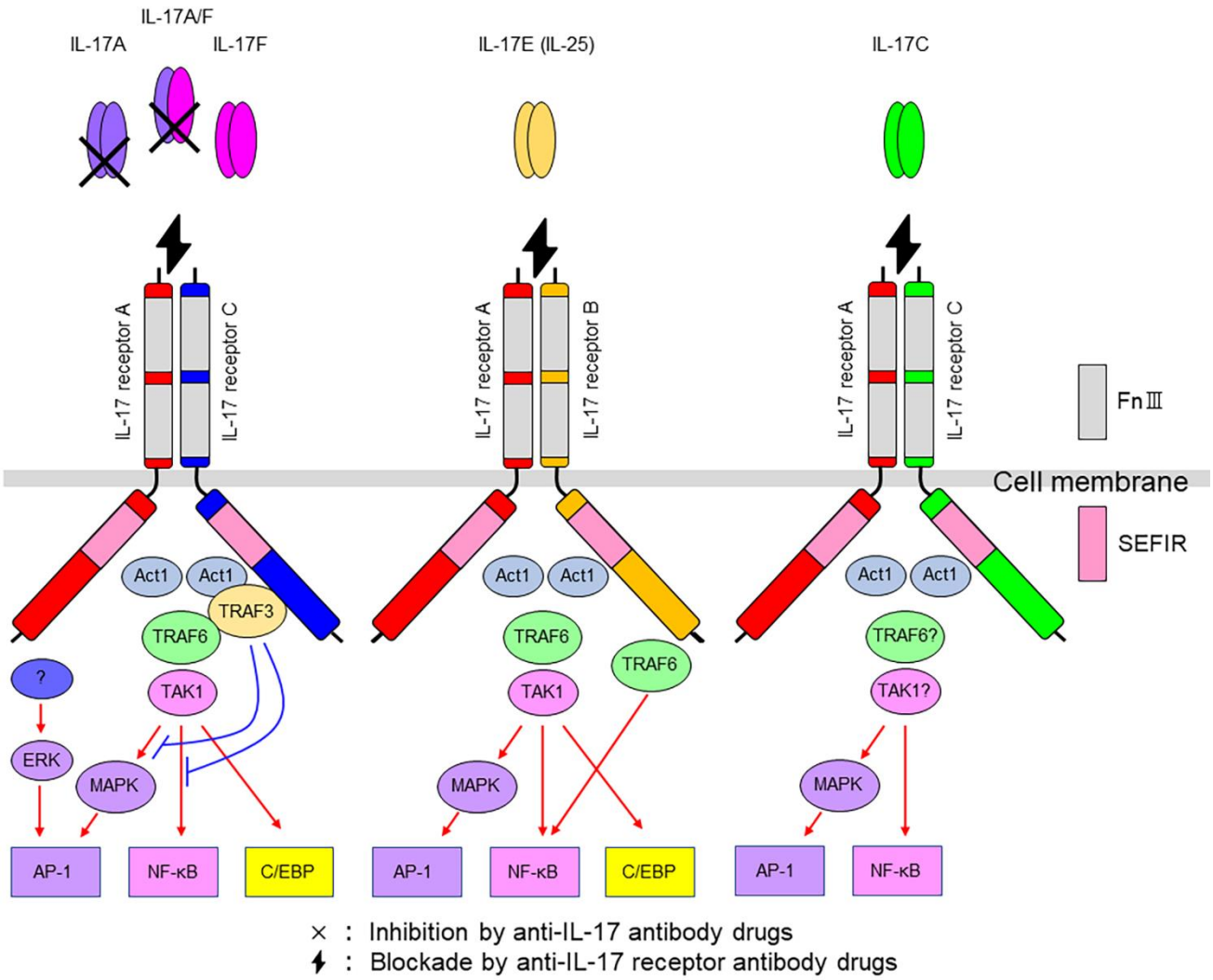

Fig 2. IL-17 Family and Mechanism of IL-17 Inhibitors. The IL-17 receptor is constitutively expressed in various cell types. Like their ligands, the receptors form a family, characterized by an extracellular fibronectin III (FnIII)-like domain and an intracellular SEFIR (Similar Expression to Fibroblast growth factor genes/IL-17R) domain, which is analogous to the TIR (Toll/IL-1R) domain in the IL-1/Toll-like receptor family. IL-17RA functions as a direct receptor for IL-17 ligands or as a co-receptor, serving as a hub for organizing IL-17 family signaling on the cell membrane. Secukinumab (brand name: Cosentyx) and ixekizumab (brand name: Taltz) are subcutaneous injectable formulations of anti-IL-17A antibodies. Brodalumab is a subcutaneous injectable formulation of a human anti-IL-17 receptor A antibody. By binding to the receptor rather than the cytokine itself, brodalumab inhibits the action of cytokines, potentially suppressing a broader range of inflammatory responses.

Abbreviations: IL-17RA: Interleukin 17 Receptor A, IL-17RB: Interleukin 17 Receptor B, IL-17RC: Interleukin 17 Receptor C, IL-17RE: Interleukin 17 Receptor E, SEFIR: Similar Expression to Fibroblast growth factor genes/IL-17R, FnIII: Fibronectin type III, MAPK: Mitogen-Activated Protein Kinase, ERK: Extracellular signal-Regulated Kinase, Act1: NF-kappa-B Activator 1 (also known as TRAF3IP2), TRAF6: TNF Receptor Associated Factor 6, TRAF3: TNF Receptor Associated Factor 3, TAK1: Transforming growth factor beta-Activated Kinase 1 (also known as MAP3K7), AP-1: Activator Protein 1, NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells, C/EBP: CCAAT/Enhancer-Binding Protein, TIR: Toll/Interleukin-1 Receptor

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