ACTA SCIENTIFIC MEDICAL SCIENCES

Volume 3 Issue 6 June 2019

Mini Review

The Potential of IL-17 in Precision Medicine Treatments for Rheumatoid Arthritis

Maria Benito*

IPN Communications, Dublin, Ireland

***Corresponding Author:** Maria Benito, Clinical, IPN Communications, Dublin, Ireland.

Received: April 01, 2019; **Published:** May 29, 2019

Abstract

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease characterized by synovitis, infiltrated inflammatory cells, cytokine production, and joint destruction. Interleukin-17, proinflammatory cytokine produced by a particular subset of T-cells, seems to play a prominent role in the process contributing to synovitis and joint destruction. The role of IL-17 and its inhibitors is being considered in the development of precision medicine in RA pathogenesis either as a biological target or as a potential biomarker of disease and treatment response.

Keywords: IL-17; Rheumatoid Arthritis; Precision Medicine; Biomarker; Biological Target

Abbreviations

ICAM-1: Intracellular adhesion molecule-1; IFN: Interferon ; IL-1β: Interleukin-1 beta ; IL-6: Interleukin-6 ; IL-8: Interleukin-8 ; IL-17: Interleukin-17; IL-21: Interleukin-21; IL-23: Interleukin-23; PI3K/AKT: Phosphoinositide-3-kinase–Protein kinase B; RA: Rheumatoid Arthritis; Th1: T Helper Cell Type 1; Th17: T Helper Cells Type 17; TNF-α: Tumor Necrosis Factor Alpha; TGF-β: Transforming Growth Factor Beta.

Introduction

The Interleukin (IL)-17 cytokine family consists of six members (from IL-17A to IL-17F) produced by different cell types and in different tissues [1]. IL-17 –and specifically IL-17A– is directly involved in early induction and late chronic stages in several inflammatory diseases. Thus, it has been demonstrated that IL-17 is a key player in psoriasis through its effects on keratinocytes [2], and induces changes in the rheumatoid synovium that leads to synovitis and perpetuation of local inflammation in rheumatoid arthritis (RA) [3]. Additionally, IL-17 acts locally on synoviocytes and osteoblasts contributing to synovitis and joint destruction [4,5].

Synovial tissue fibroblasts and infiltrated macrophages produce proinflammatory cytokines such as tumour necrosis factor-α (TNF-α), IL-1β, IL-6 in RA joints [6]. $CD4^+$ T-cells subtype –T helper cell type 1 (Th1)– produce interferon (IFN), while CD4+CD45RO+ memory T-cells subset –type 17 (Th17) cells [7]–produces IL-17. These T-cell subtypes are infiltrated immune cells present in the RA synovium.

Both cytokines –IFN and IL-17– have an additive effect on RA synoviocytes to induce IL-6, and to increase intracellular adhesion molecule-1 (ICAM-1), IL-6 and IL-8 in other cell types [8,9]. TGF-β and at least one other proinflammatory cytokine –IL-1β, IL-6, IL-21 and IL-23– are required for the differentiation of naïve T-cells into Th17 cells [10,11]. The interaction between Th17 cells and synoviocytes leads to production of IL-17, which helps to perpetuate chronic inflammation. IL-17 stimulates the production of IL-1 and TNF-α in macrophages, and enhances IL-1-mediated IL-6 production in RA synoviocytes tissue fibroblasts. In any case, the key role of IL-17 seems to be due to its synergistic effect with TNF-α and IL-1β.

In the synovium, characterized by hyperplasia of synovial lining cells due to excessive proliferation of synoviocytes and apoptosis resistance, IL-17 up-regulates anti-apoptotic and down-regulates pro-apoptotic genes [12,13]. Neoangiogenesis and activation of autophagy are crucial events in the development of the pannus in RA [14], also influenced by IL-17.

In vitro and *in vivo* experiments have identified IL-17 as a pro-inflammatory cytokine involved in both early and late stages of several auto-immune and inflammatory diseases and a key contributor to their pathogenesis [8].

Recent studies revealed that IL-17 can intensify and perpetuate inflammation by promoting angiogenesis and recruiting inflammatory cells to the RA joint, resulting in recruitment of neutrophils and monocytes, in acute phase and chronic phase, respectively, and through its effects on synoviocytes and osteoblasts contributes to synovitis and joint destruction [4,8,15,16]. It has also been shown that IL-17 induces endothelial chemotaxis [17] –via proangiogenic factors– involving the PI3K/AKT pathway [16], and monocyte migration through activation of p38 MAPK pathway [18].

Positive results have encouraged the development of biologics to target this cytokine. Despite the clear importance of IL-17, in RA, there are conflicting results when targeting this cytokine due to patient heterogeneity and mediators that participate in regulating IL-17 function [19-22]. The focal point of research is now to identify the patients that could benefit from IL-17 targeted therapies in RA, and to develop predictive biomarkers of response, leaning towards new approaches in precision medicine for the management of RA [5,23].

Precision medicine

Taking into account the information about IL-17A, this cytokine seems to play a key role in the RA pathogenic process [2] –IL-17A is higher in RA patients and its levels are correlated with destruction, whereas anti-IL-17 antibodies and immune complexes are elevated in non-destructive RA–, and is currently been considered for possible use as both, a biological target and a biomarker potentially useful to identify patients with an IL-17 driven disease that could respond better to IL-17 inhibitors.

The role of IL-17 and its inhibitors is being considered in the development of precision medicine in RA pathogenesis. The results are however somehow disappointing. So far, it has been shown that inhibitors of IL-17A have beneficial effects in psoriatic arthritis and active ankylosing spondylitis patients [21,22], but not so much in other joint diseases such as RA where some conflicting results –including a wide range of heterogenic outcomes– have been found.

Nonetheless, studies have shown that both the inhibition of Th-17 differentiation or IL-17 function considerably improves the pathogenesis of experimental arthritis models. On the other hand, neutralizing with anti-IL-17 or treatments aimed to block IL-6 have exposed an improvement of RA symptoms. These results point to anti-IL-17 therapy as a possible treatment for patients that do not respond to anti-TNF-α therapy.

To this point, clinical studies have shown the highly heterogenic and not statistically significant benefit of secukinumab (anti-IL-17A) and ixekizumab (anti-IL-17A) in RA patients, while brodalumab (anti-IL-17RA) is not effective in achieving 20% improvement in the number of tender and swollen joints [20-22,24].

A high variability of IL-17A, IL-17F and their receptor expression in RA synovitis, or low IL-17 levels in some patients [25] could be factors responsible for the contradictory results. Thus, a potential better treatment could be considering a dual inhibition with bispecific antibodies against TNFα and IL-17A in order to prevent the synergistic interaction and effects in RA [4,15,26].

Meanwhile, researchers are focused on developing predictive biomarkers of response to IL-17 inhibitors such as cell-based bioassay detecting bioactive IL-17A or differential RA patients' expression of IL-17 in synovial tissue.

Conclusion

Despite inconclusive or conflicting results, studies are focused on targeting IL-17 to improve the outcomes of RA, as well as the use of IL-17 as a possible biomarker of disease and response to treatments. Although promising results have been found in other inflammatory pathologies, further research has to be done in RA.

Acknowledgements

N/A

Conflict of Interest

No financial interest or conflict of interest exists.

Bibliography

1. Wright JF., *et al*. "Identification of an interleukin 17F/17A heterodimer in activated human CD4+ T cells". *Journal of Biological Chemistry* 282(2007): 13447-13455.

2. Beringer A., *et al*. "IL-17 in Chronic Inflammation: from discovery to targeting". *Trends in Molecular Medicine* 22.3 (2016): 230-241.

3. Smolen JS., *et al*. "Rheumatoid arthritis". *Lancet* 388 (2016): 2023-2038.

4. Hot A and Miossec P. "Effects of interleukin (IL)-17A and IL-17F in human rheumatoid arthritis synoviocytes". *Annals of the Rheumatic Diseases* 70.5 (2011): 727-732.

5. Ndongo-Thiam N and Miossec P. "A cell-based bioassay for circulating bioactive IL-17: application to destruction in rheumatoid arthritis". *Annals of the Rheumatic Diseases* 74.8 (2015): 1629-1631.

6. Chabaud M., *et al*. "Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines". *Journal of Immunology* 161.1 (1998): 409-414.

7. Park H., *et al*. "A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17". *Nature Immunology* 6(2005): 1133-1141.

8. Benedetti G. and Miossec P. "Interleukin 17 contributes to the chronicity of inflammatory diseases such as rheumatoid arthritis". *European Journal of Immunology* 44.2 (2014): 339-347.

9. Robert M. and Miossec P. "Effects of Interleukin 17 on the cardiovascular system". *Autoimmunity Reviews* 16.9 (2017): 984-991.

10. Noack M. and Miossec P. "Th17 and regulatory T cell balance in autoimmune and inflammatory diseases". *Autoimmunity Reviews* 13.6 (2014): 668-677.

11. Miossec P., *et al*. "Interleukin-17 and type 17 helper T cells". *The New England Journal of Medicine* 361(2009): 888-898.

12. Zhang Q., *et al*. "A critical role of Cyr61 in interleukin-17-dependent proliferation of fibroblast-like synoviocytes in rheumatoid arthritis". *Arthritis and Rheumatology* 60.12 (2009): 3602-3612.

13. Lee SY., *et al*. "IL-17-mediated Bcl-2 expression regulates survival of fibroblast-like synoviocytes in rheumatoid arthritis through STAT3 activation". *Arthritis Research and Therapy* 15.1(2013): R31.

14. Bottini N and Firestein GS. "Duality of fibroblast-like synoviocytes in RA: passive responders and imprinted aggressors". *Nature Reviews Rheumatology* 9(2013): 24-33.

15. Hot A., *et al*. "IL-17A- versus IL-17F-induced intracellular signal transduction pathways and modulation by IL-17RA and IL-17RC RNA interference in rheumatoid synoviocytes. *Annals of the Rheumatic Diseases* 70.2 (2011): 341-348.

16. Hwang SY., *et al*. "IL-17 induces production of IL-6 and IL-8 in rheumatoid arthritis synovial fibroblasts via NF-kappaB- and PI3-kinase/Akt-dependent pathways". *Arthritis Research and Therapy* 6(2004): R120-R128.

17. Lavocat F., *et al*. "T-cell clones from Th1, Th17 or Th1/17 lineages and their signature cytokines have different capacity to activate endothelial cells or synoviocytes". *Cytokine* 88(2016): 241-250.

18. Caruso R., *et al*. "Inhibition of monocyte-derived inflammatory cytokines by IL-25 occurs via p38 Map kinase-dependent induction of Socs-3". *Blood* 113(2009): 3512-3519.

19. Fragoulis GE., *et al*. "Therapeutic Targeting of IL-17 and IL-23 cytokines in immune-mediated diseases". *Annual Review of Medicine* 67(2016): 337-353.

20. Pavelka K., *et al*. "Efficacy, safety, and tolerability of secukinumab in patients with active ankylosing spondylitis: a randomized, double-blind phase 3 study, MEASURE 3". *Arthritis Research and Therapy* 19(2017): 285.

21. Sieper J., *et al*. "Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study". *Annals of the Rheumatic Diseases* 76.3 (2017): 571-592.

22. Braun J., *et al*. "Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study". *Annals of the Rheumatic Diseases* 76.6 (2017): 1070-1077.

23. 23. Ndongo-Thiam N., *et al*. "Negative association between autoantibodies against IL-17, IL-17/anti-IL-17 antibody immune complexes and destruction in rheumatoid arthritis". *Annals of the Rheumatic Diseases* 75.7 (2016): 1420-1422.

24. Kunwar S., *et al*. "Anti-IL-17 therapy in treatment of rheumatoid arthritis: a systematic literature review and meta-analysis of randomized controlled trials". *Rheumatology International* 36.8 (2016): 1065-1075.

25. van Baarsen LG., *et al*. "Heterogeneous expression pattern of interleukin 17A (IL-17A), IL-17F and their receptors in synovium of rheumatoid arthritis, psoriatic arthritis and osteoarthritis: possible explanation for nonresponse to anti-IL-17 therapy?". *Arthritis Research and Therapy* 16.4 (2014): 426.

26. Genovese MC., *et al*. "ABT-122, a bispecific dual variable domain immunoglobulin targeting tumor necrosis factor and Interleukin-17A, in patients with rheumatoid arthritis with an inadequate Response to methotrexate: a randomized, double-blind study". *Arthritis and Rheumatology* 70.11 (2018): 1710-1720.

Volume 3 Issue 6 June 2019