IL-17 and its role in psoriasis

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T cells are part of our innate immune system and are involved in pathogenesis of many diseases. Many subsets of T cells are continuously being discovered. Th-17 is one of them and it produces cytokines like IL-17. The family of IL-17 is involved in many inflammatory processes of diseases like psoriasis, inflammatory bowel disease, multiple sclerosis, asthma and rheumatoid arthritis.

There are six known subtypes of IL-17 including A, B, C, D, E and F. Three of them (A, C and F) have a more prominent role in psoriasis. These molecules act after binding with receptors including IL17RA, IL17RB, IL17RC, IL17RD, IL17RE and IL17RF.

IL-17 induces release of many cytokines (e.g. IL-6, G-CSF, GM-CSF, IL-1B, TGF-B, TNF-\( \infty \)), chemokines (e.g. IL-8, GRO-\( \infty \) and MCP-1) and prostaglandins such as PGE2 from fibroblasts, endothelial cells, keratinocytes and macrophages. IL-17 along with IL-22 induces antimicrobial peptide production by keratinocytes. The release of cytokines results in keratinocyte and vascular response along with enhanced cell recruitment. Keratinocytes in response produce chemokines and cytokines, which specifically cause neutrophil recruitment. IL-17 also downregulates filaggrin, leading to disruption of skin barrier. IL-17A, the best-studied member of this family, is composed of 155 amino acids with molecular weight of 15KDa. It forms heterodimers or homodimers with IL-17F, binding with IL-17RA and IL17RC subunits leading to gene activation.

Role in psoriasis

Research has shown IL23/IL17 pathway to play a central role in pathogenesis of psoriasis. Biopsies taken from active lesions of psoriasis show increased T cells and neutrophils containing IL-17.

Il-17 induces inflammatory response in skin that damages the keratinocytes and consequently activates immature dendritic cells. Different cytokines including TNF-\( \infty \), IL-1 and IL-6 are released which recruit T cells, NK cells and monocytes. These cells release IL-23 which induces Th-17 cells to produce IL-17 in combination with IL-22. IL-17 interacts with IL-17RA receptors leading to release of IL-6, antimicrobial peptides, IL-8 and CCL-20.

Due to altered immune response in psoriasis, there is unchecked IL-17 production in lesions enhancing IL-17 mediated cellular response. Neutrophils remove the damaged keratinocytes. Recruitment of new immature dendritic cells restarts the inflammatory cycle and causes progression of psoriasis (Figure 1).

IL-17 is now considered as the driver cytokine in psoriasis, and therapies targeting this cytokine are being tried. The IL-23 antibody Ustekinumab is also being used to treat psoriasis by reducing IL-17. Newer therapies targeting IL-17 are currently under clinical trials showing good clinical efficacy. The three monoclonal antibodies against IL-17 are brodalumab, ixekizumab and secukinumab.
Brodalumab is a human, anti-IL-17 receptor monoclonal antibody that binds with IL-17RA, inhibiting the activity of IL17A, IL17F and IL17A/F heterodimers and IL-17E.9

Ixekizumab is humanized immunoglobulin G4 monoclonal antibody and secukinumab is a fully human IgG1k monoclonal antibody that acts against IL-17A.10,11

The continued efforts of investigators to find new therapeutic targets in the treatment of psoriasis are validating its theory of pathogenesis. The successful use of biologicals like anti-IL-17 and anti-IL-17R will improve the patient care and will reduce the cardiovascular diseases, arthritis and other co-morbidities associated with psoriasis.

References


