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Mini Review

Rheumatoid Arthritis: An Outlook of the Main Inflammatory Cells and Mediators Involved, and Treatments to Target Inflammation

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Abstract

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease associated with bone destruction. Cytokines and other inflammatory mediators propagate and perpetuate the inflammation in RA. The dysregulation of the autoimmune response lead to chronic inflammation. Macrophages and T-cells are some of the main players that, acting through cytokine production, contribute to chronic inflammation. TNF α is involved in many aspects of immune regulation, and targeting this mediator is an effective therapy to treat RA. Managing inflammation –either targeting specific inflammatory cytokines or inhibiting the activation of T-cells with biologic disease-modifying antirheumatic drugs– is an effective target therapy for RA.

Keywords: Rheumatoid Arthritis; T-cells; TNF-α; Cytokines; Inflammation; Auto-Immunity

Abbreviations

ACPA: Anti-Citrullinated Protein Antibodies; Akt: Protein Kinase B; APC: Antigen-Presenting Cell; CCP: Cyclic Citrullinated Peptide; CD28: Cluster of Differentiation 28; CD80: Cluster of Differentiation 80; CD86: Cluster of Differentiation 86; CTLA4-Ig: Cytotoxic T-Lymphocyte-Associated Protein 4-Immunoglobulin; ERKs: Extracellular Signal-Regulated Kinases; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; HLA-DR allele: Human Leukocyte Antigen – DR isotype; IFN-γ: Interferon Gamma; IL: Interleukin; JAK: Janus Kinase; JNK: Jun N-Terminal Kinase; MAPK: Mitogen-Activated Protein Kinase; MCP-1: Monocyte Chemoattractant Protein-1; MHC: Major Histocompatibility Complex; MMPs: Matrix Metalloproteinases; PAD: Pro-Apoptotic Domains; PD-1: Programmed Cell Death Protein 1; PGE2: Prostaglandin E2; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; STAT: Signal Transducer and Activator of Transcription; Tph: T Peripheral Helper Cells; TNF-α: Tumour Necrosis Factor Alpha; TNF-RI: Tumour Necrosis Factor Receptor I; TNF-RII: Tumour Necrosis Factor Receptor II

Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory arthropathy of unknown etiology associated with immune system dysregulation and persistent inflammation of synovial joints leading to irreversible cartilage and bone damage [1-4], considered the ultimate disease manifestation in the joint. Inflammatory cytokines are the center of the complex inflammatory networks that propagate and perpetuate RA [5]. The bone erosions –found close to the insertion site of the synovial membrane– are linked to the pannus formation and the presence of osteoclasts [6-8].

Adaptive immune response in RA encompasses auto-reactive B-cells and the production of rheumatoid factor (RF) autoantibodies and anti-cyclic citrullinated peptide (CCP) antibodies. However, there are two sides to immune response [9]; while immunity predominantly provides a protective response, dysregulation of an inflammatory response may lead to chronic inflammation [10-12], which plays a major role in the propagation of the disease [4], and over a long period of time may contribute to the development of age-related diseases, including RA [13,14].

Macrophages –the first line of defense– play a pivotal role in the induction and progression of inflammatory processes, as the prolonged activation of these cells causes –through pro-inflammatory cytokines and inflammatory mediators– a dysregulated inflammatory response, which lead to a cycle of chronic inflammation [15]. The cytokines and matrix metalloproteinases (MMPs) secreted by infiltrating macrophages are involved in T-cell activation, proliferation, and cell to cell interaction, which release further tissue-damaging enzymes leading to inflammation propagation and joint damage [14-16].

Cytokines and chemokines

Cytokines –through specific receptors in other immune cells, but also in epithelial cells and fibroblasts– coordinate the immune response. In rheumatic diseases, the regulation of cytokines is unbalanced, with both, insufficient production of inhibitory cytokines and increased production of proinflammatory cytokines that contribute to the chronic inflammatory condition. Proinflammatory cytokines –such as interleukin IL-1β, IL-6, IL-8, tumour necrosis factor alpha (TNF-α), PGE2, chemokines, and interferon families (IFN) [17]– secreted in the synovial fluids and joint tissues of RA patients by infiltrating macrophages, T-cells and B-cells contribute to joint inflammation [18,19].

Monocyte chemoattractant protein-1 (MCP-1) produced from osteoclasts could be involved the IL-20 cytokine family production [20]. The IL-20 family consists of the cytokines IL-19, IL-20, IL-22, IL-24, and IL-26, along with superfamily IL-10, IL-28, and IL-29 [21,22]. IL-19 seems to have an anti-inflammatory role in arthritis while IL-20 and IL-24 have been linked to bone degradation and radiographic progression. IL-22 has also been associated with progression of bone erosion and IL-26 induces several proinflammatory cytokines in RA. The IL-20 cytokine family signal through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway primarily activating STAT3. In the case of IL-22, it can activate protein kinase B (Akt), extracellular signal-regulated kinases (ERKs), Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) [22].

TNF is a pleiotropic cytokine involved in many aspects of immune regulation [23] through binding to its receptor's TNF-RI and TNF-RII. This cytokine can be produced by multiple cell types such as T and B-cells and innate immune cells (dendritic cells (DCs), monocytes, neutrophils, mast cells). All these sources may contribute to the development of a pathological state of chronic inflammation, especially in RA. T-cells are also targets for TNF either directly, like all cells that express TNF-Rs, or indirectly as a result of antigen presentation or co-stimulation.

Activation of naive T-cells is initiated during their encounter with antigen peptide presented by mature DCs, and TNF contributes to efficient antigen presentation by inducing DCs maturation. This activation is dependent on co-activation mediated by the membrane interaction between members of the TNF/TNF-R family and other cytokines on T-cells and DCs.

In patients who display the RA susceptibility HLA-DR allele, T-cells respond to citrullinated T-cell epitopes or proapoptotic domains (PAD) peptides [24], which supports the current view of interaction between pathogenic T-cells, macrophages, and cytokines that contributes to the pathologic imbalance in RA [25] and can be targeted with biological therapies.

Interaction of T-cells with antigen presenting cells leads to differentiation into effector and memory T-cells [26]. On the other hand, diapedesis –the capacity of T lymphocytes to cross through endothelial cell junctions and invade inflamed tissue–, depend on TNF and interferon (IFN)-γ [27]. Thus, TNF possesses a distinct role in T-cell activation [28,29].

Th17 and shifting to non-classic T helper type 1 (Th1) cells –a lineage of $CD4^+$ effector T-cell that promotes cell-mediated immune responses– have been described as potential components of the pathophysiology of RA. Th1 cells promote macrophage activation, nitric oxide production, and cytotoxic T lymphocyte proliferation via IFN-γ, IL-2, IL-10, and TNF-α/β, leading to the phagocytosis and destruction of pathogens. However, exaggerated Th1 responses are associated with RA and other autoimmune diseases.

Recently, using mass cytometry technology, a new population of $CD4^+$T cells, called T peripheral helper (Tph) cells, has been identified in the synovial membrane of RA patients [30]. Tph cells are $CD4^+$ T-cells that express high levels of the immune checkpoint programmed cell death protein 1 (PD-1) and induce differentiation of plasma cells through IL-21. PD1 –a cell surface receptor that belongs to the immunoglobulin superfamily and is expressed on T-cells [31], regulates the immune response and promotes self-tolerance by suppressing T-cell in inflammatory activity, therefore preventing autoimmune diseases. PD-1 acts against autoimmunity through two mechanisms, it promotes apoptosis of antigen-specific T-cells in lymph nodes, and reduces apoptosis in the anti-inflammatory, suppressive regulatory T-cells [32,33].

Treatments

Due to the inflammatory mechanisms involved in RA, management of inflammation –via reduction of pro-inflammatory mediators to control and prevent chronic inflammatory diseases [14] - is an effective target therapy. Thus, biologic disease-modifying antirheumatic drugs [34,35] such as cytokine inhibitors have proved to play a critical role targeting TNF-α and IL-6 –and possibly also granulocyte-macrophage colony-stimulating factor (GM-CSF) [36]– in the pathogenesis of the disease. Anti-TNF biological therapy with TNF inhibitors –the first validated biological therapy for RA– has been considered a breakthrough in the treatment of chronic autoimmune diseases [37]. Currently, several other anti-cytokine drugs, lymphocyte-targeting agents and small-molecule inhibitors of signal transduction pathways are now available or in clinical trials [38].

Many patients with RA –a chronic inflammatory disease with a strong MHC class II component– develop characteristic autoantibodies towards the non-coding amino acid citrulline –anti-citrullinated protein antibodies (ACPA)–, now considered an independent predictive factor for treatment response by co-stimulation blockade by CTLA4-Ig (cytotoxic T lymphocyte-associated protein 4-immunoglobulin). Known as abatacept, this chimeric CTLA4 and IgG Fc fusion protein binds with high affinity to the B7 molecules CD80 and CD86 expressed on antigen-presenting cells modulating T-cell activation [39]. CTLA4-Ig inhibits T-cell-dependent antibody responses, significantly slow progression of autoimmune disease and have shown an immune modulatory function in several immunological disease models. Abatacept is believed to work by blocking CD28 co-stimulation and therefore interfering with T-cell antigen-presenting cell (APC) interaction and limiting T cell activation. The successful use of CTLA4-Ig as a biotherapy that blocks the CD28-CD86/CD80 interaction has highlighted once more the important role of T lymphocytes in RA [40].

The role of $CD4^+$ T-cells in RA pathophysiology may be mediated through Th1 effector functions, mainly IFN-γ secretion [41], Th17 activity or induction of ACPA [42,43], leading finally to bone and cartilage destruction. It has also been suggested that regulatory T cell (Treg) function may be impaired in RA [44].

Finally, anti-TNF drugs have the capacity to reduce inflammation by interfering with diapedesis and migration of T-cells to the joints. The inhibition of Tph by anti-TNFs [45] may prevent the differentiation of plasmablasts, precursor cells of short- and long-lived plasma cells [30].

Conclusion

The inflammatory immune process exacerbates the activation of immune cells by enduring production of proinflammatory cytokines and mediators in the synovial membrane maintaining the inflammation in RA and is responsible for further bone damage. Macrophages initiate the development of inflammation, but activation of different subtypes of T-cells has a key role in the progression and perpetuation of the process.

TNFα, via its receptors TRNR-I and TNFR-II, contributes to the pathologic state of RA by activating T-cells and DCs. The current view at the moment considers the interaction between macrophages, T-cells and cytokines key players in the pathological imbalance of the immune response in RA. Targeting TNFα with biological therapies –including the fusion protein abatacept– is an effective treatment for RA.

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