Cytokine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Review article

Immunomodulation of autoimmune arthritis by pro-inflammatory cytokines

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ARTICLE INFO

Keywords:
Adjuvant arthritis
Immunoregulation
Interferon-γ
Rheumatoid arthritis
TNF receptor 2
Tumor necrosis factor-α

ABSTRACT

Pro-inflammatory cytokines promote autoimmune inflammation and tissue damage, while anti-inflammatory cytokines help resolve inflammation and facilitate tissue repair. Over the past few decades, this general feature of cytokine-mediated events has offered a broad framework to comprehend the pathogenesis of autoimmune and other immune-mediated diseases, and to successfully develop therapeutic approaches for diseases such as rheumatoid arthritis (RA). Anti-tumor necrosis factor-α (TNF-α) therapy is a testimony in support of this endeavor. However, many patients with RA fail to respond to this or other biologics, and some patients may suffer unexpected aggravation of arthritic inflammation or other autoimmune effects. These observations combined with rapid advancements in immunology in regard to newer cytokines and T cell subsets have enforced a re-evaluation of the perceived pathogenic attribute of the pro-inflammatory cytokines. Studies conducted by others and us in experimental models of arthritis involving direct administration of IFN-γ or TNF-α; in vivo neutralization of the cytokine; the use of animals deficient in the cytokine or its receptor; and the impact of the cytokine or anti-cytokine therapy on defined T cell subsets have revealed paradoxical anti-inflammatory and immunoregulatory attributes of these two cytokines. Similar studies in other models of autoimmunity as well as limited studies in arthritis patients have also unveiled the disease-protective effects of these pro-inflammatory cytokines. A major mechanism in this regard is the altered balance between the pathogenic T helper 17 (Th17) and protective T regulatory (Treg) cells in favor of the latter. However, it is essential to consider that this aspect of the pro-inflammatory cytokines is context-dependent such that the dose and timing of intervention, the experimental model of the disease under study, and the differences in individual responsiveness can influence the final outcomes. Nevertheless, the realization that pro-inflammatory cytokines can also be immunoregulatory offers a new perspective in fully understanding the pathogenesis of autoimmune diseases and in designing better therapies for controlling them.

1. Introduction

Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-1β (IL-1β), IL-6, and IL-17 play a vital role in the pathogenesis of rheumatoid arthritis (RA), which is characterized by chronic inflammation of the synovial tissue, joint dysfunction, and tissue damage in the joints [1–5]. Collectively, these cytokines facilitate the recruitment of leukocytes into the joints to maintain chronic inflammation; induce the proliferation of synovial fibroblasts that leads to pannus formation; and contribute to the processes of angiogenesis as well as cartilage and bone degradation in the course of arthritis [2,6–9]. The roles of 3 of the pro-inflammatory cytokines, namely TNF-α, IFN-γ, and IL-17, in autoimmune arthritis are discussed in detail below. Macrophages, monocytes, and CD4+ T helper 1 (Th1) cells produce TNF-α, a key driver of inflammation [9,10]. Neutrophils, endothelial cells, and fibroblasts are among other

Abbreviations: AA, Adjuvant-induced arthritis; BCTD, Bhsp65 C-terminal determinants; Bhsp65, Mycobacterial heat-shock protein 65; CIA, Collagen-induced arthritis; EAE, Experimental autoimmune encephalomyelitis; EAU, Experimental autoimmune uveitis; FLS, Fibroblast-like synoviocytes; Foxp3, forkhead box P3; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GVHD, graft-versus-host disease; IFN-γ, interferon-γ; ILC, innate lymphoid cells; iTreg, induced Treg; JIA, Juvenile idiopathic arthritis; LNC, Lymph node cells; MMP, matrix metalloproteinases; Mtb, *Mycobacterium tuberculosis* H37Ra; mTNF, membrane-bound TNF; nTreg, natural Treg; PBMC, peripheral blood mononuclear cells; PGE2, prostaglanding E2; PGIA, Proteoglycan-induced arthritis; R465, Rhsp65 peptide 465 to 479; RA, Rheumatoid arthritis; RCTD, Rhsp65 C-terminal determinants; Rhsp65, Rat hsp65; RORγt, Retinoic acid-related orphan receptor γt; sTNF, soluble TNF; Teff, T effector; Th17, T helper 17; TNF-α, tumor necrosis factor-α; TNFR, TNF receptor; Treg, CD4 + CD25 + Foxp3 + T regulatory

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http://dx.doi.org/10.1016/j.cyto.2017.04.012
Received 2 February 2017; Received in revised form 9 April 2017; Accepted 10 April 2017

cell types that can serve as a source of this cytokine. TNF-α acts on macrophages to enhance phagocytosis as well as the production of other pro-inflammatory cytokines and prostaglandin E2 (PGE_2) [9,10]. It also serves as a chemoattractant for neutrophils, and induces chemokine expression on endothelial cell lining to facilitate trans-endothelial migration of neutrophils. TNF-α acts on fibroblast-like synoviocytes (FLS) to induce their proliferation and pannus formation, and upregulates collagenase and matrix metalloproteinases (MMPs), which participate in cartilage damage. In addition, TNF-α activates osteoclasts, which promote bone demineralization [9,10]. TNF-α also has systemic effects such as fever and cachexia. Regarding IFN-γ, the natural killer (NK) cells, Th1 cells, CD8+ cytotoxic T cells, NK T (NKT) cells, and innate lymphoid cells 1 (ILC1) are the primary source of this cytokine [11–13]. Subset of dendritic cells (DCs) and B cells are among other cellular sources of IFN-γ. Like TNF-α, IFN-γ enhances chemokine expression for leukocyte recruitment by facilitating their transfer through the endothelial layer. IFN-γ also activates macrophages and FLS to increase antigen presentation; promotes T_h1 differentiation; and activates NK cells and inducible nitric oxide synthase (iNOS) [11,12,14]. Over the past decade or so, significant attention has been focused on IL-17, which has been shown to play a critical role in the pathogenic processes involved in arthritis in both RA patients [5,15–19] and animal models of RA [20–24]. Th17 cells are one of the major sources of IL-17 in autoimmune arthritis [18]. The CD8+ T cells [24], γδ T cells [23–25], ILC3 [26], and other cell types [27] may also contribute IL-17 at the site of arthritic inflammation. IL-17 acts on FLS and other cells to increase the production/activity of other pro-inflammatory cytokines; of chemokines that attract T cells, macrophages, neutrophils and other cells into the joints; of new blood vessels (angiogenesis); and of osteoclast MMPs that contribute to joint damage [15,17,28–31].

While the pro-inflammatory cytokines can upregulate each other in the short term to promote acute inflammation, there are various negative feedback loops to dampen the inflammatory response with the progression of inflammation. For example, TNF-α can be translationally repressed by micro-RNAs. Both transgenic mice having the human TNF-α transgene with altered 3′ untranslated region (3′UTR) site [32] and mutant mice that lack 3′ adenylate-uridylate (AU)-rich element (ARE) in the TNF gene [33], a modification that prevents translational repression, develop spontaneous chronic polyarthritis. TNF receptor 1 (TNFR1) (also known as TNFR-I or p55) can also be cleaved and thus rendered soluble, which not only prevents further signaling but also permits soluble TNFR (sTNFR) to bind and sequester TNF-α. Interestingly, the prevention of TNFR1 shedding can lead to spontaneous development of arthritis [34]. For IL-17, typically IL-23 (produced by macrophage and dendritic cells) enhances IL-17 secretion, thus forming the IL-23/IL-17 axis [24]. Nevertheless, IL-17 can negatively regulate IL-23 production [35], and thus can be self-limiting. In addition, IFN-γ can inhibit IL-17 production [20,36]. Furthermore, the production of TNF-α, IFN-γ, and IL-17 can be modulated by the action of CD4+ CD25+ T regulatory (Treg) cells on the T helper cell subsets (Th1 and Th17) that produce these cytokines. (Additional details on T cell subsets are given below.) These self-regulatory mechanisms are supplemented by other mechanisms mediated via IFN-γ (Fig. 1, Table 1) and TNF-α (Fig. 2, Table 2) to control arthritic inflammation [37,38], and these mechanisms are discussed below.

To fully understand the roles of pro-inflammatory cytokines in autoimmunity, it is essential to consider the characteristics of, and the balance between, different T cell subsets, as well as the plasticity of T cell subsets [39–44]. Activation of naïve T cells under defined cytokine environment conditions facilitates the generation of distinct CD4+ T cell subsets that are characterized by the production of specific cytokines and expression of particular transcription factors. Among the T helper subsets, Th1 cells produce IFN-γ and TNF-α and express the transcription factor T-box transcription factor (T-box 21; also known as TBX21 or T-bet); Th2 cells produce IL-4 and express GATA binding protein 3 (GATA3); and Th17 cells produce IL-17 and express retinoic acid-related orphan receptor γt (RORγt; in humans, RORC) [39–43]. In contrast, Treg cells produce transforming growth factor-β (TGF-β) and IL-10 and express forkhead box P3 (FoxP3). The Th1 and Th2 cells can mutually cross-regulate each other, and Treg cells can suppress the activity of above-mentioned T helper subsets [39–44]. Interestingly, there is a reciprocal development of Th17 and Treg cells from naïve T cells, with TGF-β favoring Treg cell development and TGF-β and IL-6 facilitating Th17 cell development [41]. In RA, earlier studies showed that Th1 cells are enriched in the joints of these patients [45–47]. Subsequent studies revealed similar findings for Th17 cells in the joints of RA [48] and juvenile idiopathic arthritis (JIA) patients [49]. As previously observed for the Th1/Th2 imbalance, an imbalance in the Th17/Treg cell ratio has been suggested to be a critical factor in the pathogenesis of autoimmunity as well as a target of new therapeutic approaches aimed at re-setting this balance [5,39–43]. Furthermore, a subset of the Th17 cells infiltrating the joints of JIA patients were found to be of a dual Th1/Th17 phenotype that expressed both T-bet and RORC2 [50]. In addition, the conversion of Th17 cells into cells of a dual Th17/Th1 or Th1 phenotype was demonstrated in vitro in that study. The Th17 cells that express IFN-γ are associated with immune pathology in arthritis and multiple sclerosis (MS) [50,51]. However, in mice, the expression of T-bet and IFN-γ has also been shown in natural Treg (nTreg) cells [52]. Therefore, further studies are needed to fully define the role of IFN-γ in situations involving plasticity of T cell subsets. In another study, retinoic acid and retinoic acid receptor-α have been shown to be critical for Th1 development and for repression of the genetic program for Th17 cell development [53].

Most of the discussion below is focused on autoimmune arthritis, particularly RA and its animal models. However, for completeness and relevant comparison, examples of a few other immune-mediated diseases are also discussed at appropriate places.

2. Regulatory roles of pro-inflammatory cytokines IFN-γ and TNF-α in adjuvant arthritis

Adjuvant arthritis (AA) is a well-characterized experimental model of human RA, and it can be induced in Lewis (LEW) rats by immunization with heat-killed *M. tuberculosis* H37Ra (Mtb) [54,55]. The disease manifests as a polyarthritis, and it appears within about 8–10 days after Mtb injection. After reaching the peak phase, which lasts for about 4–5 days, there is a spontaneous regression of arthritis over the next 10–12 days. Arthritic rats raise T cell response against mycobacterial heat-shock protein 65 (Bhsp65) following Mtb injection [37,55]. The epitope region 180–188 (B180), which is nested within the longer sequence 177–191 (B177), represents the arthritogenic determinant of Bhsp65 [37,55]. Arthritic LEW rats also develop T cell response to self (rat) hsp65 (Rhsp65) [54,55]. Most information on Rhsp65 relates to its immunoregulatory role in AA [54], although it has also been proposed that crossreactivity between self and foreign Hsp65 might be involved in disease induction [55]. However, the latter phenomenon has not yet been fully addressed and needs further work. We previously showed that unlike the LEW rats, the Wistar Kyoto (WKY) rats of the same major histocompatibility complex (MHC) haplotype are resistant to AA induction [37,55].

Our previous studies revealed that the T cells against defined determinants within Bhsp65, namely the Bhsp65 C-terminal determinants (BCTD), as well as those within its self-homolog, namely the Rhsp65 C-terminal determinants (RCTD), are capable of downregulating AA [54,55]. Examination of the cytokine secretion profiles showed that surprisingly, the disease-protective T cells against the C-terminal determinant(s) secreted predominantly Th1-type cytokines [37,38,56]. Furthermore, LEW rats (AA-susceptible) had increased IFN-γ and TNF-α response during regression from arthritis, while WKY rats (AA-resistant) had a similar type of response (Th1) but temporally it was detectable early after a potentially arthritogenic challenge (Mtb injection) [37,38].