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Review

Pathogenesis of rheumatoid arthritis and c-Fos/AP-1

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c-Fos/AP-1 controls the expression of inflammatory cytokines and matrix-degrading matrix metalloproteinases (MMPs) important in arthritis via promoter AP-1 binding motif. Among inflammatory cytokines, IL-1β is the most important inducer of a variety of MMPs, and mainly responsible for cartilage breakdown and osteoclastogenesis. IL-1β and c-Fos/AP-1 influence each other's gene expression and activity, resulting in an orchestrated cross-talk that is crucial to arthritic joint destruction, where TNFα can act synergistically with them. While how to stop the degradation of bone and cartilage, i.e., to control MMP, has long been the central issue in the research of rheumatoid arthritis (RA), selective inhibition of c-Fos/AP-1 does resolve arthritic joint destruction. Thus, the blockade of IL-1β and/or c-Fos/AP-1 can be promising as an effective therapy for rheumatoid joint destruction in addition to the currently available TNFα blocking agents that act mainly on arthritis.

Introduction

Immediate early gene *c-fos* contributes significantly to arthritis. This somewhat unexpected role of c-Fos/AP-1 is by no means exceptional when considering the roles of c-Fos/AP-1 in the transactivation of the genes responsible for arthritis such as inflammatory cytokines and matrix metalloproteinases (MMPs).[1-4] Most of the genes encoding inflammatory cytokines and matrix-degrading MMPs are under the control of c-Fos/AP-1, and c-Fos/AP-1 transactivates such genes by binding directly their promoter AP-1 motifs.[1-14] How to stop the degradation of bone and cartilage, i.e., to control MMP, has long been the central issue in the research of rheumatoid arthritis (RA), since cartilaginous matrix can only be degraded after the first attack of collagen fibrils by MMP.[15,16] Here I review the pathogenesis of rheumatoid joint destruction in relation transcription factor including c-Fos/AP-1.

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Cell Cycle and Arthritis

Cell cycle is organized by a family of cyclin-dependent protein kinases (cdks). There are several lines of evidence suggesting that cell cycle progression is distorted in RA. First, the manner of the growth of rheumatoid synovial cell is 'tumor-like': cells with 'transforming' appearance containing abundant cytoplasm, large pale nuclei and prominent nucleoli with karyotypic alteration are typically found adjacent to the affected joints in human RA and experimental animal model of arthritis.[17-19] Second, the transcription factors acting at the G_1 phase of cell cycle including c-Fos/AP-1,[20,21] Erg-1,[22] CREB[23] and C/EBP[24] are increased, whereas the proportion of $PCNA^+$ or $Ki\text{-}67^+$ cells is decreased[25,26] in rheumatoid synovial. Third, Wee1 kinase which inhibits mitotic cell division by phosphorylating cdc2 is under the control of c-Fos/AP-1, and Wee1 is increased simultaneously with c-Fos/AP-1 in RA.[10,11] The findings suggest that mitotic cell division is arrested in face of heightened cell proliferation in RA due to upregulated c-Fos/AP-1 and Wee1, thereby causing a 'tumor-like' synovial overgrowth, an important, classical attribute of rheumatoid synovia.[27]

Factors that Initiate Arthritis

Arthritic joint destruction is, needless to say, heralded by arthritis. The initial phase of arthritis is characterized by (1) 'tumor-like' synovial cellular overgrowth not necessarily accompanied by lymphocytes,[17-19] (2) peri-articular osteoporosis seen as early as a few month after the onset of RA,[28] and (3) loss of cartilage typically seen within 1 year after disease onset. Matrix-degrading MMPs and inflammatory cytokine IL-1β released from synovial cell and/or osteoclast, appear to be responsible for the initiation of arthritis (Fig. 1A). IL-1β is the most important inducer of a variety of MMPs including MMP1, 3, 8, 13 and 14,[29] and IL-1β can activate osteoclasts[30] and degrade cartilaginous matrix most strongly[29,31,32] and vice versa, MMPs cleave IL-1β into its active forms.[33] Time course studies in animal experiment show that IL-1β, IL-6 and MMP-3 are initially increased in arthritis,[34,35] and IL-6, and possibly TNFα, appears activated subsequent to IL-1β in collagen-induced arthritis (CIA) and human synovial cells (Fig. 1B).[31,36-38] IL-1β is increased in sera, synovia and joints of patients with RA,[39-41] and serum levels of IL-1β correlate with its disease severity.[42,43]

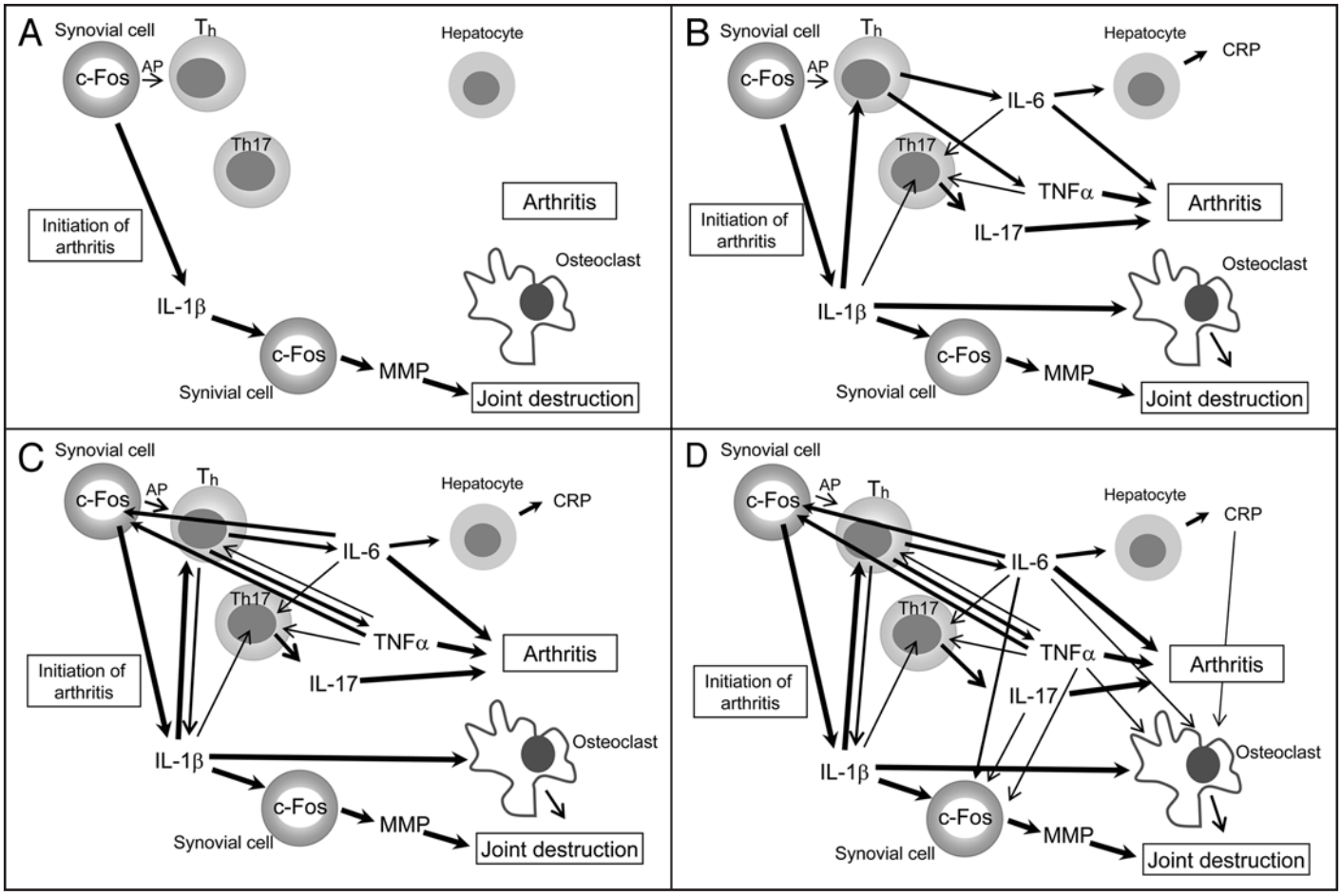

Figure 1. Relationship between inflammatory cytokines, c-Fos/AP-1 and matrix degrading MMPs in arthritis and arthritic joint destruction. (A) On initiation of arthritis, c-Fos/AP-1 is upregulated in the cell and IL-1β and matrix-degrading MMPs are released. IL-1β and the increase of c-Fos/AP-1 in the cell stimulate osteoclast to degrade joints. AP, antigen presentation. (B) In full-blown arthritis, IL-1β stimulates Th to release IL-6 and TNFα. IL-1β, IL-6 and TNFα then stimulate Th17 cell to release IL-17. Inflammatory cytokines IL-6, TNFα and IL-17 play essential roles in arthritis. Besides, IL-6 also acts on hepatocyte to release C-reactive protein (CRP). (C) In the advanced phase of arthritis, IL-6 and TNFα stimulate synovial cell to release IL-1β and then mutual positive interaction between IL-1β, IL-6 and TNFα is established. (D) At later stage, IL-1β, IL-6 and TNFα stimulate osteoclast and synovial cells to release MMPs to enhance farther destruction of joints.

Factors that Aggravate Arthritis

TNFα, IL-6 and IL-17 are the main players in full-blown arthritis (Fig. 1B). TNF-blocking agents, infliximab, etanercept and adalimumab, not only inhibit arthritis but also halt radiologic joint destruction.[44-49] TNFα is produced from lymphoid cells quickly in response to infection or inflammation via NFκB-dependent and NFκB non-dependent pathways, the latter including ATF2, c-Jun, Erg 1 and Sp1.[50,51] TNFα upregulates NFκB directly and c-Fos/AP-1 indirectly via MAPK/JNK pathway.[1,52] TNFα phosphorylates ATF2, thereby upregulating IL-6,[52] IL-17,[53,54] and TNFα itself[50] (Fig. 1B). TNFα increases MMP1, 3 and 9 and inhibits bone formation via Dickkopf-1 (Dkk-1).[55-58] However, TNFα cannot stimulate osteoclasts directly, just helping M-CSF- or RANKL-induced osteoclast formation.[29] The direct effect of TNFα on MMPs is far weaker than that of IL-1β.[29,31,32]

IL-1β and TNFα promote Th17 cell commitment and IL-17 production, a process principally driven by IL-6 and TGFβ (Fig. 1B).[59] Here, the presence of IL-6 is of particular importance, because stimulation of CD4 T cell with IL-6 plus TGFβ potently induces Th17 differentiation whereas stimulation with TGFβ triggers the development of regulatory T cells.[60-62] IL-17 is increased in the synovial tissue and synovial fluid of patients with RA.[63-67] IL-17 induces IL-1β, TNFα, IL-6, IL-8 and macrophage inflammatory protein (MIP)-1α, MMPs and receptor activator of NFκB ligand (RANKL) (Fig. 1C).[65,68-73] IL-17 acts in synergy with IL-1β and TNFα to induce cytokine or chemokine[74] and cartilage destruction[73,75] in vitro. While inhibition of IL-17 substantially improves arthritis,[76-79] the effect of IL-17 blockade appears clinically modest as compared with a dramatic effect of IL-1β blockade.[51,80]

IL-6 receptor (IL-6R) blockade also inhibits arthritis significantly. IL-6 is a major inducer of C-reactive protein from liver and thus a key mediator of inflammation[29] During inflammation, IL-1β acts on bone marrow to release neutrophils[81] and on endothelial cells to release IL-6, and IL-6 thus-released increases

C-reactive protein and thryombocytosis.[81,82] IL-6 vice versa, induces IL-1β, TNFα and c-Fos/AP-1.[50,84] Although C-reactive protein is an independent risk factor for bone loss and fracture and IL-6 can differentiate Th17 cells in cooperation with TGFβ thereby increasing RANKL on osteoclasts (Fig. 1D),[29,85] IL-6R blockade is less protective on radiologic joint destruction.[86-88]

Factors for Arthritic Joint Destruction

A recombinant form of the drug of naturally occurring IL-1 receptor antagonist (IL-1ra) is with lower clinical efficacy for RA.[89-91] This could be due to the fact that a 50% inhibition of IL-1 activity requires approximately 100-fold excess of IL-1ra, however, IL-1ra is on the other hand highly effective in the treatment of IL-1β-centered autoinflammatory syndrome.[92] This would mean that cascades of inflammatory cytokine are responsible for the pathogenesis of RA, and thus IL-1β blockade alone appears less effective. Nevertheless, IL-1β is the most important inducer of a variety of MMPs,[29,93] even compared in molar basis.[30,94] It induces the release of latent form of MMPs such as MMP3 or MMP13 crucial for collagen breakdown[95] and of active aggrecanase which is the dominant enzyme responsible for proteogycan loss.[30,96,97] There are additive effects on the induction of MMPs between IL-1β and other cytokines or growth factors including TNFα, oncostatin M, FGF and PDGF.[29] Cartilage damage is fully dependent, even in TNF-triggered arthritis, on IL-1.[29] IL-1β is 100-fold potent than TNFα in inducing cartilage destruction in vivo, where IL-1β can act synergistically with TNFα,[97,98] suggesting that IL-1 is a key link between synovitis and cartilage breakdown (Fig. 1D). IL-1β also facilitates osteoclast formation and significantly enhance RANKL-induced osteoclastogenesis.[29,90,91] A total lack of chronic erosive arthritis is noted in IL-1β-deficient mice,[96] and arthritic joint destruction in TNFα transgenic mice is totally inhibited by anti-IL-1R antibody in face of still increased serum TNFα.[99] Arthritis in IL-1ra-deficient mice are highly progressive.[38] Thus, IL-1 is crucially important in the progression of joint destruction in RA and all animal models.[37,95]

c-Fos/AP-1 and Joint Destruction

The invasive front of rheumatoid pannus, a granulation tissue degrading cartilage and bone, is composed of synovial mesenchymal cells, but not lymphocytes.[17] The synovial mesenchymal cells, which can present antigen to T cells[100-102] and release IL-1β and other inflammatory mediators, are driven by upregulated c-Fos/AP-1 in RA.[6,20,21] Upregulated c-Fos/AP-1 in RA causes synovial overgrowth[103,104] and osteoporosis[8,28] typically seen in arthritis. We found that selective inhibition of c-Fos/AP-1 resolved arthritis by the use of a specific small-molecule inhibitor of c-Fos/AP-1 designed and synthesized using 3D pharmacophore modeling based on the crystal structure of the AP-1-DNA complex.[35] c-Fos/AP-1 controls the expression of the inflammatory cytokines and matrix-degrading MMPs important in arthritis via promoter AP-1 binding motif.[1-5,12-14] This inhibitor[35] inhibits most of the matrix-degrading MMPs, including MMP3, 9 and 13, as well as inflammatory cytokines including IL-1β. While specific inhibition of individual MMPs, such as MMP3, cannot ameliorate CIA possibly owing to compensation by another MMP,[105] broad-spectrum MMP inhibition successfully reduces the clinical severity and cartilage destruction of arthritis.[35] Interestingly, c-Fos/AP-1 and IL-1β influence each other's gene expression and activity, resulting in an orchestrated cross-talk that is crucial to arthritic joint destruction,[2,12-14,30,106,107] both c-Fos/AP-1 and IL-1β are indispensable for arthritic joint destruction.[30,36-38,99,108-110]

Concluding Remarks

A controversy exists regarding the importance of mesenchymal synovial cell and/or lymphocyte in the pathogenesis of RA. It is clear that synovial mesenchymal cells are responsible for joint destruction, however, T cell-centered immunity is also important with regards to triggering antigen. A representative mediators released from mesenchymal synovial cells would be IL-1β, c-Fos/AP-1, MMP and/or TNFα and those of lymphocytes would be TNFα and/or IL-6. There are substantial cross-talk between them, and the change in one mediator would surely influence the others. However, as discussed, TNFα, IL-6 and IL-17 are important for arthritis, and IL-1β and c-Fos/AP-1 for joint destruction. Thus, c-Fos/AP-1 inhibitor appears to be a promising drug for rheumatoid joint destruction. However, the fact that c-Fos/AP-1 acts mainly on mesenchymal cells and also upregulates Wee1 kinase opens a new application of c-Fos/AP-1 inhibitor for sleep disturbance. We recently showed that there is a mutual interaction between biological clock gene *Cry* and Wee1 kinase. Arthritis is extremely aggravated in the absence of circadian rhythmicity and vice versa, arthritis disturbs the circadian rhythm of the host.[111]

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