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REVIEW ARTICLE

Inflammation and its resolution and the musculoskeletal system

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Summary Inflammation, an essential tissue response to extrinsic/intrinsic damage, is a very dynamic process in terms of complexity and extension of cellular and metabolic involvement. The aim of the inflammatory response is to eliminate the pathogenic initiator with limited collateral damage of the inflamed tissue, followed by a complex tissue repair to the preinflammation phenotype. Persistent inflammation is a major contributor to the pathogenesis of many musculoskeletal diseases including ageing-related pathologies such as osteoporosis, osteoarthritis, and sarcopaenia.

The translational potential of this article: Understanding the mechanisms of inflammation and its resolution is therefore critical for the development of effective regenerative, and therapeutic strategies in orthopaedics.

Introduction

Inflammation contributes to all nontraumatic musculoskeletal diseases, causing pain and disability in millions of people worldwide [1]. These orthopaedic and rheumatic diseases inflict an enormous burden for society and any health care system. At the same time, inflammatory processes play a critical role in tissue integrity and

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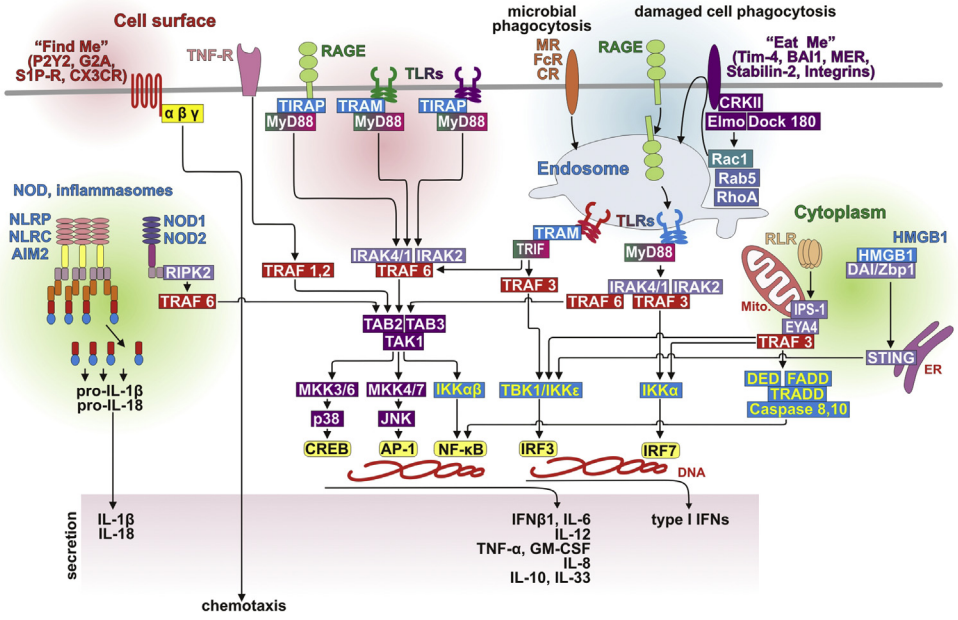

Figure 1 Mechanisms of macrophage sensing of apoptotic bodies and various external and internal danger signals and intracellular pathways involved in the macrophage response. Macrophages sense "find me," DAMP, and "eat me" stimulators by several classes of receptors such as GPCR for "find me signals"; TLR, RAGE, NLR, CLR, TNF-R, RLR, and HMGB for DAMP signals; and several various receptors allowing phagocytosis of microbial pathogens or "eat me" signals for apoptotic cells. Receptors recognise various ligands as exemplified in Table 2. Binding of "find me" signals to GPCRs (7-transmembrane domain-containing protein) such as P2Y2, G2A, S1P-R, and CX3CR induces conformational changes allowing the coupling of the receptor to the three subunits of G protein and promotes the exchange of GDP for GTP on the α subunit. As a consequence, chemotaxis and other biological responses are induced, including cell activation, survival, cell—cell interaction, and adhesion. Extracellular, endosomal, and intracellular PRR sense various microbial and endogenous stimuli specified in Table 2, which could trigger the production of inflammatory signals represented mostly by cytokines. Extracellular PRR receptors such as TLR-1, -2, -6, -5, -11 stimulated by bacterial lipoprotein, flagellin, etc., trigger the activation and translocation of transcription factors NF-κB, AP-1, and CREB to the nucleus. Described pathways involved in the activation of NF-κB, AP-1, and CREB are stimulated also by LPS, calcium- and zinc-binding proteins S100 [predominantly found as calprotectin (S100A8/A9)], and HMGB1, all sensed by RAGE, and upon ligation of TNF-α to its receptor (TNF-R). LPS also activates its primary extracellular receptor, TLR-4, which could contribute to the activation of IRF3, a transcription factor involved in the regulation of expression of several proinflammatory cytokines. After endocytosis of microbial pathogens or apoptotic cells, DAMPs stimulate membrane-anchored TLR-3, -7, -8, -9, but some DAMPS could be released into cytosol, for example after endosomal rupture, and could interact with NOD receptors or with inflammasomes. Inflammasomes represent a heterogeneous group of protein complexes forming either NLRP, NLRC, or AIM2. After interaction with the LRR domain, selected DAMPs induce conformational changes leading to NLRP, NLRC caspase-1 activation allowing cleavage of cytokine precursors pro-IL-1β and pro-IL-18 to active IL-1β and IL-18, which are subsequently released from the cell. NODs are activated by bacterial flagellin, RNA, muramyl dipeptide (MDP). NLRP and NLRC are activated in a biphasic manner consisting of (1) their transcription initiated with contribution of transcription factors NF-κB and probably AP-1 and IRF3, and (2) their subsequent activation through various DAMPS. Bacterial and viral nucleic acids could stimulate inflammation through TLR-3, -7, -8, -9, which signal through IRAK4 and IRAK1 to activate TRAF 6 but also TRAF 3 and subsequently IRF7, transcription factor involved in the regulation of transcription of several members of the IFN-α family, and other transcription factors mentioned above. Nucleic acids could also stimulate inflammation through cytosolic helicases: RIG-I and MDA5 signalling through mitochondrial membrane-associated adaptor IPS-1 involved in activation of TBK1/IKKε, NF-κB, and MAPK-dependent AP-1. Double-stranded cytosol-localised DNA could also be sensed by DNA-binding protein DAI signalling through endoplasmic reticulum-associated stimulator of interferon genes (STING), which interacts with TBK1/IKKε. Furthermore, HMGB1—DNA complexes released from damaged cells could be captured by surface-exposed RAGE; endocytosed and DNA within endosome is recognised by TLR7 or TLR9. Similarly, autoantibodies recognising self-DNA or -RNA could facilitate endocytosis of antibody—DNA complexes for endosomal TLR7 and TLR9 recognition. All the above pathways merge on a few transcription factors CREB, NF-κB, AP-1, and IRF3 involved in transcription of proinflammatory cytokines IFN-β1, IL-6, IL-12, TNF-α, GM-CSF, IL-8, IL-10, IL-33, as well as IL-1β and IL-18. The fifth depicted transcription factor IRF7 is responsible for transcription of several members of the IFN-α family. Finally, phagocytes engulf dead cells or apoptotic bodies through their recognition by virtue of a characteristic "eat me" signal exposed on their surface. A typical "eat me" signal is phosphatidylserine, a cell plasma membrane component that is kept in healthy cells exclusively on the inner