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Review

Macrophages in rheumatoid arthritis

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Summary. In rheumatoid arthritis (RA) tissue macrophages release growth factors, matrix metalloproteinases, cytokines, and chemokines. While in normal joints there is a balance between proinflammatory and anti-inflammatory cytokines, an imbalance between these inducers and inhibitors of inflammation occurs in RA, where macrophages are responsible for inducing inflammation, matrix destruction and angiogenesis.

Key words: Chemokine, Cytokine, Macrophage, Metalloproteinase, Rheumatoid arthritis

Introduction

The mononuclear phagocyte system is defined as a population of cells derived from progenitor cells in the bone marrow, which differentiate to form blood monocytes, circulate in the blood, and then enter tissues to become resident tissue macrophages (Van Furth, 1992). Metchnikoff was the first person in 1893 to use the term "macrophage" to describe a large cell able to take up microorganisms (Tauber and Chernyak, 1991).

Macrophages are derived from CD34 positive bone marrow progenitors that continually proliferate and shed their progeny in the bloodstream as promonocytes. They then develop into monocytes and extravasate into tissues where they differentiate into a specific type of "resident" tissue macrophage (Ross and Auger, 2002). The phenotype of these "resident" macrophage can vary markedly within tissues, from that of microglial cells in the brain, Kupferr cells in the liver, and Langerhans cells in the skin. "Resident" macrophages share a set of common functions, including their ability to intervene against microbial infections, to regulate normal cell turnover and tissue remodeling, and to help repair sites of injury (Ross and Auger, 2002).

Almost any local disturbance of tissue normality, be it infection, normal cell turnover or wounding, immune response or malignancy, caused rapid recruitment of macrophages. Recruited macrophages exhibit many phenotypic differences from resident tissue macrophages. The generic term, "macrophages activation" is commonly used to describe this process, but the nature of an "activated macrophage" population depends upon both the nature of the recruiting stimulus and the location.

It is now well established that the functional domain of the macrophage extends far beyond its originally recognized role as a scavenger cell. Its rich array of secretory products, anatomic diversity and functional heterogeneity is unmatched by any other cell type. As a result of this remarkable versatility, the macrophage is able to influence every facet of the immune response and inflammation as well as playing a central role in the etiology and/or pathogenesis of a number of disease processes.

Inflammation and macrophages

Macrophages infiltrate inflammatory tissues. In these sites macrophages, activated by tumour necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-12, interferon gamma (INF-γ), immune complexes, opsonized particles, T-lymphocytes, ligation of chemokine receptors, pathological collagen deposition, hypoxia, play a regulatory role through the production of cytokines and growth factors, such as IL-1, IL-6, IL-12, TNF-α, transforming growth factor beta (TGF-ß), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP), IL-10 and prostaglandin E_2 (PGE_2) (Lake et al., 1994; Albina et al., 1995; Cook et al., 1995; Voll et al., 1997; Fadok et al., 1998; Aliberti et al., 1999; Duffield et al., 2001; Gerber and Mosser, 2001). Moreover, macrophages are responsible for inflammation damage through the release of matrix metalloproteinase-2 (MMP)-2, MMP-7, MMP-

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9, MMP-12 (Gibbs et al., 1999).

Macrophages are also responsible for inducing apoptosis of parenchymal and stromal cells (Desmouliere et al., 1995; Meszaros et al., 2000) through the production of free radicals, such as nitric oxide (NO) or H_2O_2 (Duffield et al., 2001a; Duffield and Savill, 2001b; Kipari and Hughes, 2002). The phagocytosis of these apoptotic cells signals macrophages to stop the production of proinflammatory cytokines and to start an anti-inflammatory effect through the production of IL-4, IL-10, PGE_2 and TGF-ß (Voll et al., 1997; Fadok et al., 1998; Duffield et al., 2001a). Moreover, IL-4 and TGF-ß may induce macrophages to favour matrix deposition (Gratchev et al., 2001).

Macrophages in rheumatoid arthritis (RA)

The type A synovial cells (the macrophage) interdigitate with the type B cell (the fibroblast) in the synovial membrane (Athanasou, 1995). In the normal condition, the predominant cell type in the synovium is the type B cells, while in rheumatoid condition synovium lining type A cell number is greatly increased (Athanasou, 1995). Synovial macrophages are mainly derived from circulating monocytes (Athanasou, 1995). In some circumstances they may differentiate into osteoclast-like cells and become involved in bone resorption (Chang et al., 1992).

Macrophages play an important role in RA. The number of macrophages is higher in the inflamed synovial membrane and in the pannus of inflammatory vascular tissue in RA than in normal joints and is well-correlated with radiological damage (Mulherin et al., 1996) and with joint pain and inflammation (Tak et al., 1997).

In RA tissues macrophages overexpress major histocompatibility complex class II molecules, which indicate their activation and promotion of inflammation and tissue damage (Kinne et al., 2000a). Moreover, circulating monocytes are markedly activated (Burmester et al., 1997; Kinne et al., 2000b; Stuhlmüller et al., 2000) and $CD14^+$ myelomonocytic cells in the bone marrow prematurely express human leucocyte antigen (HLA)-DR^+ (Hirohata et al., 1996).

In about 50% of patients with RA a diffuse synovitis without a cellular organization is recognizable. In the remaining 50% the formation of ectopic germinal centers, where macrophages are organized together with lymphoid cells, and/or T cell-B cell aggregates (Klimiuk et al., 1997, 2001; Page et al., 2002; Park et al., 2004) are detectable. Macrophages contribute to the formation of ectopic germinal centers in RA inflammatory tissue via the production of the chemokine CXCL13, also known as B cell-attracting chemokine 1 (BCA-1) or B-lymphocyte chemoattractant (BLC), which is considered a lymphoid neogenic factor in mice and probably also in humans (Carlsen et al., 2004).

Macrophage activation has been observed in RA tissues, where growth factors and cytokines, including TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1, IL-6, IL-8, IL-10, IL-13, IL-15, IL-18, migration inhibitory factor (MIF) and chemokines, including MIP-1, MCP-1 and fractalkine, are released (Bazan et al., 1997; Burmester et al., 1997; Bresnihan, 1999; Gracie et al., 1999; Kinne et al., 2000b; Ruth et al., 2001; Volin et al., 2001; Morand et al., 2003). An increase in the levels of macrophage-derived proteases, such as leucocyte elastase, and matrix metalloproteinases (MMPs), including MMP-1, MMP-3 and MMP-9, has also been described at the site of articular destruction (Tetlow et al., 1993).

Macrophages and proinflammatory cytokines in RA

Macrophages can synthesize a variety of proinflammatory cytokines, present in joints of patients affected by RA, such as TNF-α, IL-1, IL-8, IL-15, IL-18, TGF-ß and MIF (Edwards et al., 1987; McInnes et al., 1996a, 1997; Badolato et al., 1997; Sebbag et al., 1997; Dinarello, 1999; Morand et al., 2003).

TNF-α has a primary role in RA pathogenesis by inducing the production of PGE_2, MMP-1, cytokines and adhesion molecules in the synovium (Dayer and Fenner, 1992). TNF-α stimulates macrophages to produce reactive oxygen species (Miesel et al., 1996) which contribute to inflammation in RA joints. Moreover, macrophages over-produce NO in RA synovium (Sakurai et al., 1995; McInnes et al., 1996b) that induces synovial cells to produce TNF-α, favouring inflammation and bone destruction (Neidel et al., 1995; McInnes et al., 1996b; Chae et al., 1997).

IL-1 production is correlated with joint inflammation and is responsible for the articular destruction in RA by inhibiting proteoglycan synthesis, degradating proteoglycan (von den Hoff et al., 1995) and stimulating the release of MMP-1 and MMP-3 (Arend et al., 1998). In RA patients the release of IL-1 and TNF-α by macrophages is stimulated by IL-15 (Badolato et al., 1997), produced by macrophages themselves and by T cells (McInnes et al., 1996a), and by IL-17, produced by T-helper cells (Aarvak et al., 1999).

Macrophages produce TGF-ß and TGF-ß receptors, responsible for matrix production and degradation in RA tissue (Edwards et al., 1987). TGF-ß may also induce macrophages to release reactive oxygen species via expression of the FcγRIII receptor (Wahl et al., 1992) and promotes leucocytes-chemoattraction and monocyte adhesion (Wahl et al., 1993). It stimulates the synthesis of MMP-13 in chondrocytes, favouring cartilage destruction (Moldovan et al., 1997).

MIF is a cytokine produced by macrophages which has both paracrine and autocrine effects, being responsible for their activation. Morand et al. (2003) have shown higher levels of MIF in RA serum, synovial fluid, and cultured synovial fibroblasts (Leech et al., 1999) and a correlation between the serum C-reactive protein level, which is an indicator of the disease activity, and levels of MIF in RA synovial fluid (Morand

et al., 2002). *In vitro* studies have shown that MIF activates macrophage production of TNF-α, IL-1, IL-6, IL-8 and IL-18 (Calandra et al., 1995; Donnelly et al., 1997; Gracie et al., 1999) and fibroblast-like synoviocyte production of PGE_2, via cytoplasmic phospholipase A2 and cyclooxygenase2 (COX-2) (Sampey et al., 2001; Morand et al., 2003).

MIF also plays also a role in cartilage degradation because it induces fibroblast-like synoviocytes to produce MMP-1 and MMP-3 (Onodera et al., 2000). Onodera et al. (2002) have demonstrated that MIF promotes rat calvarial osteoblasts to release MMP-9 and MMP-13 which may be responsible for MIF mediated-bone destruction. The importance of MIF in the regulation of inflammation and tissue destruction in RA has also been seen in studies in which treatments with anti-MIF antibodies are responsible for amelioration in experimental animal arthritis models (Mikulowska et al., 1997; Leech et al., 1998; Santos et al., 2001).

Macrophages and anti-inflammatory cytokines in RA

In normal joints there is a balance between proinflammatory and anti-inflammatory cytokines. An imbalance between these inducers and inhibitors of inflammation is responsible for the persistence of inflammation in rheumatoid joints (Miossec and van den Berg, 1997; Arend et al., 1998).

IL-4 is responsible for an anti-inflammatory effect by reducing IL-1ß TNF-α and TNF-α receptors macrophage production (Allen et al., 1993; Hart et al., 1996). TNF-α macrophage production is also down-regulated by IL-11 (Trepicchio and Dorner, 1998) and IL-13 (Bessis et al., 1996), which also reduces the production of IL-1 (Isomaki et al., 1996a). In RA, macrophage subsets also release anti-inflammatory cytokines, including IL-10, which inhibits macrophage synthesis of GM-CSF (Isomaki et al., 1996b) and IL-1 receptor antagonist (Allen et al., 1993).

Macrophages and chemokines in RA

MIP-1, MCP-1, fractalkine and CXCL13 have a role on macrophage activity and chemotaxis in RA.

MIP-1 has been considered important in favouring the production of IL-1, IL-6 and TNF-α by murine macrophages (Szekanecz et al., 1998; Szekanecz and Koch, 2001).

MCP-1 is over-expressed in synovial fluids and sera of RA patients (Koch et al., 1992; Akahoshi et al., 1993), where it exerts its chemotactic activity on macrophages.

In RA synovium macrophages produce fractalkine, a cellular adhesion molecule and a chemotactic chemokine for monocytes and lymphocytes (Bazan et al., 1997; Ruth et al., 2001; Volin et al., 2001), and CXCL13, important in the formation of ectopic germinal centers (Carlsen et al., 2004).

Macrophages and MMPs in RA

Macrophages, together with fibroblasts and endothelial cells, play a role in cartilage matrix destruction by producing MMPs (Konttinen et al., 1999; Cunnane et al., 2001). Secretion of IL-1 and TNF-α and overexpression of CD147 are responsible for fibroblast activation and production of MMP-1, MMP-2 and MMP-3 (Konttinen et al., 2000; Tomita et al., 2002; Zhu et al., 2005). CD147 also activates the production of MMPs by macrophages (Zhu et al., 2005). Cartilage degradation has been demonstrated *in vitro* in cocultures of mouse fibroblasts and macrophages (Janusz and Hare, 1993), and of purified human synovial fibroblasts and myelomonocytic cells (Scott et al., 1997). Anti-IL-1 and anti-TNF-α monoclonal antibodies can block cartilage degradation, emphasizing the importance of macrophage in cartilage destruction (Kinne et al., 2000a).

Macrophages and angiogenesis in RA

Macrophages in RA synovial tissue produce vascular endothelial growth factor (VEGF) (Fava et al., 1994) through TNF, TGFα, and IL-1 stimulation (DiGiovine et al., 1988; Fava et al., 1989; Wahl et al., 1990).

Macrophages release also another angiogenic cytokine, IL-8, (Koch et al., 1991, 2001) that enhances the expression of leukocyte adhesion molecule (De Gendt et al., 1996) and epithelial-neutrophil activating protein-78 (ENA-78; CXCL5) (Koch et al., 1994), an angiogenic chemokine involved in the chemotaxis of neutrophils (Walz et al., 1991, 1996; Strieter et al., 1996; Koch et al., 2001).

Another angiogenic chemokine, released by macrophages in RA synovial tissue, is fractalkine which enhances angiogenesis both *in vitro* and *in vivo* (Ruth et al., 2001; Volin et al., 2001).

Park et al. (2004) have demonstrated that macrophages, when they were organized in the RA lymphoid microstructures, did not produce thrombospondin 2 (TSP2), an important antiangiogenic factor. On the contrary, macrophages in the lining layer or in the stroma of diffuse synovitis produce TSP2, even if this production is smaller than the TSP2-production by CD146-expressing endothelial cells and synovial fibroblasts (Park et al., 2004). TSP2 has been seen responsible in vivo of reducing inflammation and the number of neoangiogenic vessels in RA tissue. In fact, RA characterized by diffuse synovitis, without organizated cellular structures, is the less aggressive pattern, with lower IFNγ and TNF-α levels (Park et al., 2004).

Concluding remarks

The diversity of functions of macrophages provides a link between innate and acquired immunity and the numerous physiological changes that contribute to host

defence. Otherwise, disordered macrophage biology causes much of the pathology of infectious, inflammatory, such as RA, and malignant diseases.

With the combined availability of complete genome and transcriptome sequences, gene expression array technology and markers allowing purification of tissue macrophages, the future will provide an opportunity to fully characterize macrophages in RA.

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