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REVIEW

Cytokines Focus

GM-CSF in inflammation

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Granulocyte–macrophage colony-stimulating factor (GM-CSF) has many more functions than its original in vitro identification as an inducer of granulocyte and macrophage development from progenitor cells. Key features of GM-CSF biology need to be defined better, such as the responding and producing cell types, its links with other mediators, its prosurvival versus activation/differentiation functions, and when it is relevant in pathology. Significant preclinical data have emerged from GM-CSF deletion/depletion approaches indicating that GM-CSF is a potential target in many inflammatory/autoimmune conditions. Clinical trials targeting GM-CSF or its receptor have shown encouraging efficacy and safety profiles, particularly in rheumatoid arthritis. This review provides an update on the above topics and current issues/questions surrounding GM-CSF biology.

Introduction

GM-CSF (CSF2) was originally defined as a hemopoietic growth factor due to its ability to form colonies of granulocytes and macrophages in vitro by proliferation and differentiation of bone marrow progenitor cells (Burgess and Metcalf, 1980). It later became apparent that GM-CSF could act on mature myeloid cells (Handman and Burgess, 1979; Hamilton et al., 1980), such as macrophages and neutrophils, as a prosurvival and/or activating factor with a potential role in inflammation (Hamilton et al., 1980). Consistent with these other roles, GM-CSF gene–deficient mice showed minimal changes in steady state myelopoiesis but developed pulmonary alveolar proteinosis (PAP) as the major phenotype indicating GM-CSF involvement in lung surfactant homeostasis (Dranoff et al., 1994; Stanley et al., 1994); this finding indicated a role for GM-CSF in alveolar macrophage development, which has been found to be dependent on the transcription factor PPARγ (Schneider et al., 2014). It has been proposed recently that GM-CSF is required for cholesterol clearance in alveolar macrophages, with a reduction in this clearance being the primary macrophage defect driving PAP (Sallese et al., 2017; Trapnell et al., 2019). This lung data suggest a fundamental role for GM-CSF in lipid (cholesterol) metabolism consistent with a proposed protective role in atherosclerosis (Ditiatkovski et al., 2006; see below).

In addition to providing an update on GM-CSF–dependent cell biology and signaling pathways, this review highlights preclinical data confirming a role for GM-CSF in inflammation and pain. Finally, a summary of the latest clinical trial findings targeting GM-CSF and its receptor in inflammatory/autoimmune disease is provided. Throughout the article, attempts are made to indicate outstanding issues/controversies as well as to suggest new directions for research to address these. The reader is referred to earlier reviews on GM-CSF biology for additional information (for example, Hamilton, 2008; Hamilton and Achuthan, 2013; Becher et al., 2016; Wicks and Roberts, 2016; Hamilton et al., 2017; Dougan et al., 2019).

GM-CSF cell biology and signaling

Receptor structure

The GM-CSF receptor (GM-CSFR) is a type I cytokine receptor comprising, in a multimeric complex, a binding (α) subunit and a signaling (β) subunit, the latter shared with the IL-3 and IL-5 receptors (Hansen et al., 2008; Broughton et al., 2016). The various myeloid cellular responses (survival, proliferation, activation, and/or differentiation) that occur at different GM-CSF concentrations appear to be explained by a dose-dependent sequential model of GM-CSFR activation with a hexamer binding the ligand, followed by assembly into a dodecamer configuration for the initiation of receptor signaling (Hansen et al., 2008; Broughton et al., 2016).

Signaling pathways

Key downstream signaling of the GM-CSFR has been shown to involve JAK2/STAT5, ERK, NF-κB, and phosphoinositide 3-kinase–AKT pathways (Lehtonen et al., 2002; Hansen et al., 2008; Perugini et al., 2010; van de Laar et al., 2012; Achuthan et al., 2018), with ERK activity linked to GM-CSF promotion of human monocyte survival in vitro (Achuthan et al., 2018).

The hemopoietic-specific transcription factor, interferon regulatory factor 4 (IRF4), is a key signaling molecule regulating

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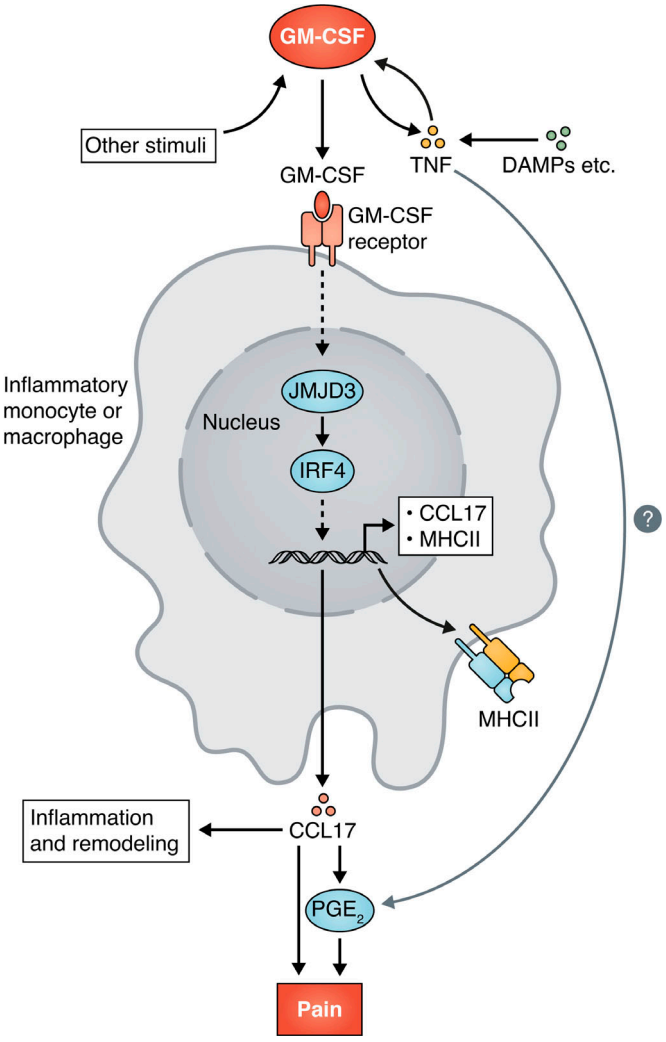

Figure 1. **A GM-CSF–IRF4–CCL17 pathway in inflammation and pain.** During an inflammatory reaction, GM-CSF, generated following TNF-dependent and -independent stimulation, induces in monocytes and macrophages the formation of CCL17 through a signaling pathway involving the induction of the transcription factor, IRF4, via the activity of the demethylase, JMJD3 (Achuthan et al., 2016). By unknown mechanisms, secreted CCL17 can result in inflammation and tissue remodeling, for example, in arthritic joints, as well as drive the development of pain; the latter response appears to require a contribution from an eicosanoid (for example, PGE_2). GM-CSF–IRF4 signaling can in addition control expression in monocytes and macrophages of other potential proinflammatory effectors, such as surface-bound MHC class II. GM-CSF and TNF, potentially produced by numerous cell types (not shown) in response to various stimuli, including damage-associated molecular patterns (DAMPs), can engage in a cytokine loop, thus potentially linking TNF biology to the GM-CSF–CCL17 pathway (Cook et al., 2018b).

the adoption of dendritic cell (DC)–like properties in GM-CSF–treated precursors such as monocytes (Lehtonen et al., 2005; Gao et al., 2013; Williams et al., 2013; Yashiro et al., 2018). We recently reported that in GM-CSF–treated monocytes/macrophages in vitro, IRF4 regulates the formation of CCL17 as a critical pathway with possible relevance to the proinflammatory and algesic actions of GM-CSF (Achuthan et al., 2016; see Fig. 1 and below); mechanistically, GM-CSF up-regulates IRF4 expression by enhancing JMJD3 demethylase activity. These data are surprising, since IRF5, rather than IRF4, has been reported to be important for GM-CSF–mediated macrophage polarization (Krausgruber et al., 2011). The data are also surprising in that IRF4 is usually considered to have an antiinflammatory role in macrophages because it down-regulates their production of proinflammatory cytokines such as TNF and IL-1β (Honma et al., 2005; Negishi et al., 2005; Eguchi et al., 2013) and indicate that the GM-CSF→CCL17 pathway is separate from the GM-CSF–driven pathways in monocytes/macrophages, leading to the expression of these other cytokines (Achuthan et al., 2016). Thus GM-CSF can be included in the list of cytokines, such as IL-4 and thymic stromal lymphopoietin, that can up-regulate CCL17 expression in monocytes/macrophages. GM-CSF–IRF4 signaling also up-regulates MHC class II expression in mouse bone marrow cultures (Suzuki et al., 2004b; Van der Borght et al., 2018) and macrophages (Lee et al., 2019; Fig. 1). In contrast to pathways associated with potential proinflammatory functions of GM-CSF, a time- and dose-dependent licensing process by GM-CSF in mouse and human monocytes in vitro has been described that disables their inflammatory functions and promotes their conversion into suppressor cells (Ribechini et al., 2017): this two-step licensing requires activation of the AKT/mTOR/mTORC1 signaling cascade by GM-CSF, followed by signaling through the IFNγR/IRF-1 pathway.

Consistent with the dose-dependent signaling responses noted above, dose-dependent effects of a neutralizing anti–GM-CSF mAb on monocyte-derived cell activation/polarization versus cell number levels were found in an inflammation model (Louis et al., 2015); also, monocytes/macrophages generated in vitro from bone marrow precursors with different doses of GM-CSF differed in function, with possible implications for GM-CSF–dependent pathology (Sun et al., 2018). Most signal transduction studies for GM-CSF have been in monocytes/macrophages, but more should be performed with other responsive cell types such as neutrophils and eosinophils (Hamilton, 2008; Griseri et al., 2015; Hamilton et al., 2017). More signal transduction information, particularly that linked with the role of GM-CSF in inflammation, is described below.

Cellular sources of GM-CSF and GM-CSF networks

Both hemopoietic (e.g., lymphocytes and innate lymphoid cells [ILCs]) and nonhemopoietic cell populations (e.g., fibroblast, endothelial, and epithelial populations; see below) can produce GM-CSF, although they usually require an activating stimulus (Hamilton, 2008; Campbell et al., 2011; Rauch et al., 2012; Willart et al., 2012; Becher et al., 2016; Pearson et al., 2016; Anzai et al., 2017; Sheih et al., 2017; Chen et al., 2018; Hu et al., 2019). Consistent with this requirement, in the steady state, GM-CSF circulates at low levels and is usually expressed basally in nonsterile tissues such as lung, gut, and skin (Metcalf and Nicola, 1995; Hamilton and Achuthan, 2013). Even though in inflammation, GM-CSF can serve as a communication conduit between tissue-invading lymphocytes and myeloid cells, there is some controversy as to which factors can induce GM-CSF production in T helper (Th) cells (Becher et al., 2016). In murine models of autoimmunity, such as experimental autoimmune encephalomyelitis (EAE), GM-CSF has been shown to be the

critical effector cytokine produced by IL-23-stimulated Th17 cells in mice, leading to the concept that GM-CSF is a Th17-related cytokine (Sonderegger et al., 2008; Codarri et al., 2011; El-Behi et al., 2011; Hamilton et al., 2017); however, it has been put forward that a novel subset of Th cells (Th-GM) predominantly produces GM-CSF but not IL-17 and is essential for EAE development (Sheng et al., 2014; Komuczki et al., 2019), and IL-12–polarized Th1 cells produce GM-CSF and induce EAE independently of IL-23 (Carbajal et al., 2015; Grifka-Walk et al., 2015). Also, (i) in humans a distinct subset of $CD4^+$ T cells that produces only GM-CSF has recently been identified (Noster et al., 2014), (ii) Th1 cells have been claimed to be the predominant Th cell subset that produces GM-CSF in the rheumatoid arthritis (RA) joint (Yamada et al., 2017), and (iii) Th1 $CD4^+$ T cells have been proposed to trigger chronic autoimmune valvulitis in patients with acute rheumatic fever (Kim et al., 2018). In addition, an expansion of GM-CSF–producing $CD4^+$ and $CD8^+$ T cells in the blood and synovial fluid of patients with axial spondyloarthritis has been observed, with possible therapeutic implications (Al-Mossawi et al., 2017). GM-CSF–producing autoreactive $CD4^+$ T cells have been identified in type 1 diabetes patients (Knoop et al., 2018).

A GM-CSF–producing B cell population, termed innate response activator B cells, has been identified and appears capable of protecting against sepsis and pneumonia (Rauch et al., 2012; Weber et al., 2014; Hamilton et al., 2017). Patients with multiple sclerosis (MS) have been reported to have elevated numbers of GM-CSF–secreting B cells (Li et al., 2015). Splenic ILCs release GM-CSF, thereby coopting neutrophils, leading to increased antibody production from marginal zone B cells (Magri et al., 2014). These unexpected links to B cell biology could be beneficial when fighting infections but are potentially detrimental in chronic inflammatory and/or autoimmune diseases (Hamilton et al., 2017). GM-CSF–producing ILCs can initiate experimental autoimmune arthritis and are present in the inflamed joints of RA patients (Hirota et al., 2018). $IL\text{-}17A^+$ $GM\text{-}CSF^+$ neutrophils have been reported to be the major infiltrating cells in interstitial lung disease in an autoimmune arthritis model (Kwon et al., 2018), while basophils are believed to have a role in lung macrophage imprinting via their GM-CSF production (Cohen et al., 2018).

In contrast, in line with resident tissue cells being potential GM-CSF sources (Hamilton, 1993a,b, 2008), GM-CSF production by fibroblast-like synoviocytes helps initiate experimental autoimmune arthritis (Hirota et al., 2018), and its expression by cardiac fibroblasts has been implicated in the pathogenesis of Kawasaki disease (Stock et al., 2016) as well as in experimental autoimmune myocarditis and myocardial infarction (Chen et al., 2018). Epithelial cells have been proposed to produce GM-CSF in response to allergenic stimuli as a critical early signal during allergic sensitization (Willart et al., 2012; Sheih et al., 2017).

To help understand mechanisms governing the chronicity of certain inflammatory/autoimmune reactions, a "CSF network" hypothesis was originally put forward in which there is an interdependent coregulation of GM-CSF with proinflammatory cytokines, such as IL-1 and TNF, as part of a positive feedback loop between monocyte/macrophages and adjacent populations such as fibroblasts, endothelial cells, etc. (Hamilton, 1993a,b, 2002, 2008). This concept has been enlarged to include cytokines, such as IL-23 and IL-6, as components of an autocrine/paracrine network involving macrophages, DCs, and Th cells (Sonderegger et al., 2008; Codarri et al., 2011; Hamilton and Achuthan, 2013). Recently, other positive feedback loops have also been proposed involving GM-CSF in intestinal inflammation, inflammatory-dilated cardiomyopathy, and breast cancer metastasis, with possible implications for disease maintenance and progression (Su et al., 2014; Wu et al., 2014; Pearson et al., 2016).

GM-CSF→CCL17 pathway in inflammation and pain

The chemokine, CCL17 (formerly called thymus and activation-regulated chemokine [TARC]), was originally implicated in the preferential attraction of Th2 lymphocytes and thus considered a M2 cytokine (Alferink et al., 2003); however, it can also attract effector/memory Th1 lymphocytes and regulatory T cells (Iellem et al., 2001; Alferink et al., 2003). It was mentioned above that in monocytes/macrophages, GM-CSF dramatically up-regulates CCL17 formation in an IRF4- and JMJD3-dependent manner (Achuthan et al., 2016). This pathway appears to be important in controlling GM-CSF–mediated inflammatory arthritis and associated pain, as well as GM-CSF–driven inflammatory pain (Achuthan et al., 2016; Fig. 1). This new GM-CSF→CC17 pathway appears to be active in RA patients, since circulating CCL17 levels dramatically decline upon anti–GM-CSFR therapy (Guo et al., 2019). More recently it has been reported that the GM-CSF→CCL17 pathway can be linked with TNF activity (Cook et al., 2018b; Fig. 1) as well as regulate experimental osteoarthritic pain and optimal disease as judged by histology score (Lee et al., 2018). The latter data led to a clinical trial in hand osteoarthritis (OA) using a CCL17 inhibitor (ClinicalTrials.gov identifier NCT03485365; Conaghan et al., 2019).

CCL17 may not necessarily be acting as a T cell chemokine in its control of inflammation and its associated pain; i.e., it appears that CCL17 has other, hitherto undefined, functions (Weber et al., 2011; Heiseke et al., 2012; Cook et al., 2018b; Lee et al., 2018). In this connection CCL17-driven inflammatory pain is cyclooxygenase 2 dependent, suggesting eicosanoid involvement (Fig. 1; Achuthan et al., 2016). There are conflicting data as to whether the CCL17 receptor, CCR4, is expressed in neurons (Oh et al., 2001; Thakur et al., 2014; Li et al., 2016; Cook et al., 2018a); such expression would indicate the possibility of their direct activation by CCL17. Human microglial cells have been reported to express CCR4 (Etemad et al., 2012), suggesting that CCL17 could act at this level in pain development; however, blockade of arthritic pain by systemic anti-CCL17 mAb administration suggests a peripheral algesic action of CCL17, at least in the models studied (Achuthan et al., 2016; Cook et al., 2018a; Lee et al., 2018). Intriguingly, as regards the role of CCL17 in inflammation, CCL17 depletion can result in regulatory T cell expansion in atherosclerosis and colitis models, leading to disease reduction (Weber et al., 2011; Heiseke et al., 2012).

GM-CSF biology: Current issues and questions

Monocytes, macrophages, and DC biology

There has been recent debate as to whether GM-CSF can give rise to monocyte-derived DCs (MoDCs) in vivo (Greter et al., 2012; Ko et al., 2014; Louis et al., 2015; Chow et al., 2016; Hamilton et al., 2017), even though GM-CSF, often in combination with IL-4, is widely used to generate in vitro murine and human DC populations from bone marrow precursors and blood monocytes, respectively (Inaba et al., 1992; Suzuki et al., 2004a; Conti and Gessani, 2008; van de Laar et al., 2012). However, cell populations derived by GM-CSF in mouse bone marrow cultures are heterogeneous (Lari et al., 2007; Helft et al., 2015; Na et al., 2016; Rogers et al., 2017; Erlich et al., 2019), and their nomenclature is debated as to whether they should be called DCs or macrophages (Lacey et al., 2012; Hume et al., 2013; Xue et al., 2014; Erlich et al., 2019). The in vivo counterparts of these various in vitro–generated populations need to be better defined. Perhaps varying levels of GM-CSF to which responding cells are exposed in the different in vitro and in vivo studies contribute to the phenotypes of the resulting populations (Jiao et al., 2014; Sun et al., 2018). It has been proposed that the effector functions of GM-CSF–expanded myeloid cells in vivo are influenced by their tissue microenvironment (Spath et al., 2017).

In the EAE model of MS, it was concluded that GM-CSF responsiveness was required in Ly6C^{hi} CCR2^{+} monocytes infiltrating the central nervous system before their differentiation into MoDC (Croxford et al., 2015a); however, it was concluded that GM-CSF initiates mouse cardiac disease in resident tissue macrophages (Stock et al., 2016). Murine CD103^{+} DCs from different tissues have distinct functional activities; there has been disagreement about the contribution of GM-CSF in their development in vivo (King et al., 2010; Edelson et al., 2011; Greter et al., 2012; Hamilton et al., 2017), with varying levels of GM-CSF perhaps helping to explain the discrepancies across different studies (Jiao et al., 2014).

In chronic inflammation and autoimmunity, myeloid populations (for example, monocyte/macrophages and neutrophils) are the cell populations that are potentially responsive to GM-CSF; they are thus likely candidates to be regulating tissue damage and inflammation, being capable of releasing mediators, such as cytokines, chemokines, proteases, and reactive oxygen species, as part of this response (Hamilton, 2008; Croxford et al., 2015a,b; Achuthan et al., 2016; Becher et al., 2016). Consistent with a role in autoimmunity/inflammation, GM-CSF upregulates class II MHC (Alvaro-Gracia et al., 1989; Hornell et al., 2003; Achuthan et al., 2018) and CD1 expression (Kasinrerk et al., 1993; Reynolds et al., 2016) in human monocytes in vitro. Even though increased mRNA expression for TNF, IL-1β, and IL-6 is noted in GM-CSF–treated monocytes/macrophages in vitro, unlike for CCL17 mentioned above (Achuthan et al., 2016), significant cytokine secretion usually requires another stimulus, such as LPS (Hart et al., 1988; Achuthan et al., 2016; Borriello et al., 2017). Based only on the increased expression of such proinflammatory cytokines, GM-CSF–treated monocytes/macrophages have been termed "M1-like" (Fleetwood et al., 2007), but such cells have also been viewed to have features of both M1 and M2 cells (Willart et al., 2012; Däbritz, 2015). It has been recommended that M1/M2 polarization nomenclature not be applied to GM-CSF–treated monocytes/macrophages (Lacey et al., 2012; Murray et al., 2014; Achuthan et al., 2016; Hamilton et al., 2017).

Endogenous mediators can contribute to the phenotypes of GM-CSF–treated monocytes/macrophages (Lacey et al., 2012). GM-CSF–induced polarization (Sierra-Filardi et al., 2011; Lacey et al., 2012) and PPARγ expression (Nieto et al., 2018) in human monocytes in vitro have been reported to be modulated by endogenous activin A. Likewise, endogenous TGF-β has also been invoked to have a similar role in the development and homeostasis of alveolar macrophages (Yu et al., 2017). CSF-1 could be another endogenous mediator contributing to the phenotype of GM-CSF–treated human monocytes. Since mediators involved in the host inflammatory response to injury and/or infection are likely to be endeavoring to be beneficial by restoring homeostasis (see below), it is important to explore such a role for GM-CSF in its action on monocytes/macrophages.

The gene expression profile of human monocytes differentiated for 7 d in GM-CSF has been compared with that for the corresponding population treated with another CSF, namely CSF-1 (M-CSF; Lacey et al., 2012). Their profiles differed substantially, and they also displayed distinct bioenergetic profiles (Izquierdo et al., 2015). CSF-1 could be another endogenous mediator contributing to the phenotype of GM-CSF–treated human monocytes (Hamilton, 1994). Since in the steady state, monocytes/macrophages are in general likely to be exposed to CSF-1, it has been proposed that proinflammatory stimuli, such as GM-CSF, IFNγ, and LPS, lead to a cellular state of CSF-1 "resistance" or compromised CSF-1 signaling (Hamilton, 2008).

Neutrophils and eosinophils

GM-CSF can up-regulate neutrophil properties such as their survival, adhesion and trafficking, oxidative burst, phagocytosis, and formation of extracellular traps (Yong et al., 1992; Yousefi et al., 2009; Cowburn et al., 2011; Goldmann and Medina, 2013; Wright et al., 2013). Again, whether prosurvival/developmental or activation/polarization responses are more important in vivo may depend on the context and GM-CSF concentration. Likewise, many aspects of eosinophil biology, including their development, survival, activation, and migration, have been suggested to be controlled by GM-CSF in inflammation (Curran and Bertics, 2012; Griseri et al., 2015; Liu et al., 2015; Willebrand and Voehringer, 2016; Nobs et al., 2019).

GM-CSF, nervous system, and pain

GM-CSF has neuroprotective effects in models of neurological diseases and injury which have been proposed to be a result of direct action of GM-CSF on neurons (Schäbitz et al., 2008; Kelso et al., 2015). GM-CSFR has been reported to be expressed on neurons (Schweizerhof et al., 2009; Stösser et al., 2011; Ridwan et al., 2012; Bali et al., 2013) and to sensitize nerves to mechanical stimuli via a direct action on neurons (Schweizerhof et al., 2009; Zhang et al., 2019). However, such expression has been questioned (Cook et al., 2018a; Nicol et al., 2018), and interestingly, in one model of GM-CSF–driven arthritic pain, a cyclooxygenase inhibitor could block such pain, suggesting the involvement of

eicosanoids (Cook et al., 2013). Further research is needed to clarify how GM-CSF interacts with the nervous system.

GM-CSF administration and targeting in preclinical models

Autoimmune/inflammatory disease models, in which GM-CSF levels are modulated, potentially offer answers to some of the questions raised above in the context of pathology and can be used to test the concepts proposed above. Since the effects of GM-CSF administration, depletion, or gene deletion in preclinical models of inflammatory and autoimmune disease have been reviewed recently (Hamilton, 2015; Becher et al., 2016; Wicks and Roberts, 2016; Hamilton et al., 2017), these topics will be briefly summarized below; however, very recent studies around these topics are incorporated into the review.

GM-CSF can exacerbate certain inflammatory/autoimmune disease models (Campbell et al., 1997; Bischof et al., 2000; Llop-Guevara et al., 2014; van Nieuwenhuijze et al., 2014); however, its administration can also improve outcomes (Hamilton, 2008; Ganesh et al., 2009; Egea et al., 2010; Hamilton and Achuthan, 2013; Alnek et al., 2015; Bhattacharya et al., 2015; Dougan et al., 2019), with the promotion of tolerogenic DCs being the proposed mechanism (Ganesh et al., 2009; Alnek et al., 2015). Conflicting roles for GM-CSF have been observed in different pulmonary fibrosis models, with its administration either promoting or ameliorating the condition (reviewed in Fleetwood et al., 2005). It is worth pointing out again that, even though it may do so, the effect of high doses of systemically administered GM-CSF on a particular disease may not necessarily inform about the role of endogenous ligand in that condition (Hamilton, 2008; Hamilton et al., 2017).

GM-CSF genetic deletion or mAb blockade was initially found to ameliorate inflammatory arthritis and EAE(Campbell et al., 1998; Cook et al., 2001; McQualter et al., 2001; Yang and Hamilton, 2001). These strategies have subsequently been effective in inflammatory and autoimmune models, including skin inflammation (Schön et al., 2000; Samavedam et al., 2014; Scholz et al., 2017), lung inflammation and chronic obstructive pulmonary disease (Bozinovski et al., 2002; Yamashita et al., 2002; Cates et al., 2004; Vlahos et al., 2006; Shiomi et al., 2014; Nobs et al., 2019), renal injury/nephritis (Kitching et al., 2002; Timoshanko et al., 2005), peritonitis (Cook et al., 2003, 2004), EAE and neuroinflammation (Ponomarev et al., 2007; Codarri et al., 2011; El-Behi et al., 2011; Ifergan et al., 2017; Sterner et al., 2019), cardiovascular disease (Shaposhnik et al., 2007; Ye et al., 2013; Hilgendorf et al., 2014; Stock et al., 2016; Wu et al., 2016; Anzai et al., 2017), colitis (Khajah et al., 2011; Griseri et al., 2015; Song et al., 2015; Kabat et al., 2016), arthritis (Greven et al., 2015; van Nieuwenhuijze et al., 2015), periodontal disease (Lam et al., 2015), dry eye disease (Dohlman et al., 2017), graft-versus-host disease (Tugues et al., 2018), and autoimmune prostatitis (Liu et al., 2019). This area has been reviewed in Hamilton (2008); Hamilton (2015); Hamilton and Achuthan (2013); Hamilton et al. (2017); and Wicks and Roberts (2016). Of course, data obtained using the *Csf2*$^{-/-}$ mouse may not necessarily parallel that resulting from a neutralizing mAb strategy. As mentioned earlier, GM-CSF is implicated in the regulation of inflammatory and arthritic pain via its regulation in turn of CCL17 (Achuthan et al., 2016; Cook et al., 2018b; Lee et al., 2018).

In contrast to studies indicating benefit in models of atherosclerosis (Shaposhnik et al., 2007; Hilgendorf et al., 2014) and colitis (Khajah et al., 2011; Griseri et al., 2012, 2015; Song et al., 2015; Kabat et al., 2016), exacerbations have been noted when GM-CSF neutralization/deletion strategies were adopted for these indications (Ditiatkovski et al., 2006; Xu et al., 2008; Hamilton et al., 2017). Also, aged GM-CSF–deficient mice have been shown to develop a systemic lupus erythematosus–like disorder associated with impaired phagocytosis of apoptotic cells (Enzler et al., 2003). As mentioned elsewhere (Hamilton, 2015), any conflicting model-specific findings are likely to be due to different pathogenic mechanisms and/or variation in the degree of GM-CSF depletion (Khajah et al., 2011).

GM-CSF and preclinical models: Perspectives for clinical studies

It is apparent from the data obtained from preclinical models that GM-CSF can be a key driver of tissue inflammation and its associated pain, acting mainly on myeloid cell numbers and/or function locally but also perhaps systemically. In addition to being able to preferentially control putative moDC numbers in antigen-induced mouse peritonitis, GM-CSF could regulate macrophage numbers in the inflamed peritoneal cavity (Cook et al., 2004, 2016; Louis et al., 2015). Whether this regulation of monocyte-derived populations was due to effects of GM-CSF on cell trafficking in or out of a lesion and/or cell survival or even proliferation is unknown (Louis et al., 2015; Cook et al., 2016), although effects on survival in other inflammatory/autoimmune models have been discounted (Ko et al., 2014; Stock et al., 2016). Interestingly, in this context, it has been suggested that GM-CSF controls mouse DC survival in nonlymphoid tissues as the mechanism for their homeostasis (Greter et al., 2012). There is also evidence that during an inflammatory response, GM-CSF may act systemically to promote hemopoietic cell mobilization and development (King et al., 2009; Cook et al., 2011; Griseri et al., 2012; Wang et al., 2014; Stock et al., 2016), as well as the monocytosis that can be observed (Hamilton and Tak, 2009).

Given the potentially wide range of lymphoid and nonlymphoid cellular sources of GM-CSF, human conditions that involve acquired and/or innate immunity could fall within the realm of GM-CSF influence. Nevertheless, presumably like other similar mediators responding to insult or infection, GM-CSF will be endeavoring to restore homeostasis. Evidence for this lies in the beneficial role of GM-CSF in PAP and possibly in Crohn's disease and atherosclerosis. Therefore, as for all cytokine antagonists, careful monitoring of relevant parameters, such as lung function in this case, is needed in any clinical assessment of GM-CSF targeting.

Clinical studies targeting GM-CSF and its receptor

As a result of some of the basic biology outlined above and GM-CSF expression in the particular human condition, a number of clinical trials using neutralizing mAbs to target GM-CSF or its

Table 1. **The most recent clinical trials targeting GM-CSF or its receptor in inflammatory/autoimmune disease**

Target	Molecule	Company	Indication	Phase	Status	ClinicalTrials.gov identifier	Reference
GM-CSFR	Mavrilimumab/KPL-301 (previously CAM-3001)	MedImmune	RA	IIb	Completed	NCT01706926	Burmester et al., 2017
			RA	IIb	Completed	NCT01715896	Guo et al., 2018; Weinblatt et al., 2018
			RA	II (OLE)	Terminated	NCT01712399	Burmester et al., 2018
		Kiniksa	GCA	II	Recruiting	NCTC5827018	
GM-CSF	GSK 3196165/Otilimab (previously MOR103)	GSK	RA	IIb	Completed	NCT02504671	
			RA	IIa	Completed	NCT02799472	Genovese, M.C., et al. 2018. ACR/ARHP Annual Meeting. Abst. 2510.
			RA	III	Recruiting	NCT03970837	
			RA	III	Recruiting	NCT03980483	
			Hand OA	IIa	Completed	NCT02683785	Schett, G., et al. 2018. ACR/ARHP Annual Meeting. Abst. 1365.
	Namilumab (previously MT203)	Takeda	RA	Ib	Completed	NCT01317797	Huizinga et al., 2017
			RA	II	Terminated	NCT02393378	
			RA	II	Completed	NCT02379091	Taylor et al., 2019
			Plaque psoriasis	II	Completed	NCT02129777	Papp et al., 2019
		Izana Bioscience	Axial SpA	IIa	Recruiting	NCT03622658	
	Lenzilumab (previously KB003)	Humanigen	Asthma	II	Completed	NCT01603277	Molfino et al., 2016
	TJM2	I-Mab Biopharma		I	Recruiting	NCT03794180	

GCA, giant cell arteritis; SpA, spondyloarthritis.

receptor in inflammatory/autoimmune diseases have been performed and are continuing. Since many of these trials have been reviewed recently (Hamilton, 2015; Wicks and Roberts, 2016; Hamilton et al., 2017; Cook and Hamilton, 2018), a short summary of this information is provided below as well as information on the most recent human studies (Table 1).

Mavrilimumab (KPL-301)

Mavrilimumab (formerly known as CAM-3001) is an IgG4 mAb that was developed by MedImmune against the α-chain of the GM-CSFR. Early small and short-term trials in RA were encouraging (Burmester et al., 2011, 2013; Takeuchi et al., 2015). A subsequent 24-wk, phase IIb, randomized, double-blind, dose-escalating, placebo-controlled study (ClinicalTrials.gov identifier NCT01706926) was performed in RA patients (n = 326) and on background methotrexate (Burmester et al., 2017; Table 1). Mavrilimumab treatment significantly resulted in greater reductions from baseline in the DAS28-CRP score at week 12 and a greater percentage of ACR20 responders at week 24. The highest dose (150 mg) was most effective, and the safety profile was acceptable.

A 24-wk randomized, double-blind, phase IIb exploratory study (ClinicalTrials.gov identifier NCT01715896) compared the efficacy and safety of mavrilimumab with golimumab (anti-TNF mAb), on top of methotrexate in RA patients (n = 68; Guo et al., 2018; Weinblatt et al., 2018; Table 1). Once again, efficacy and an acceptable safety profile were noted. Peripheral biomarkers and pathophysiological pathways modulated by mavrilimumab and golimumab were also assessed in the study. A number of mediators were suppressed by both mAbs. Interestingly, in the context of the GM-CSF→CCL17 pathway discussed above, serum levels of CCL17 and CCL22 (macrophage-derived chemokine [MDC]), which share CCR4 as a common receptor, were suppressed only by mavrilimumab, and only mavrilimumab was able to induce sustained differential suppression of peripheral disease markers in anti-TNF–inadequate responders. The authors concluded that mavrilimumab treatment, but not treatment with golimumab, may lead to greater long-term disease control in anti-TNF–inadequate responders (Guo et al., 2018).

The long-term efficacy and safety of mavrilimumab has been explored in an open-label extension (OLE) study (ClinicalTrials.gov identifier NCT01712399) in RA patients (n = 442;

Burmester et al., 2018; Table 1). The median duration of mavrilimumab treatment was 2.5 yr, and the cumulative safety exposure was 899 patient-years. No new safety signals were seen, and long-term mavrilimumab treatment was also associated with clear and sustained benefits in measures of RA disease outcomes (Burmester et al., 2018). In this OLE study, biomarker analyses confirmed the sustained suppression of CCL17 and CCL22 in mavrilimumab-treated patients over a longer follow-up period, supporting the hypothesis of a special link of these mediators to GM-CSF. A new trial (ClinicalTrials.gov identifier NCT05827018) with mavrilimumab/KPL-301 is recruiting patients with giant cell arteritis (Table 1).

GSK3196165/otilimab

GSK3196165 (formerly known as MOR-103) is an IgG1 mAb developed by MorphoSys AG that binds to GM-CSF and prevents its interaction with GM-CSFRα. A short-term phase I/II study in RA patients (n = 96; ClinicalTrials.gov identifier NCT01023256) showed MOR103 to be well tolerated, with evidence of rapid and sustained efficacy. More recent phase IIa/IIb trials in RA patients assessing the efficacy and safety of GSK3196165, in combination with methotrexate (ClinicalTrials.gov identifiers NCT02504671 and NCT02799472; Table 1) have been performed; clinical efficacy with consistent improvement in magnetic resonance imaged synovitis was observed, and the reagent was well tolerated, with no significant adverse effects (Genovese, M.C., et al. 2018. ACR/ARHP Annual Meeting. Abst. 2510). Circulating CCL17 levels declined only in the GSK3196165 group, again supporting the existence of the GM-CSF→CCL17 pathway in humans. Encouragingly, GSK has just announced the start of a phase III clinical development program (ContRAst) with otilimab in RA patients who have had an inadequate response to disease-modifying antirheumatic drugs or targeted therapies. This program includes ContRAst-1 (NCT03970837) and ContRAst-2 (NCT03980483; Table 1).

The results of an exploratory, 12-wk, phase IIa study of GSK3196165 in subjects with hand OA (n = 44; ClinicalTrials.gov identifier NCT02683785) have been reported, and, while not statistically significant, reductions in pain, accompanied by improvement in functional impairment, were noted (Schett, G., et al. 2018. ACR/ARHP Annual Meeting. Abst. 1365).

A phase Ib study (NCT0151782; Constantinescu et al., 2015) with GSK3196165 has been performed in patients with MS to investigate drug safety; the treatment was generally well tolerated in individuals with relapsing-remitting MS and secondary progressive MS. Given the encouraging data targeting GM-CSF in EAE (McQualter et al., 2001; Ponomarev et al., 2007; Codarri et al., 2011; El-Behi et al., 2011; Ifergan et al., 2017) and the elevated GM-CSF expression in MS patients (Carrieri et al., 1998; Noster et al., 2014; Rasouli et al., 2015), as well as the link between GM-CSF and central nervous system–invading monocyte-derived cells in EAE (Croxford et al., 2015a), it has been argued that blocking GM-CSF in MS patients might be efficient in reducing MS relapses (Croxford et al., 2015b).

Namilumab

Namilumab (formerly known as MT203), an IgG1-neutralizing anti–GM-CSF mAb, has been investigated in a double-blind, placebo-controlled, randomized, dose-escalating phase Ib study in RA patients (n = 24; ClinicalTrials.gov identifier NCT01317797; Table 1). It was generally well tolerated, with demonstrable preliminary efficacy (Huizinga et al., 2017). Another RA (phase II) trial was terminated (ClinicalTrials.gov identifier NCT02393378). The findings of a phase II, randomized, double-blind, placebo-controlled, dose-escalating, 12-wk trial in RA patients (n = 108; ClinicalTrials.gov identifier NCT02379091) have just been reported (Table 1; Taylor et al., 2019). The study met its primary endpoint, with a clear dose–response effect and an acceptable tolerability profile. There were no notable changes from baseline of cell types known to demonstrate GM-CSF responsiveness. A phase II, randomized, double-blind, placebo-controlled trial in plaque psoriasis (ClinicalTrials.gov identifier NCT02129777; Table 1) has been completed but concluded that GM-CSF blockade is not critical for the suppression of key inflammatory pathways underlying psoriasis (Papp et al., 2019). Patients are being recruited for a phase IIa trial using namilumab in axial spondyloarthritis (ClinicalTrials.gov identifier NCT03622658; Table 1).

Lenzilumab

When known as KB003, lenzilumab, an IgG1-neutralizing anti–GM-CSF mAb, was tested in a randomized phase II trial in RA (ClinicalTrials.gov identifier NCT00995449) which was terminated due to a program refocus. A phase II, randomized, double-blind, placebo-controlled, 24-wk study in asthma patients (n = 311; ClinicalTrials.gov identifier NCT01603277; Table 1) has been performed; overall, there were no effects on asthma control or exacerbation rates, although there were improvements in patients with eosinophilic asthma (Molfino et al., 2016). As indicated (Molfino et al., 2016), further studies are required to select a dose and a candidate asthma phenotype for evaluating the role of GM-CSF in severe asthma or other airway conditions. A phase I trial using lenzilumab in patients with chronic myelomonocytic leukemia has been completed (ClinicalTrials.gov identifier NCT02546284).

TJM2

TJM2 is an IgG1-neutralizing anti–GM-CSF mAb, and a phase I trial has commenced (ClinicalTrials.gov identifier NCT63794180; Table 1).

Clinical studies targeting GM-CSF activity: Perspectives

As for the targeting of all inflammatory mediators, safety concerns must be high on the agenda. Encouragingly, no serious adverse events have been noted so far, even as regards infections and compromised lung function, with the data from the long-term OLE study in RA patients being particularly encouraging (Burmester et al., 2018). Unlike TNF targeting, no increase in tuberculosis has been noted. As mentioned, idiopathic autoimmune PAP is characterized by high levels of anti–GM-CSF autoantibodies (Uchida et al., 2009); these can be divided into five distinct groups with nonoverlapping GM-CSF binding epitopes

(Wang et al., 2013). Of relevance to potential safety issues surrounding GM-CSF targeting, unlike polyclonal anti–GM-CSF Abs, single neutralizing anti–GM-CSF mAbs may not be harmful, since they may not be effective as polyclonals in reducing the amount of bioavailable GM-CSF in vivo (Piccoli et al., 2015). Continued monitoring of potential side effects is still warranted, including those related to any compromised lung and gut function.

As regards efficacy, it appears so far that GM-CSF targeting has therapeutic potential in RA and perhaps in some forms of asthma. It may have particular benefit in controlling inflammatory pain (for example, that associated with OA; Conaghan et al., 2019). It could be that CCL17 may be a useful biomarker (Burmester et al., 2018) to aid in patient selection as well as provide clues as to the identity of relevant downstream pathways, with implications for possible additional therapeutic strategies. It would be useful to know whether targeting either GM-CSF or GM-CSFR can be differentiated; so far, the clinical data in RA patients look similar for these strategies, and the data are similar in mouse arthritis and inflammation models (Cook et al., 2016). It would also be useful to know whether such targeting will be effective in patients who are responsive or not to therapies that target other inflammatory mediators, such as TNF and IL-6. Obviously, larger trials are needed in RA and for other potential indications.

Clinical studies with GM-CSF administration

When given to patients with Felty's syndrome to correct the neutropenia, GM-CSF exacerbated their arthritis (Hazenberg et al., 1989), data paralleling those in murine models (Campbell et al., 1997; Bischof et al., 2000; Llop-Guevara et al., 2014; van Nieuwenhuijze et al., 2014). There are studies suggesting that intestinal inflammation in Crohn's disease may result from a primary deficiency of innate immunity (Korzenik, 2007). Elevated endogenous GM-CSF antibody levels are associated with increased rates of stricturing behavior and surgery in Crohn's disease (Gathungu et al., 2013) and can predict the recurrence of inflammatory bowel disease (Däbritz, 2015), even though higher levels of GM-CSF secretion have been detected in patients with inflammatory bowel disease (Ina et al., 1999; Noguchi et al., 2001). Based in part on these studies, the safety and efficacy of recombinant GM-CSF (sargramostim) has been evaluated in Crohn's disease patients (Däbritz, 2014). Even though benefit has been reported in some patients, a Cochrane review demonstrated that sargramostim does not appear to be more effective than placebo for remission induction; further studies are needed to enable a final verdict (Roth et al., 2012).

As regards cancer, out of a number of proinflammatory mediators tested, only GM-CSF most effectively induced long-lasting, specific antitumor immunity in a tumor vaccine model for melanoma (Dranoff et al., 1993). That seminal paper led to the subsequent clinical development of GM-CSF–secreting tumor vaccines, the idea being to transduce live tumor cells to secrete GM-CSF, thus delivering a proinflammatory mediator along with a variety of tumor-associated antigens. Encouraging clinical data appear when this type of strategy is used in combination with other immunotherapy such as anti-CTLA4 (ipilimumab) or anti–PD-1 mAb (pembrolizumab; Hodi et al., 2014; Andtbacka et al., 2015; Puzanov et al., 2016). As noted above for preclinical models, the effect of systemically administered, high-dose GM-CSF on a particular condition may or may not be predictive of the effect of suppressing endogenous GM-CSF activity (Hamilton, 2008; Hamilton et al., 2017).

Concluding remarks and future perspectives

It would appear from the above that GM-CSF–dependent inflammatory pathways in monocytes (and macrophages), as well as in neutrophils and eosinophils, are likely to be critical for the purported role of GM-CSF in inflammation, pain, autoimmunity, and host defense. The available GM-CSF levels in an inflamed tissue at a particular time point may determine the nature of these pathways and whether GM-CSF can overflow into the circulation. Consideration of this parameter may help to resolve some of the issues and questions raised above. Such levels may also impact in turn on the effectiveness and route of administration of an inhibitory therapeutic such as a mAb.

In addition to attempting to summarize the relevant literature on inflammation/autoimmunity and pain, I have tried to highlight some of the contentious issues and questions currently being debated. Such issues, some of which I have endeavored to represent diagrammatically (Fig. 2), are (i) when, how, and at what concentrations GM-CSF controls cell number and/or activation/differentiation (polarization) in vivo; (ii) when and how endogenous GM-CSF can act systemically in addition to locally in tissues; (iii) whether GM-CSF controls MoDC development in vivo; (iv) the nature of GM-CSF–induced cell polarization; (v) whether IRF4- or IRF5-dependent pathways are more important for GM-CSF–dependent biology; and (vi) how relevant are the effects of systemically administered GM-CSF to the actions of endogenous GM-CSF.

As evidenced by the latest basic research literature and clinical trial activity presented in this review, there is burgeoning interest in targeting GM-CSF in inflammatory/autoimmune disorders and for the associated pain. Obviously, determining when and where GM-CSF activity is important and, as for other mediators involved in restoring homeostasis in response to external insults, how to modulate its function without compromising its beneficial effects, will continue to be critical. The uniqueness of the biology surrounding the interaction of GM-CSF with most likely myeloid cells holds promise that targeting GM-CSF could be beneficial and specific for a diverse range of maladies. Again, as for other inflammatory mediators, even when GM-CSF is shown to be involved in progression of a particular disease, biomarkers are needed so that patient stratification can be made to allow more precise use of the appropriate therapy. CCL17 may be such a biomarker. Other useful information for clinical studies, such as when and how (i) GM-CSF regulates cell numbers and/or function, either locally and/or systemically, and (ii) GM-CSF links with other proinflammatory cytokines, hopefully will result from further research.

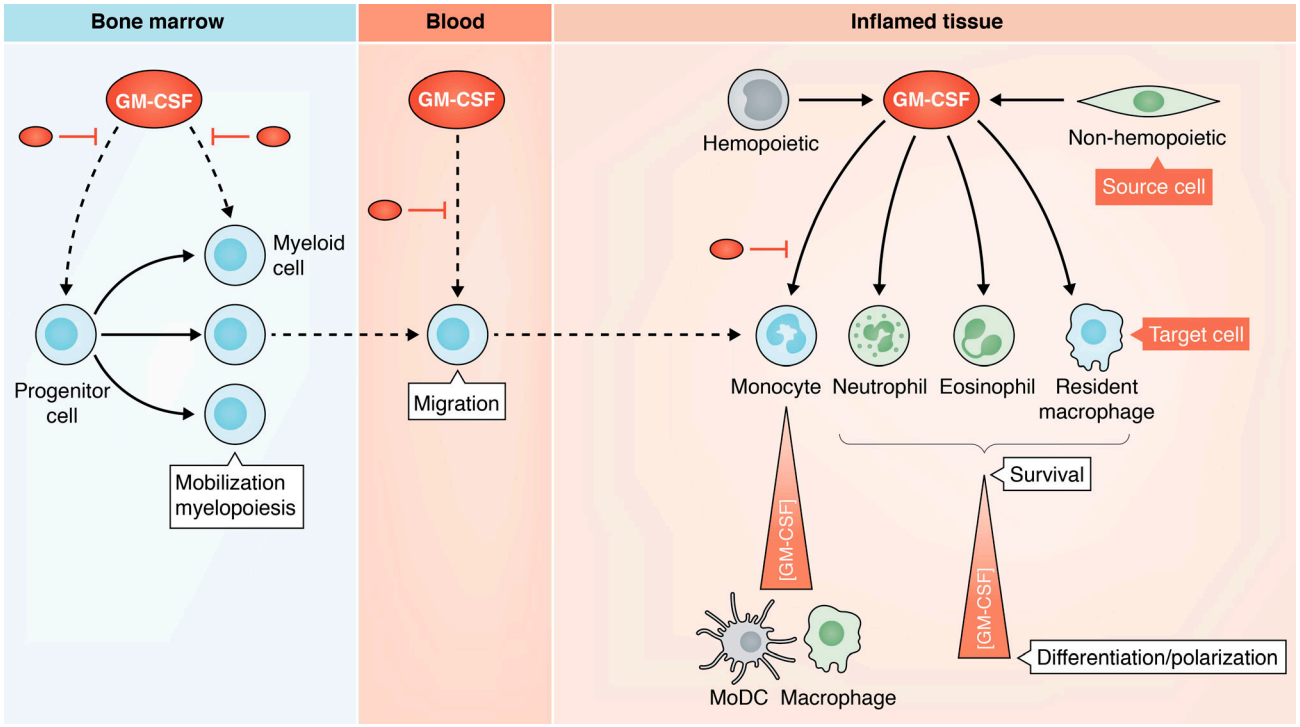

Figure 2. **GM-CSF and control of target cell numbers and function in inflammation.** During an inflammatory reaction, it is likely that the major actions of endogenous GM-CSF are in the inflamed tissue in which GM-CSF can act in a concentration-dependent manner on resident macrophages and/or migrated monocytes, neutrophils, and eosinophils to promote their survival and/or modify their differentiation/polarization, such as the maturation of the monocytes into MoDCs and macrophages. Myeloid cell trafficking in (or out) of the inflamed tissue may also be under GM-CSF control. The cell differentiation/polarization can be characterized by the production of proinflammatory mediators such as cytokines, chemokines, proteases, reactive oxygen species, etc. (not shown); monocyte/macrophages may also proliferate (not shown). The tissue-derived GM-CSF may also act systemically in the blood and/or bone marrow, either directly or indirectly via its cellular targets in the tissue (not shown), to activate myeloid cells in the blood before their migration into the inflamed tissue and contribute to this migration; it may contribute as well as to myeloid mobilization/cell migration from the bone marrow, where it may also promote lineage-specific myelopoiesis from progenitor cells. Whether the particular highlighted actions of GM-CSF operate is currently debated and is likely to depend on the nature of the inflammatory reaction and the levels of GM-CSF attained from hemopoietic (e.g., lymphocyte) and nonhemopoietic (e.g., fibroblast) cell populations. GM-CSF targeting (depicted by inhibitory lines) could occur locally in the inflamed tissue and systemically to control disease.

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