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A Comprehensive Study On The Role Of GM-CSF In Various Diseases

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Abstract

Granulocyte macrophage-colony stimulating factor (GM-CSF), a cytokine, was first discovered to have the ability to stimulate bone marrow progenitors' proliferation and differentiation into granulocytes and macrophages in vitro. Numerous preclinical studies have shown that GM-CSF affects myeloid cells in a variety of tissues, and GM-CSF deletion/depletion studies suggest that it may be a significant therapeutic target in a number of inflammatory and autoimmune diseases, including rheumatoid arthritis. This review is a comprehensive approach to understandthe structure and biology of GM-CSF, its role in different diseases like inflammatory, infectious and autoimmune disorders, beneficial and contradictory effects etc.

Keywords: Granulocyte macrophage-colony stimulating factor, preclinical studies, autoimmune diseases, rheumatoid arthritis,

Introduction

Granulocyte macrophage-colony stimulating factor (GM-CSF, CSF2) was initially classified as a hemopoietic growth factor because of its capacity to induce the proliferation and differentiation of bone marrow progenitor cells to produce granulocyte and macrophage colonies in vitro[1]. The first instance of granulocyte-macrophage colony-stimulating factor (GM-CSF, or CSF2) was found in the conditioned medium of mouse lung tissue after LPS injection, which induced the growth of bone marrow-derived macrophages and granulocytes [2]. Activated T cells, B cells, macrophages, monocytes, mast cells, vascular endothelial cells, and fibroblasts are just a few of the cell types that can create GM-CSF[3]. It has the capacity to control a wide range of cellular processes, including the growth of dendritic cells, the differentiation of macrophages and granulocytes, and the preservation of homeostasis.It binds precisely to its receptor, which is made up of a beta-chain shared with the interleukin-3 and interleukin-5 receptors and an alpha-chain exclusive to the cytokine (GM-CSF receptor alpha-chain, GMR) [4]. Granulocytes and macrophages are guided in their early growth by GM-CSF. It is essential to their development and activation, assisting the body in protecting itself from threats from within and outside, and demonstrating the incredible resilience of cells. This pivotal function in immune regulation sustains a symbiotic equilibrium that gives the body the tools it needs to face challenges while preserving stability[5,6].

Structure of GM CSF

The 2377 bp long GM-CSF gene has four exons and three introns. The 144 amino acid long, 22 KDa molecular weight GM-CSF protein is encoded by a transcript with a length of 783 bp. The human cDNA clone's single long open reading frame generates a mature protein with 127 amino acids by combining a

precursor protein with 144 amino acid residues and a 17 amino acid signal peptide. It is a small, globular protein with -helical and -sheet structures, as well as four cysteine residues that create two disulfide bonds. Depending on the type of cells from which it originates, it is an acidic glycoprotein with a molecular mass of 18,000–30,000 and an isoelectric point that ranges from 4.0 to 5.2.

The GM-CSF structure in ternary complex was discovered to be a 2:2:2 hexamer made up of two c chains, two GMR chains, and two GM-CSF molecules[7]. Given that the GM-CSF receptor complex exhibits a protein concentration-dependent shift in molecular weight and consequently stoichiometry, this is most likely due to variations in the total protein concentration at which the complex is formed. Rozwarski et al. first reported a similar arrangement in the year 1996. The structure of the isolated cytokine[8] and the structure adopted by GM-CSF in the ternary complex appear to be extremely similar. The structure of the isolated c subunit[9] revealed the identical tangled c homodimer.Domain 4 has rotated 3° towards the crystallographic diad that runs through the centre of the hexameric complex [10] when comparing the complex's c chain to the structure of the isolated molecule. Although the conformation of the linker area closely mimics that seen in the isolated molecule, the hinge region about which the rotation has happened is positioned near to domain 1 in the linker region joining domains 3 and 4. Two cytokine receptor homology modules (CRMs), which themselves are made up of two fibronectin type III (FnIII) domains, make up each c chain. The N-terminal "knob" domain is followed by one CRM in the GMR chain.However, we only detect a strong electron density for the GMR domain 2's C-terminal FnIII domain. Although the N-terminal FnIII domain (GMR domain 1) has a lower quality electron density, it was nevertheless sufficient to identify the core sheet, allowing for the construction and improvement of a partial model.

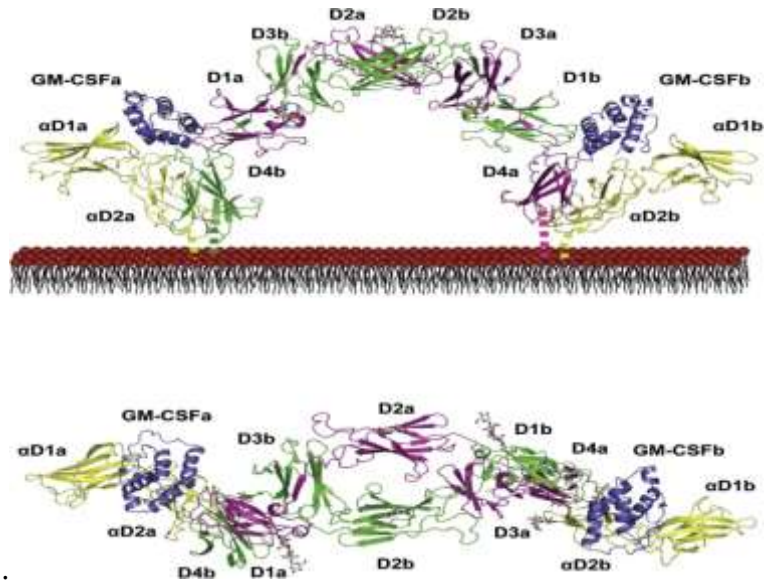

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Figure 1 Structure of the GM-CSF Receptor Ternary Complex
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Biology of GM CSF

The multimeric GM-CSFR, which consists of a signal-transducing subunit that is shared by the interleukin-3 (IL-3) and IL-5 receptors and a particular low-affinity ligand-binding subunit, binds to GM-CSF. When GM-CSFR is activated, two pathways are activated: (i) the MEK/ERK, phosphatidylinositol 3-kinase (PI3K), and NF-B pathways13; and (ii) the Janus Kinase (JAK) 2 and Janus Kinase (JAK) 2 [7,11,12]pathways. This commonly results from the phosphorylation of the GM-CSFR subunit, which then binds STAT5. Interferon regulatory factor 4 (IRF4), a hemopoietic-specific transcription factor, is a crucial signalling component for the development of dendritic cell (DC)-like characteristics in GM-CSF-treated progenitors, such as monocytes[14,15].It was recently discovered that the GM-CSF/CCL17 axis, which refers to the crucial process by which the stimulation of monocytes and/or macrophages by GM-CSF results in the synthesis of CCL17 via IRF4, occurs in vitro. IRF4 expression is upregulated by GM-CSF in a mechanism that involves increased JMJD3 demethylase activity [16]. Additionally, during in vivo inflammation, GM-CSF-IRF4 signalling promotes the polarisation of pro-inflammatory macrophages and improved antigen presentation capabilities (i.e. higher MHC class II expression) [17]. IRF4 has been thought to play an anti-inflammatory role in macrophages (for example, greater interleukin (IL)-10 and reduced TNF production)[19], but some research suggests that IRF5, but not IRF4, is significant for GM-CSF-induced macrophage polarization[18].

Impact of GM CSF in different disease conditions

Inflammatory Arthritis

Early research assessing cytokines in the blood and synovial fluid of RA patients revealed elevated levels of GM-CSF as well as elevated GM-CSFR expression in inflamed synovial tissue. When GM-CSF was given to RA patients, the condition worsened. According to a genome-wide association analysis, CSF2 (the gene that encodes GM-CSF) mutations contribute to RA genetic vulnerability.[20] It was recently proposed that GM-CSF neutralisation be taken into consideration as a viable therapeutic strategy for the treatment of ankylosing spondylitis, in part due to the priming of blood monocytes with GM-CSF.[21]

It is well established in the literature that GM-CSF has a role in the pathophysiology of experimental inflammatory arthritis. In various inflammatory arthritis models, such as collagen-induced arthritis (CIA), antigen-induced arthritis (AIA), zymosan-induced arthritis (ZIA), and K/BxN serum-transfer arthritis (STA), GM-CSF-deficient mice fail to develop arthritis and related discomfort. In these models, the injection of neutralising GM-CSF mAbs improved the condition of the disease.[22,23] Regarding the significance of GM-CSF in relation to arthritic pain, it has already been stated that GM-CSF regulates inflammatory and arthritic pain via CCL17.24 It's interesting to note that high levels of circulating GM-CSF have been linked to RA patients' receptivity to anti-TNF medications.The reduction in circulating CCL17 levels observed in RA patients receiving anti-GM-CSFR mAb (mavrilimumab) is consistent with the idea of the GM-CSF/CCL17 axis and raises the possibility that CCL17 may serve as a biomarker for anti-GM-CSF or anti-GM-CSFR therapy.[25]

Osteoarthritis

Osteoarthritis (OA) was once thought to be a non-inflammatory arthropathy, but it is now widely acknowledged that there can be a major inflammatory component contributing to OA clinical symptoms, such as chronic pain. In OA synovial tissue, GM-CSF expression and its receptor have been discovered, and they have been shown to be adversely linked with pain.[25] In contrast, GM-CSF-deficient mice were shielded from the discomfort and osteophyte growth associated with an OA model that involved collagenase-induced joint instability.[22] According to these findings, neutralising anti-GM-CSF mAb significantly reduced discomfort in the same model.[22,23] In this model, pain relief was shown whether the neutralising mAb was given early or late, but early administration was necessary for joint injury prevention.[23] Early OA lesions are frequently more characterised by synovial inflammation, which is characterised by macrophage infiltration, whereas late OA is more frequently connected to structural abnormalities (such as cartilage degradation and/or osteophyte production).[26] Given that GM-CSF controls a variety of macrophage activities, it's possible that patients with early OA disease may see the best clinical improvement as opposed to those with advanced OA disease.

Multiple Sclerosis

Demyelination and consequent axonal degradation are hallmarks of the chronic autoimmune/inflammatory disease known as multiple sclerosis (MS), which affects the central nervous system (CNS). Although it is widely accepted that TH17 cells are the primary source of encephalitogenic activity in EAE,[27] the most popular MS model, it has been discovered that their primary secreted cytokine, IL-17, is not necessary for the onset of EAE.[28,29] Instead, it was eventually discovered that the primary cytokine causing encephalitogenicity[30] is GM-CSF released by TH17 cells as a result of activating microglia in the CNS.[31] Tumour necrosis factor (TNF), interleukin (IL)-1, and interleukin (IL)-6 are among the extremely neurotoxic chemicals produced by GM-CSF-activated microglia, which assume an M1-like (inflammatory) phenotype[32].It has been suggested that GM-CSF encourages the blood brain barrier to break down, allowing circulating Ly6Chi monocytes to enter, and accelerates the development of antigen-presenting cells produced from monocytes.These developed cells have a profile that is similar to macrophages reported in active MS lesions [33,34].Additional mice investigations have shown that GM-CSF deletion decreases the number of monocyte-derived cells that migrate into the CNS parenchyma after EAE induction, while GM-CSF injection increases the number of cells that do so.[35] Patients with active MS have been observed to have elevated GM-CSF levels in their cerebrospinal fluid.[36] In mice with EAE, glitiramer acetate, an FDA-approved medication to treat MS, has been demonstrated to increase regulatory T cells and decrease GM-CSF levels.[37] These studies show that GM-CSF is crucial to EAE and suggest that GM-CSF may be a therapeutic target for MS.

Inflammatory Bowel Disease

The two main subtypes of inflammatory bowel disease (IBD) are Crohn's disease (CD) and ulcerative colitis (UC). IBD is a chronic immune-mediated disease that affects the gastrointestinal system.[38] Impairment of

innate immunity is a major pathogenic factor in IBD.[39] In colitis model organisms, GM-CSF has been identified as a crucial mediator of chronic inflammation.[40,41] GM-CSF-deficient mice exhibited more severe colitis, according to other research utilising dextran sodium sulphate (DSS) to produce colitis.[42,43] According to one theory, GM-CSF produced by type 3 ILCs regulates the macrophage phenotype to prevent intestinal fibrosis.[44] GM-CSF administration can improve IBD in some patients and in experiments, which is consistent with GM-CSF having a possible positive effect on IBD153,152,154. Additionally, it has been discovered that a worse prognosis for CD correlates with high levels of circulating anti-GM-CSF autoantibodies.[45,46]

Interstitial Lung Disease

Various inflammatory lung parenchyma diseases known as interstitial lung disease (ILD) can cause alveolitis and ultimately fibrosis. It is another severe side effect linked to systemic rheumatic disorders.[47] In an experimental setting, the Zap-70 gene-mutant SKG mouse[48,49] develops spontaneous arthritis, ILD, and IBD.[50] SKG mice's lungs exhibit pathological traits similar to human ILD, including fibrosis and severe GM-CSF+ IL-17A+ neutrophil infiltrates.[51] In SKG mice, GM-CSF inhibition diminishes these characteristics, notably the level of fibrosis, but IL-17 blockade has a lesser impact.[52] It's interesting to note that peritoneal fibrosis has been linked to macrophages that express CCL17.[53]Further research into the involvement of the GM-CSF/CCL17 axis in lung fibrosis is necessary in light of these findings as well as data from lung inflammation models showing that GM-CSF inhibition affected CCL17 expression in alveolar macrophages[54].

Aortic Aneurysm

Aortic aneurysm dissection is a serious and frequently fatal disorder. According to a study, mice lacking the Krueppel-like factor 6 (Kif6) gene experienced poorer aortic aneurysm development. GM-CSF was found to be an effector molecule downstream of Krueppel-like factor 6 in the same study, and its injection accelerated the development of aortic aneurysms while its antagonist, GM-CSF, had the opposite effect.[55] Anti-GM-CSF mAb treatment reduces inflammation and dilatation in the aortic root by inducing CD11b+ Gr-1+ Ly6Chi inflammatory monocyte concentration.[56] These results imply that GM-CSF blocking may be a useful therapeutic strategy for aortic aneurysm.

Allergic Disease

According to reports, GM-CSF activates DCs to contribute to the TH2 response in allergic airway inflammation.[57] Epithelial cells exposed to allergens in a mouse model of asthma release GM-CSF, which activates DCs and increases eosinophil survival. Taking a mAb that neutralises GM-CSF also lowered allergic hyperresponsiveness.[58] As a result, a Phase II trial for severe asthma has evaluated an anti-GM-CSF mAb (see below). It's interesting to note that CCL17 produced by alveolar DCs plays a crucial role in airway inflammation.The expression of CCL17 in the airways and the severity of asthmatic illness are correlated.[59,60] These findings, in our opinion, call for a thorough investigation of the function of the GM-CSF/CCL17 axis in asthma, with CCL17 as a possible therapeutic target for allergic disease and/or a biomarker for selection of patient.

Obesity and Its Associated Meta-Inflammation

Obesity is now frequently seen as a low-grade, chronic inflammatory disease that increases the risk of insulin resistance, ectopic lipid accumulation, and metabolic dysfunction.[61,62] Adipose tissue macrophages (ATMs) are thought to play a significant role in metabolic inflammation, insulin resistance, and the deterioration of adipocyte function as obesity progresses.[63] In addition, GM-CSF is necessary for the inflammation caused by diet-induced obesity (DIO) in adipose tissue, as evidenced by the reduced number of infiltrating ATMs and crown-like features in adipose tissue in GM-CSF gene-deficient mice,[64] despite higher body weight and adiposity levels.[65,66]The metabolic status of GM-CSF gene-deficient mice, namely their insulin sensitivity to glucose, was shown to be better in comparison to that of their wild-type counterparts, and myeloid cells that are GM-CSF responsive are thought to play a significant role in this improvement. Because of this, it has been suggested that GM-CSF is a crucial mediator whose actions could account for the distinction between obese people with normal glucose tolerance (metabolically "healthy") and people with type 2 diabetes (metabolically "unhealthy").[67] Other obesity-exacerbated diseases, such as the obesity-mediated increase of breast cancer metastasis, have also been linked to GM-CSF in addition to type 2 diabetes.183 It is yet unknown how GM-CSF affects obesity-related meta-inflammation.

Cancer

Direct Administration of GM-CSF

In patients with acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), Hodgkin- and non-Hodgkin- lymphomas (HL/NHL), recombinant human GM-CSF (Sargramostim or Leukine®) is used to stimulate early stem cells in donors before their harvesting for peripheral stem cell transplant and to stimulate recovery of HPCs after bone marrow transplant [68].Sargramostim (GM-CSF) has been demonstrated to be helpful as an immunostimulatory adjuvant to elicit antitumor immunity and enhance the patient's general state in patients receiving chemotherapy for solid tumours [69]. Patients with surgically resected stage III/IV melanoma had a two-year increase in survival when GM-CSF was administered subcutaneously at a dose of 125 g/m^2 for 14 days in various cycles over the course of a year [70,71]. 19 patients with breast cancer, recurrent ovarian cancer, metastatic endometrial cancer, and recurrent squamous cell cancer of the cervix uteri who had previously failed chemotherapy experienced complete remission in 5% of cases and partial remission in 31.5 percent of cases after receiving low-dose GM-CSF [72].

GM CSF against infectious diseases

Influenza

From 1973 until 1980, GM-CSF was employed to guard against acute lung damage, subsequent bacterial pneumonia, and influenza. These latest research have led to a new application for providing GM-CSF to the alveolar space to prevent various lung illnesses, in addition to the FDA-approved application for treating bone marrow suppression with GM-CSF. This study expands on those results, resolves a contentious problem, and discusses several novel applications of GM-CSF for treating influenza.The first piece of supporting evidence was that pulmonary GM-CSF, which activates pulmonary innate immunity via alveolar macrophages, offers exceptional defence against several IAV strains [73]. Through increased AM proliferation, production of TNF, MCP-1, and amphiregulin, a growth factor, as well as expression of PU.1 in AMs, we have demonstrated here that intranasal delivery of GM-CSF protects wild type mice with different genotypes that express two different MHC molecules, C57Bl/6 and Balb/c. This supports our earlier findings and the most recent research by Schnider et al. on the role of AMs as the primary innate immune subsets that protect mice against lethal IAV infections after receiving GM-CSF in the lungs [74,75]. Macrophages and other immune cell subsets may also aid in protection of GM-CSF [76]. Additionally, it highlights the function of amphiregulin in influenza disease and supports previous observations on the hormone's ability to guard against bacterial co-infection of the lungs[77,78]. By boosting innate immune responses that rely on alveolar macrophages, GM-CSF confers resistance to influenza. This cytokine may be delivered through the lungs to lower influenza-related morbidity and mortality.

Tuberculosis

The ability of rhu-GM-CSF to stimulate human monocyte-derived macrophages in a manner that prevents the intracellular growth of or eradicates Mycobacterium avium complex (MAC) bacteria was investigated by Bermudez et al. [79]. They discovered that TNF- may enhance the death of MAC by activating macrophages to suppress intracellular proliferation or kill MAC. A beige mouse model was used by Bermudez et al. to demonstrate the impact of rhu-GM-CSF on disseminated MAC infection in vivo. In comparison to mice treated only with antimicrobials, GM-CSF treatment resulted in a considerable decrease in the amount of viable bacteria in the blood, livers, and spleens[80]. According to research by Denis and Ghadirian, rhu-GM-CSF inhibits M. tuberculosis development in human monocyte-derived macrophages in vitro as compared to untreated cells.Reactive oxygen species production was not necessary for the tuberculous bacilli's intracellular development to slow down[81].

Pulmonary group B streptococcal infection

When compared to GM+/+ mice, pulmonary clearance of intratracheally given GBS was decreased in GM-/- animals. When mouse GM-CSF was expressed in the respiratory epithelium of GM-/- mice under the control of the SP-C promoter and when GM-CSF was administered acutely to GM+/+ mice, bacterial clearance increased to levels higher than in wild-type mice. While the ability of macrophages to phagocytose bacteria was comparable in GM-/- and GM+/+ mice, the production of superoxide radical and hydrogen peroxide was significantly reduced in alveolar macrophages from GM-/- animals. These results lend credence to the idea that GM-CSF plays a significant role in pulmonary host defence, which is partly mediated by elevated oxygen radical generation and bacterial death by alveolar macrophages[82].

Surprisingly, defects in macrophage phagocytosis were not linked to decreased pulmonary clearance of GBS in GM-/- animals. Previous in vitro investigations showed that GM-CSF improved neutrophil phagocytosis

of serum-opsonized Staphylococcus aureus [83] and macrophage phagocytosis of Cryptococcus neoformans [84,85]. The lack of aberrant phagocytosis in the current study suggests that other in vivo mechanisms may be able to make up for the loss of GM-CSF. For instance, BAL from GM-/- mice has significantly higher levels of the surfactant proteins A and D (SP-A, SP-D) [86]. The host's defence against bacterial infections is significantly aided by these surfactant proteins. Surfactant proteins A and D promote the chemotaxis of macrophages[87,88], and SP-A improves bacterial attachment to macrophages [89]. Mice lacking the SP-A gene are extremely vulnerable to GBS infection [90].Therefore, the maintenance of phagocytic activity by alveolar macrophages may have been aided by the elevated amounts of SP-A and SP-D in BAL fluid from GM-/- animals.

HIV

In a dose-dependent manner, GM-CSF reliably inhibits HIV-1 replication in human MDM. The inhibitory impact is distinct since adding neutralising MAb 4D4 completely reverses it, but adding non-neutralizing anti-GM-CSF control MAb 4A12 does not. The amount of MDM maturation at the time of GM-CSF stimulation or HIV infection had no bearing on the inhibitory impact of GM-CSF. E21R GM-CSF has no impact on HIV-1 replication because it only binds to the GM-CSF receptor's -chain, which concludes that GM-CSF inhibits HIV-1 replication via signalling via the receptor's -chain[91].

Our study addressed a long-standing debate in the literature, where the majority of early studies reported increased viral production [92,93-98]or no changeand two more recent studies suggested that GM-CSF inhibits HIV-1 replication in MDM[99,100]. Such variance may be influenced by a variety of laboratory conditions. To understand why our results are different from those of certain earlier studies, we have carefully looked at potential confounders. We replicated the assay parameters utilised by other researchers, including the HIV-1 strain, the supply and concentration of GM-CSF, and the timing of cytokine incubation in relation to cell maturity and HIV-1 infection. No matter the experimental setup, we saw decreased HIV-1 replication. According to research results, the inhibition of HIV-1 replication in macrophages brought on by GM-CSF is mostly the result of a disruption at specific replication phases following the synthesis of the proviral DNA. A model of the delay of HIV infection in vivo may therefore be provided by the inhibition of HIV replication in GM-type macrophages[101,102].

Contradictory effects of GM CSF

Promoting theTumor-Associated Macrophages and Myeloid Derived Suppressor Cells

The main pro-tumorigenic immune cells in the cancer microenvironment are tumor-associated macrophages (TAMs). By secreting cytokines, chemokines, and growth factors that support tumour growth and progression, TAMs block antitumor immune responses. The chemokine ligand C-C motif chemokine ligand 2 (CCL2) [103], which is released by the tumour and surrounding cells, regulates the polarisation of TAMs into the tumor-promoting M2 phenotype [104]. To exert its tumor-promoting action, CCL2 binds to its specific receptor CCR2[105,106]. GM-CSF can cause the synthesis of CCL2 from T cells in the tumour microenvironment and the expression of CCR2 on macrophages, polarising them to the metastasis-promoting M2 phenotype[107] while being primarily an M1-inducing agent[105,106].Nasopharyngeal carcinoma (NPC) with Epstein-Barr virus (EBV) association differentiates monocytes to a TAM-like phenotype by secreting GM-CSF in an NK-B-dependent way. Then, TAMs release CCL-18, causing EMT. In line with these results, it was discovered that neutralising GM-CSF greatly decreased NPC metastasis [108]. High expression of GM-CSF and HIF1 is linked to perineural invasion (PNI) and unfavourable clinical outcomes in individuals with pancreatic ductal adenocarcinoma (PDAC) [109] Nitrosamine 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a cigarette carcinogen, is known to accelerate PDAC growth by activating the cyclic AMP response element-binding protein (CREB) through GM-CSF. TAM recruitment and regulatory T cell (Treg) growth caused by GM-CSF were reported to be blocked by CREB inhibition [110].In a different PDAC study, Waghray et al. discovered that GM-CSF, which is released by cancer-associated mesenchymal stem cells (CA-MSCs), promotes the growth and metastasis of PDAC cells [111].

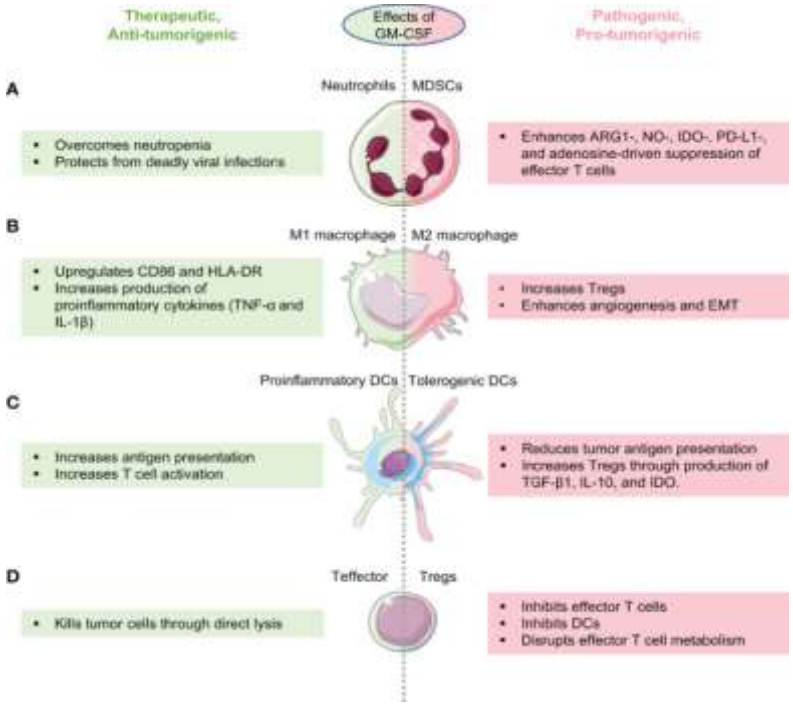

Fig.2-Therapeutic and pathogenic effects of GM-CSF on anti-cancer immune surveillance.

Recombinant GM CSF

Recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) has gained popularity in recent years for its healing ability. Animal studies and clinical trials have supported the efficacy of rhGM-CSF treatment [112,113], but clinical safety study of rhGM-CSF is insufficient, and the results are dubious. Further a study conducted on the recombinant GM CSF on leg ulcers revealed that, pathogenesis, size, and length of the ulcers appeared to be the most crucial factors affecting rhGM-CSF's ability to heal wounds. None of the patients experienced clinical side effects or anomalies in their peripheral blood cell counts while receiving medication, and none of the ulcers grew larger. After six months of follow-up, all of the results mentioned were steady. The medication appears to have local rather than systemic effects, as evidenced by the lack of change in the peripheral leucocyte count and the size-dependent therapeutic impact[114]. In addition, a randomized control trial on the role of rhGM-CSF on acute lung injury did not show any positive impact, where, patients with acute lung injury/acute respiratory distress syndrome who received granulocyte-macrophage colony stimulating factor treatment did not experience an increase in the number of ventilator-free days[115].

Conclusion

In summary, GM-CSF plays an important role in the reduction or maintenance of many diseases like inflammatory, infectious or autoimmune diseases by reducing free radical stress. Apart from beneficiary effects, it also exhibits a pro tumorigenic effect, where an extra caution is required during its use in different cancers. And, crucial insights into effectively using GM-CSF for treating cancer will come from the existing and future technological and scientific advancements in understanding the effects of GM-CSF at a single-cell, geographic, and temporal level in cancers. Further, recombinant GM-CSF exhibits multiple benefits similar to the natural GM-CSF, however, more research is needed to evident its beneficial impact.

References

1. Burgess, A. W. & Metcalf, D. The nature and action of granulocyte-macrophage colony stimulating factors. *Blood* 56, 947–958 (1980).
2. Shiomi, A. & Usui, T. Pivotal roles of GM-CSF in autoimmunity and inflammation. *Mediators Inflamm* 2015, (2015).
3. Ponomarev, E. D. *et al.* GM-CSF Production by Autoreactive T Cells Is Required for the Activation of Microglial Cells and the Onset of Experimental Autoimmune Encephalomyelitis. *The Journal of Immunology* 178, 39–48 (2007).

4. Shi, Y. *et al.* Granulocyte-macrophage colony-stimulating factor (GM-CSF) and T-cell responses: what we do and don't know. *Cell Res* 16, 126–133 (2006).
5. McCormick, T. S., Hejal, R. B., Leal, L. O. &Ghannoum, M. A. GM-CSF: Orchestrating the Pulmonary Response to Infection. *Front Pharmacol* 12, 735443 (2022).
6. Rösler, B. & Herold, S. Lung epithelial GM-CSF improves host defense function and epithelial repair in influenza virus pneumonia-a new therapeutic strategy? *Mol Cell Pediatr* 3, (2016).
7. Hansen, G. *et al.* The structure of the GM-CSF receptor complex reveals a distinct mode of cytokine receptor activation. *Cell* 134, 496–507 (2008).
8. D A Rozwarski, K. D. R. H. T. B. P. A. K. Refined crystal structure and mutagenesis of human granulocyte-macrophage colony-stimulating factor. *Proteins* 26, 304–313 (1996).
9. Carr, P. D. *et al.* Structure of the complete extracellular domain of the common beta subunit of the human GM-CSF, IL-3, and IL-5 receptors reveals a novel dimer configuration. *Cell* 104, 291–300 (2001).
10. Carr, P. D., Conlan, F., Ford, S., Ollis, D. L. & Young, I. G. An improved resolution structure of the human beta common receptor involved in IL-3, IL-5 and GM-CSF signalling which gives better definition of the high-affinity binding epitope. *ActaCrystallogr Sect F StructBiolCrystCommun* 62, 509–513 (2006).
11. Lehtonen, A., Matikainen, S., Miettinen, M. &Julkunen, I. Granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced STAT5 activation and target-gene expression during human monocyte/macrophage differentiation. *J LeukocBiol* 71, 511–519 (2002).
12. Perugini, M. *et al.* Alternative modes of GM-CSF receptor activation revealed using activated mutants of the common β-subunit. *Blood* 115, 3346–3353 (2010).
13. Van De Laar, L., Coffer, P. J. &Woltman, A. M. Regulation of dendritic cell development by GM-CSF: molecular control and implications for immune homeostasis and therapy. *Blood* 119, 3383–3393 (2012).
14. Gao, Y. *et al.* Control of T helper 2 responses by transcription factor IRF4-dependent dendritic cells. *Immunity* 39, 722–732 (2013).
15. Williams, J. W. *et al.* Transcription factor IRF4 drives dendritic cells to promote Th2 differentiation. *Nat Commun* 4, (2013).
16. Achuthan, A. *et al.* Granulocyte macrophage colony-stimulating factor induces CCL17 production via IRF4 to mediate inflammation. *J Clin Invest* 126, 3453–3466 (2016).
17. Lee, M.-C. *et al.* GM-CSF- and IRF4-Dependent Signaling Can Regulate Myeloid Cell Numbers and the Macrophage Phenotype during Inflammation. *J Immunol* 202, 3033–3040 (2019).
18. Weiss, M., Blazek, K., Byrne, A. J., Perocheau, D. P. &Udalova, I. A. IRF5 is a specific marker of inflammatory macrophages in vivo. *Mediators Inflamm* 2013, (2013).
19. Ahyi, A.-N. N., Chang, H.-C., Dent, A. L., Nutt, S. L. & Kaplan, M. H. IFN regulatory factor 4 regulates the expression of a subset of Th2 cytokines. *J Immunol* 183, 1598–1606 (2009).
20. Okada, Y. *et al.* Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. *Nat Genet* 44, 511–516 (2012).
21. Shi, H. *et al.* GM-CSF Primes Proinflammatory Monocyte Responses in Ankylosing Spondylitis. *Front Immunol* 11, (2020).
22. Cook, A. D. *et al.* Granulocyte-macrophage colony-stimulating factor is a key mediator in inflammatory and arthritic pain. *Ann Rheum Dis* 72, 265–270 (2013).
23. Cook, A. D., Braine, E. L., Campbell, I. K., Rich, M. J. & Hamilton, J. A. Blockade of collagen-induced arthritis post-onset by antibody to granulocyte-macrophage colony-stimulating factor (GM-CSF): requirement for GM-CSF in the effector phase of disease. *Arthritis Res* 3, 293–298 (2001).
24. Lee, M. C. *et al.* CCL17 blockade as a therapy for osteoarthritis pain and disease. *Arthritis Res Ther* 20, (2018).
25. Burmester, G. R. *et al.* Mavrilimumab, a Fully Human Granulocyte-Macrophage Colony-Stimulating Factor Receptor α Monoclonal Antibody: Long-Term Safety and Efficacy in Patients With Rheumatoid Arthritis. *Arthritis Rheumatol* 70, 679–689 (2018).
26. Klein-Wieringa, I. R. *et al.* Inflammatory Cells in Patients with Endstage Knee Osteoarthritis: A Comparison between the Synovium and the Infrapatellar Fat Pad. *J Rheumatol* 43, 771–778 (2016).
27. Yasuda K, Takeuchi Y, Hirota K. The pathogenicity of Th17 cells in autoimmune diseases. SeminImmunopathol. 41(3):283–297 (2019).
28. Haak S, Croxford AL, Kreymborg K, et al. IL-17A and IL-17F do not contribute vitally to autoimmune neuro-inflammation in mice. *J Clin Invest*. 2009;119(1):61–69.

29. Codarri L, Gyulveszi G, Tosevski V, et al. RORgammat drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. *Nat Immunol*. 2011;12(6):560–567. doi: 10.1038/ni.2027
30. El-Behi M, Ciric B, Dai H, et al. The encephalitogenicity of T(H)17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF. *Nat Immunol*. 2011;12(6):568–575. doi: 10.1038/ni.2031
31. Ponomarev ED, Shriver LP, Maresz K, Pedras-Vasconcelos J, Verthelyi D, Dittel BN. GM-CSF production by autoreactive T cells is required for the activation of microglial cells and the onset of experimental autoimmune encephalomyelitis. *J Immunol*. 2007;178(1):39–48. doi: 10.4049/jimmunol.178.1.39
32. King IL, Dickendesher TL, Segal BM. Circulating Ly-6C+ myeloid precursors migrate to the CNS and play a pathogenic role during autoimmune demyelinating disease. *Blood*. 2009;113(14):3190–3197. doi: 10.1182/blood-2008-07-168575
33. Vogel DY, Kooij G, Heijnen PD, et al. GM-CSF promotes migration of human monocytes across the blood brain barrier. *Eur J Immunol*. 2015;45(6):1808–1819. doi: 10.1002/eji.201444960
34. Duncker PC, Stoolman JS, Huber AK, Segal BM. GM-CSF promotes chronic disability in experimental autoimmune encephalomyelitis by altering the composition of central nervous system-infiltrating cells, but is dispensable for disease induction. *J Immunol*. 2018;200(3):966–973.
35. McQualter JL, Darwiche R, Ewing C, et al. Granulocyte macrophage colony-stimulating factor: a new putative therapeutic target in multiple sclerosis. *J Exp Med*. 2001;194(7):873–882. doi: 10.1084/jem.194.7.873
36. Perrella O, Carrieri PB, De Mercato R, Buscaino GA. Markers of activated T lymphocytes and T cell receptor gamma/delta+ in patients with multiple sclerosis. *Eur Neurol*. 1993;33(2):152–155. doi: 10.1159/000116923
37. Aharoni R, Eilam R, Schottlender N, et al. Glatiramer acetate increases T- and B -regulatory cells and decreases granulocyte-macrophage colony-stimulating factor (GM-CSF) in an animal model of multiple sclerosis. *J Neuroimmunol*. 2020;345:577281. doi: 10.1016/j.jneuroim.2020.
38. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol. 2015;12(4):205–217. doi: 10.1038/nrgastro.2015.34
39. Marks DJ, Rahman FZ, Sewell GW, Segal AW. Crohn's disease: an immune deficiency state. *Clin Rev Allergy Immunol*. 2010;38(1):20–31. doi: 10.1007/s12016-009-8133-2
40. Griseri T, McKenzie BS, Schiering C, Powrie F. Dysregulated hematopoietic stem and progenitor cell activity promotes interleukin-23-driven chronic intestinal inflammation. *Immunity*. 2012;37(6):1116–1129. doi: 10.1016/j.immuni.2012.08.025
41. Griseri T, Arnold IC, Pearson C, et al. Granulocyte macrophage colony-stimulating factor-activated eosinophils promote interleukin-23 driven chronic colitis. *Immunity*. 2015;43(1):187–199. doi: 10.1016/j.immuni.2015.07.008
42. Xu Y, Hunt NH, Bao S. The role of granulocyte macrophage-colony-stimulating factor in acute intestinal inflammation. *Cell Res*. 2008;18(12):1220–1229. doi: 10.1038/cr.2008.310
43. Dabritz J. Granulocyte macrophage colony-stimulating factor and the intestinal innate immune cell homeostasis in Crohn's disease. *Am J PhysiolGastrointest Liver Physiol*. 2014;306(6):G455–465. doi: 10.1152/ajpgi.00409.2013
44. Pearson C, Thornton EE, McKenzie B, et al. ILC3 GM-CSF production and mobilisation orchestrate acute intestinal inflammation. *Elife*. 2016;5:e10066.
45. Gathungu G, Zhang Y, Tian X, et al. Impaired granulocyte-macrophage colony-stimulating factor bioactivity accelerates surgical recurrence in ileal Crohn's disease. *World J Gastroenterol*. 2018;24(5):623–630. doi: 10.3748/wjg.v24.i5.623
46. Denson LA, Jurickova I, Karns R, et al. Genetic and transcriptomic variation linked to neutrophil granulocyte-macrophage colony-stimulating factor signaling in pediatriccrohn's disease. *Inflamm Bowel Dis*. 2019;25(3):547–560. doi: 10.1093/ibd/izy265
47. Atzeni F, Gerardi MC, Barilaro G, Masala IF, Benucci M, Sarzi-Puttini P. Interstitial lung disease in systemic autoimmune rheumatic diseases: a comprehensive review. *Expert Rev Clin Immunol*. 2018;14(1):69–82. doi: 10.1080/1744666X.2018.1411190
48. Sakaguchi N, Takahashi T, Hata H, et al. Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. *Nature*. 2003;426(6965):454–460. doi: 10.1038/nature02119

49. Guerard S, Boieri M, Hultqvist M, Holmdahl R, Wing K. The SKG mutation in ZAP-70 also confers arthritis susceptibility in C57 black mouse strains. *Scand J Immunol*. 2016;84(1):3–11. doi: 10.1111/sji.12438
50. Benham H, Rehaume LM, Hasnain SZ, et al. Interleukin-23 mediates the intestinal response to microbial beta-1,3-glucan and the development of spondyloarthritis pathology in SKG mice. *Arthritis Rheumatol*. 2014;66(7):1755–1767. doi: 10.1002/art.38638
51. Kwon OC, Lee EJ, Chang EJ, et al. IL-17A(+)GM-CSF(+) neutrophils are the major infiltrating cells in interstitial lung disease in an autoimmune arthritis model. *Front Immunol*. 2018;9:1544. doi: 10.3389/fimmu.2018.01544
52. Shiomi A, Usui T, Ishikawa Y, Shimizu M, Murakami K, Mimori T. GM-CSF but not IL-17 is critical for the development of severe interstitial lung disease in SKG mice. *J Immunol*. 2014;193(2):849–859. doi: 10.4049/jimmunol.1303255
53. Chen YT, Hsu H, Lin CC, et al. Inflammatory macrophages switch to CCL17-expressing phenotype and promote peritoneal fibrosis. *J Pathol*. 2020;250(1):55–66. doi: 10.1002/path.5350
54. Lee KM, Jarnicki A, Achuthan A, et al. CCL17 in inflammation and pain. *J Immunol*. 2020;205(1):213–222. doi: 10.4049/jimmunol.2000315
55. Son BK, Sawaki D, Tomida S, et al. Granulocyte macrophage colony-stimulating factor is required for aortic dissection/intramural haematoma. *Nat Commun*. 2015;6(1):6994. doi: 10.1038/ncomms7994Ye
56. P, Chen W, Wu J, et al. GM-CSF contributes to aortic aneurysms resulting from SMAD3 deficiency. *J Clin Invest*. 2013;123(5):2317–2331. doi: 10.1172/JCI67356
57. Nouri-Aria KT, Masuyama K, Jacobson MR, et al. Granulocyte/macrophage-colony stimulating factor in allergen-induced rhinitis: cellular localization, relation to tissue eosinophilia and influence of topical corticosteroid. *Int Arch Allergy Immunol*. 1998;117(4):248–254. doi: 10.1159/000024019
58. Cates EC, Fattouh R, Wattie J, et al. Intranasal exposure of mice to house dust mite elicits allergic airway inflammation via a GM-CSF-mediated mechanism. *J Immunol*. 2004;173(10):6384–6392. doi: 10.4049/jimmunol.173.10.6384
59. Yamashita N, Tashimo H, Ishida H, et al. Attenuation of airway hyperresponsiveness in a murine asthma model by neutralization of granulocyte-macrophage colony-stimulating factor (GM-CSF). *Cell Immunol*. 2002;219(2):92–97. doi: 10.1016/S0008-8749(02)00565-8
60. Yuan L, Zhang X, Yang M, et al. Airway epithelial integrin beta4 suppresses allergic inflammation by decreasing CCL17 production. *ClinSci (Lond)*. 2020;134(13):1735–1749. doi: 10.1042/CS20191188
61. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. *Nature*. 2017;542(7640):177–185. doi: 10.1038/nature21363
62. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444(7121):860–867. doi: 10.1038/nature05485
63. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003;112(12):1821–1830. doi: 10.1172/JCI200319451
64. Boi SK, Buchta CM, Pearson NA, et al. Obesity alters immune and metabolic profiles: new insight from obese-resistant mice on high-fat diet. *Obesity (Silver Spring)*. 2016;24(10):2140–2149. doi: 10.1002/oby.21620
65. Shaw OM, Pool B, Dalbeth N, Harper JL. The effect of diet-induced obesity on the inflammatory phenotype of non-adipose-resident macrophages in an in vivo model of gout. *Rheumatology (Oxford)*. 2014;53(10):1901–1905. doi: 10.1093/rheumatology/keu174
66. Kim DH, Sandoval D, Reed JA, et al. The role of GM-CSF in adipose tissue inflammation. *Am J PhysiolEndocrinolMetab*. 2008;295(5):E1038–1046. doi: 10.1152/ajpendo.00061.2008
67. Plubell DL, Fenton AM, Wilmarth PA, et al. GM-CSF driven myeloid cells in adipose tissue link weight gain and insulin resistance via formation of 2-aminoadipate. *Sci Rep*. 2018;8(1):11485. doi: 10.1038/s41598-018-29250-8
68. Sohn S, Kim J, Seo K, Chae Y, Jung J, Suh J, et al.. Gm-Csf-Based Mobilization Effect in Normal Healthy Donors for Allogeneic Peripheral Blood Stem Cell Transplantation. *Bone Marrow Transplant* (2002) 30(2):81–6. doi: 10.1038/sj.bmt.1703598
69. Lazarus HM, Ragsdale CE, Gale RP, Lyman GH. Sargramostim (Rhu Gm-Csf) as Cancer Therapy (Systematic Review) and an Immunomodulator. A Drug Before Its Time *Front Immunol* (2021) 12:3196. doi: 10.1038/sj.gt.3301885
70. Spitler LE, Weber RW, Allen RE, Meyer J, Cruickshank S, Garbe E, et al.. Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor (Gm-Csf, Sargramostim) Administered for 3 Years

as Adjuvant Therapy of Stages Ii (T4), Iii, and Iv Melanoma. *J Immunother* (2009) 32(6):632–7. doi: 10.1097/CJI.0b013e3181a7d60d

71. Spitler LE, Cao H, Piironen T, Whiteside TL, Weber RW, Cruickshank S. Biologic Effects of Anti-Granulocyte-Macrophage Colony-Stimulating Factor (Gm-Csf) Antibody Formation in Patients Treated With Gm-Csf (Sargramostim) as Adjuvant Therapy of Melanoma. *Am J Clin Oncol* (2017) 40(2):207. doi: 10.1097/COC.0000000000000124
72. Kurbacher CM, Kurbacher JA, Cramer E-M, Rhiem K, Mallman PK, Reichelt R, et al.. Continuous Low-Dose Gm-Csf as Salvage Therapy in Refractory Recurrent Breast or Female Genital Tract Carcinoma. *Oncology* (2005) 19(4 Suppl 2):23–6.
73. Huang FF, Barnes PF, Feng Y, Donis R, Chroneos ZC et al. (2011) GM-CSF in the lung protects against lethal influenza infection. Am J Respir Crit Care Med 184: 259–268. 201012-2036OC [pii]; pmid:21474645
74. Ghoneim HE, Thomas PG, McCullers JA (2013) Depletion of alveolar macrophages during influenza infection facilitates bacterial superinfections. J Immunol 191: 1250–1259. jimmunol.1300014 [pii]; pmid:23804714
75. Schneider C, Nobs SP, Heer AK, Kurrer M, Klinke G et al. (2014) Alveolar macrophages are essential for protection from respiratory failure and associated morbidity following influenza virus infection. PLoSPathog 10: e1004053. ;PPATHOGENS-D-13-02507 [pii]. pmid:24699679
76. Subramaniam R, Barnes PF, Fletcher K, Bogarram V, Hillberry Z et al. (2013) Protecting against post-influenza bacterial pneumonia by increasing phagocyte recruitment and ROS production. J Infect Dis. jit830 [pii];
77. Lin KL, Suzuki Y, Nakano H, Ramsburg E, Gunn MD (2008) CCR2+ monocyte-derived dendritic cells and exudate macrophages produce influenza-induced pulmonary immune pathology and mortality. J Immunol 180: 2562–2572. 180/4/2562 [pii]. pmid:18250467
78. Jamieson AM, Pasman L, Yu S, Gamradt P, Homer RJ et al. (2013) Role of tissue protection in lethal respiratory viral-bacterial coinfection. Science 340: 1230–1234. science.1233632 [pii]; pmid:23618765
79. Bermudez L.E., Young, LS. Recombinant human granulocyte-macrophage colony-stimulating factor activates human macrophages to inhibit growth or kill *Mycobacterium avium* complex. J LeukBiol 1990:48:67-73.
80. Bermudez L.E., Martinelli J., Petrofsky M., Kolonoski P. and Young L.S. Recombinant granulocyte-macrophage colony-stimulating factor enhances the effects of antibiotics against *Mycobacterium avium* complex infection in the beige mouse model. J Infec Dis 1994;169:575-80
81. Denis M., Ghadirian E. Granulocyte-macrophage colony-stimulating factor restricts growth of tubercle bacilli in human macrophages. Immunol Lett 1990;24:203-6.
82. LeVine AM, Reed JA, Kurak KE, Cianciolo E, Whitsett JA. GM-CSF–deficient mice are susceptible to pulmonary group B streptococcal infection. The Journal of clinical investigation. 1999 Feb 15;103(4):563-9.
83. Fleischmann, J, Golde, DW, Weisbart, RH, Gasson, JC. Granulocyte-macrophage colony-stimulating factor enhances phagocytosis of bacteria by human neutrophils. *Blood* 1986. 68:708-711.
84. Collins, HL, Bancroft, GJ. Cytokine enhancement of complement-dependent phagocytosis by macrophages: synergy of tumor necrosis factor-α and granulocyte-macrophage colony-stimulating factor for phagocytosis of *Cryptococcus neoformans*. *Eur J Immunol* 1992. 22:1447-1454.
85. Chen, GH, et al. Effect of granulocyte-macrophage colony-stimulating factor on rat alveolar macrophage anticryptococcal activity in vitro. *J Immunol* 1994. 152:724-734.
86. Dranoff, G, et al. Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis. *Science* 1994. 264:713-716.
87. Wright, JR, Youmans, DC. Pulmonary surfactant protein A stimulates chemotaxis of alveolar macrophages. *Am J Physiol* 1993. 264:L338-L344.
88. Crouch, EC, Persson, A, Griffin, GL, Chang, D, Senior, RM. Interactions of pulmonary surfactant protein D (SP-D) with human blood leukocytes. *Am J Respir Cell MolBiol* 1995. 12:410-415.
89. van Iwaarden, F, Welmers, B, Verhoef, J, Haagsman, HP, van Golde, LMG. Pulmonary surfactant protein A enhances the host-defense mechanisms of rat alveolar macrophages. *Am J Respir Cell MolBiol* 1990. 2:91-98.
90. LeVine, AM, et al. Surfactant protein A-deficient mice are susceptible to group B streptococcal infection. *J Immunol* 1997. 158:4336-4340.

91. Lopez A, Shannon M, Hercus T. et al. Residue 21 of human granulocyte macrophage colony stimulating factor is critical for biological activity and for high but not low affinity binding. EMBO J 1992, 11: 909 –916.
92. Koyanagi Y, O'Brien WA, Zhao JQ, Golde DW, Gasson JC, Chen ISY. Cytokines alter production of HIV-1 from primary mononuclear phagocytes. Science 1988, 241: 1673 –1675.
93. Perno CF, Yarchoan R, Cooney DA. et al. Replication of human immunodeficiency virus in monocytes. :Granulocyte/macrophage colony-stimulating factor (GM-CSF) potentiates viral production yet enhances the antiviral effect mediated by 3×-azido-2×3×-dideoxythymidine (AZT) and other dideoxynucleoside congeners of thymidine. J Exp Med 1989, 169: 933 –951.
94. Schuitemaker H, Kootstra NA, van Oers MH, van Lambalgen R, Tersmette M, Miedema F. Induction of monocyte proliferation and HIV expression by IL-3 does not interfere with anti-viral activity of zidovudine. Blood 1990, 76: 1490 –1493.
95. Perno CF, Cooney DA, Gao WY. et al. Effects of bone marrow stimulatory cytokines on human immunodeficiency virus replication and the antiviral activity of dideoxynucleosides in cultures of monocytes/macrophages. Blood 1992, 80: 995 –1003.
96. Wang J, Roderiquez G, Oravecz T, Norcross A. Cytokine regulation of human immunodeficiency virus type 1 entry and replication in human monocytes/macropohages through modulation of CCR5 expression. J Virol 1998, 72: 7642 –7647.
97. Folks TM, Justement J, Kinter A, Dinarello CA, Fauci AS. Cytokine-induced expression of HIV-1 in a chronically infected promonocyte cell line. Science 1987, 238: 800 –802.
98. Pomerantz RJ, Feinberg MB, Trono D, Baltimore D. Lipopolysaccharide is a potent monocyte/macrophage specific stimulator of human immunodeficiency virus type 1 expression. J Exp Med 1990, 172: 253 –261.
99. Kornbluth RS, Oh PS, Munis JR, Cleveland PH, Richman DD. Interferons and bacterial lipopolysaccharide protect macrophages from productive infection by human immunodeficiency virus in vitro. J Exp Med 1989, 169: 1137 –1151.\
100. Hammer SM, Gillis JM, Pinkston P, Rose RM. Effect of zidovudine and granulocyte-macrophage colony stimulating factor on human immunodeficiency virus replication in alveolar macrophages. Blood 1990, 75: 1215 –1219.
101. Matsuda S, Akagawa K, Honda M, Yokota Y, Takebe Y, Takemon T. Suppression of HIV replication in human monocyte derived macrophages induced by granulocyte macrophage colony stimulating factor. AIDS Res Hum Retroviruses 1995, 11: 1031 –1038.
102. Di Marzio P, Tse J, Landau N. Chemokine receptor regulation and HIV type 1 tropism in monocyte-macrophages. AIDS Res Hum Retroviruses 1998, 14: 129 –138.
103. Lin Y, Xu J, Lan H. Tumor-Associated Macrophages in Tumor Metastasis: Biological Roles and Clinical Therapeutic Applications. *J HematolOncol* (2019) 12(1):1–16. doi: 10.1186/s13045-019-0760-3
104. Roca H, Varsos ZS, Sud S, Craig MJ, Ying C, Pienta KJ. Ccl2 and Interleukin-6 Promote Survival of Human Cd11b+ Peripheral Blood Mononuclear Cells and Induce M2-Type Macrophage Polarization. *J BiolChem* (2009) 284(49):34342–54. doi: 10.1074/jbc.M109.042671
105. Owen JL, Torroella-Kouri M, Handel-Fernandez ME, Iragavarapu-Charyulu V. Gm-Csf Up-Regulates the Expression of Ccl2 by T Lymphocytes in Mammary Tumor-Bearing Mice. *Int J Mol Med* (2007) 20(1):129–36. doi: 10.3892/ijmm.20.1.129
106. Sierra-Filardi E, Nieto C, Domínguez-Soto Á, Barroso R, Sánchez-Mateos P, Puig-Kroger A, et al.. Ccl2 Shapes Macrophage Polarization by Gm-Csf and M-Csf: Identification of Ccl2/Ccr2-Dependent Gene Expression Profile. *J Immunol* (2014) 192(8):3858–67. doi: 10.4049/jimmunol.1302821
107. Jeannin P, Paolini L, Adam C, Delneste Y. The Roles of Csf S on the Functional Polarization of Tumor-Associated Macrophages. *FEBS J* (2018) 285(4):680–99. doi: 10.1111/febs.14343
108. Huang D, Song S-J, Wu Z-Z, Wu W, Cui X-Y, Chen J-N, et al.. Epstein–Barr Virus-Induced Vegf and Gm-Csf Drive Nasopharyngeal Carcinoma Metastasis *Via* Recruitment and Activation of Macrophages. *Cancer Res* (2017) 77(13):3591–604. doi: 10.1158/0008-5472.CAN-16-2706
109. Wang H, Jia R, Zhao T, Li X, Lang M, Lan C, et al.. Hif-1α Mediates Tumor-Nerve Interactions Through the Up-Regulation of Gm-Csf in Pancreatic Ductal Adenocarcinoma. *Cancer Lett* (2019) 453:10–20. doi: 10.1016/j.canlet.2019.03.036
110. Srinivasan S, Totiger T, Shi C, Castellanos J, Lamichhane P, Dosch AR, et al.. Tobacco Carcinogen–Induced Production of Gm-Csf Activates Creb to Promote Pancreatic Cancer. *Cancer Res* (2018) 78(21):6146–58. doi: 10.1158/0008-5472.CAN-18-0579

111. Waghray M, Yalamanchili M, Dziubinski M, Zeinali M, Erkkinen M, Yang H, et al.. Gm-Csf Mediates Mesenchymal–Epithelial Cross-Talk in Pancreatic Cancer. *Cancer Discovery* (2016) 6(8):886–99. doi: 10.1158/2159-8290.CD-15-0947
112. Jones TC. Recombinant human GM-CSF: present clinical results and potential use in oncologic and hematologic disorders. Bull Cancer. 1991;78(12):1155-9. PMID: 1786428.
113. Lazarus HM, Pitts K, Wang T, Lee E, Buchbinder E, Dougan M, Armstrong DG, Paine R 3rd, Ragsdale CE, Boyd T, Rock EP, Gale RP. Recombinant GM-CSF for diseases of GM-CSF insufficiency: Correcting dysfunctional mononuclear phagocyte disorders. Front Immunol. 2023 Jan 5;13:1069444. doi: 10.3389/fimmu.2022.1069444. PMID: 36685591; PMCID: PMC9850113.
114. Bianchi L, Ginebri A, Hagman JH, Francesconi F, Carboni I, Chimenti S. Local treatment of chronic cutaneous leg ulcers with recombinant human granulocyte-macrophage colony-stimulating factor. Journal of the European Academy of Dermatology and Venereology. 2002 Nov;16(6):595-8.
115. Wexler LH, Weaver-McClure L, Steinberg SM, Jacobson J, Jarosinski P, Avila N, Pizzo PA, Horowitz ME. Randomized trial of recombinant human granulocyte-macrophage colony-stimulating factor in pediatric patients receiving intensive myelosuppressive chemotherapy. Journal of clinical oncology. 1996 Mar;14(3):901-10.