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Macrophages: Contribution to Diseases Development and Progression

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Short Title: Macrophages and Diseases

Abstract: ***Macrophages are versatile cells. They are derived from CD34+ bone marrow progenitors. Macrophages act as the first line of defence in the body against bacterial and viral infection. They also accumulate in acute and chronic inflammation and have an important role in healing and repair process. Studies have also indicated that macrophages participate in the development and progress of chronic disease such as rheumatoid arthritis and atherosclerosis. Many studies have suggested that macrophages play an important role in tumour cell invasion, growth, proliferation, and metastasis to distant organs. This review will summarise the role of macrophages in certain benign diseases. We also discuss the role of macrophages in tumour growth, progression and metastases.***

Keywords: Macrophages, Tumour, Rheumatoid arthritis, Atherosclerosis, Inflammatory bowel diseases

1. Introduction

1.1 Origin, development and function

Macrophages are versatile inflammatory cells derived from $CD34^+$ bone marrow cells and provide an important level of protection against bacterial and viral infection [1]. In the bone marrow, monoblasts arise from a common myeloid progenitor through a myeloblast stage. The monoblasts then divide to produce promonocytes which then differentiate into monocytes [2]. Monocytes travel in the circulation for about one or two days and then migrate to tissues where they differentiate into resident macrophages *(Figure 1.1)*[3]. Tissue macrophages are called *histocytes* in connective tissue, *kupffer cells* in liver, *microglial cells* in neural tissue, *osteoclasts* in bone and *sinusoidal liningcells* in splenic red pulp [2]. Other examples of tissue macrophages include tangible body in the germinal centre of the lymph nodes, dendritic cells, langerhans cells, lipid laden macrophages (foam cells), alveolar macrophages and macrophages of tonsils and dermis [2]. In general, macrophages are big irregular cells measuring 25-50 µm in diameter and contain a peripheral nucleus, between one and two prominent nucleoli and an abundant granular cytoplasm. To achieve their functions, macrophages have a large number of surface receptors, such as the Fc region of the IgG, IgA and IgE molecules, receptors for cytokines such as interleukin (IL)-1, IL-3, IL-10 and colony stimulating factor (CSF-1) also known as macrophage colony stimulating factor (M-CSF) [4],hormonal receptors such as insulin [5] and angiotensin [6]. Among these receptors, the Fc region of the IgG molecule receptor was the first macrophage receptor to be identified [7]. Through the binding of the Fc part of the IgG to these receptors, macrophages can perform many functions such as endocytosis, phagocytosis and secretion of certain cytokines and chemokines[1].

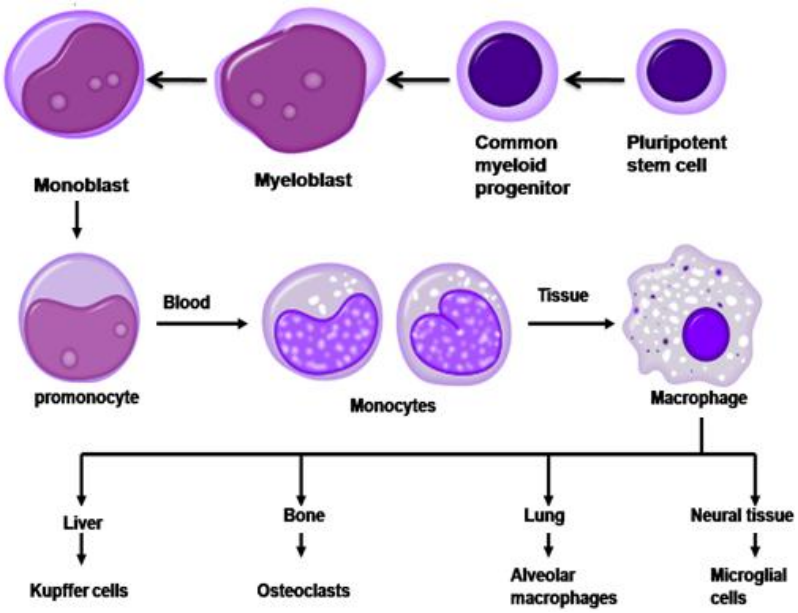

Figure 1.1: Origin and types of macrophage

A common myeloid progenitor dividesin the bone marrow to produce monoblasts via amyeloblast stage, the monoblasts then differentiate into promonocytes which then differentiate into monocytes. Monocytes circulate in the blood for about one or two days (depending on the species) before they then migrate to tissues where they differentiate into resident macrophages. Tissue macrophages are called kupffer cells in liver, osteoclasts in bone, alveolar macrophages in lung and microglial cells in neural tissue.

Macrophages engulf pathogens to form the phagosome which then fuses with the lysosome to digest the microbes. Engulfment of pathogens by macrophages starts with the binding of the macrophages to the pathogen through recognition molecules, the opsonins, such as IgG and fragments of the third component of complement [8]. In addition, macrophages present protein antigen to helper T cells by transferring them to the cell surface and coating them with glycoprotein encoded by class II and sometimes class I genes of the Major Histocompatibility Complex (MHC) [9,10]. Macrophages are drawn into diseased sites along trails of chemotactic stimuli in order to eliminate bacteria, virus and other pathogens [11]. Response of macrophages to different chemoattractants takes place as a result of specific receptors onthe macrophage cell surface thatcansometimes be activated in the presence of low concentrations of chemoattractant. *N*- formylated peptides, leukotriene B4, and CCL2 (monocyte chemotactic protein-1(MCP-1)) are the most well know chemoattractant factors for monocytes/macrophages [12,13]. Macrophages release a wide array of proteins including a large number of cytokines, chemokines, growth factors, and enzymes [14]. The main functions of macrophages are summarized in table 1.1.

Studying of cell surface receptors using monoclonal antibodies has indicated heterogeneity in of macrophage phenotype. Heterogeneity among peripheral blood monocytes has also been identified which highlights the heterogeneity in myeloid cell line [15]. In mice, monocytes are subdivided according to their expression of CCR2, CD62L and CX_3C- chemokines receptor into two subsets. One subset express CCR2, CD62L and low level of CX_3C whereas the other express only CX_3C. CCR2+ monocytes are attracted to CCR2 ligand and accumulated in inflammatory sites [16] therefore it is known as inflammatory subset [17,18]. At the inflammatory sites, monocytes express high level of CD11c and MHC class II and live Shorty [15]. In contrast, the second monocyte subset, CX_3C+ shows longer life span and is released into peripheral blood in abscess of inflammation. Both subsets cab be differentiated into DC [15].

Table1.1: Main functions of macrophages [1]

Function	*Mechanism*
Phagocytosis	Engulf necrotic debris and pathogens such as bacteria, viral, fungus and protozoa guided by chemotactic factors secreted by theses pathogens
Antigen presentation	T cell activation and presentation of antigen by integrating it into cell membrane and displaying it attached to MCH class II or class I
Chemotaxis	Macrophages are attracted toward microbes through activation of certain chemoattractant factors such as macrophage chemotactic protein
Secretion	Enzymes, enzyme and cytokine inhibitors, complement component, reactive oxygen intermediates, arachidonic acid intermediates, coagulation factors and cytokine.
Tumour cell control	Inhibit tumour cell division, lyse antibody-coated tumour cells by antibody- dependent cellular cytotoxicity and lyse tumour cells through macrophage-mediated tumour cytotoxicity.
Promotion of tumours	Macrophages are thought to promote tumour growth and metastasis by the secretion of cytotoxic and angiogenic factors.

1.2 Resident macrophages

Blood monocytes circulate for 1-3 days and then migrate into tissues to differentiate into resident tissue macrophages [2]. The main forms of tissue resident macrophages are listed below.

Kupffer cells

Kupffer cells are macrophages derived from monocytes and are found within the lining of the liver sinusoids. Their main function is to phagocytose bile debris, bacteria and dead red blood cells (RBCs) [19]. They are also involved in liver infections as they inhibit the proliferation of micro-organism by producing inflammatory mediators such as IL6, IL-12 and TNF-α[20,21] and also attract monocytes and neutrophils into the liver to control any infection [22]. In addition, Kupffer cells are also involved in the control of malignant liver diseases; they have a cytotoxic effect toward metastatic adenocarcinoma [23] and can also induce Fas mediated apoptosis in some metastatic malignant cells [24].

Microglial cells

Microglial cells are the main immunological cells in the central nervous system (CNS) [25]. They constitute 20% of the total glial cell population in the CNS. They migrate to the CNS during embryological development and are derived from circulating blood monocytes in adult life. They express macrophage markers (e.g. CD11b and CD68) and use the phagocytic and cytotoxic system to eliminate foreign bodies [26]. They also act as antigen presenting cells to activate T cells. Many CNS diseases such as infectious and degenerative diseases are associated with activated microglial cells [27].

Osteoclasts

Osteoclasts are multinucleate giant cells in the bone derived from circulating monocytes [28]. They are formed by the fusion of multiple monocyte/macrophage cells. They have a foam (vacuolated) cytoplasm and may contain up to 200 nuclei. However, the majority of osteoclasts contain between 5-20 nuclei. Osteoclasts produce many enzymes such as alkaline phosphatase and cathepsin K. They lie in a small groove on the bone surface called Howship's lacunae. Osteoclasts are responsible for bone resorption[29] - a process that is important for bone growth and repair [30]. Osteoclasts decalcify the bone by acid secretion and then engulf the fragmented bone and breakdown the organic part of the bone, collagen, and the non-organic part, calcium and phosphorus, where they release these products into the circulation [31].

Dendritic cells

Dendritic cells are found mainly in skin, nose, lung and gastrointestinal lining where there is contact with the external environment[32,33]. There are two main types of dendritic cells, myeloid dendritic cells and plasmacytoid dendritic cells. They act as antigen presenting cells, activate T cells and stimulate B cell differentiation and have highly endocytic activity. Immature dendritic cells engulf and process pathogen and then start their maturation, where they migrate to lymphoid tissue to present antigens to T cells [34,35].

Alveolar macrophages

Macrophages are predominant cells in the lung [36,37] and they contain membrane-bounded cytoplasmic inclusions containing proteolytic enzymes [38]. Lung macrophages are involved in the defence against foreign bodies and pathogens [39] and have a major role in chronic granulomatous diseases such as sarcoidosis and tuberculosis [40,41].

2. Role of Macrophages in Some Benign Conditions

As macrophages form an important part of the immune system and are resident in nearly all tissues of the body, they play a role in many benign diseases some of which are discussed in this section.

Macrophages have a significant role in the inflammatory response [42,43] and play an important role in injury and repair [44,45]. They can attack and engulf more than 100 bacteria before they die by their own digesting enzymes. Macrophages can either use these digesting enzymes or induce apoptosis to kill pathogens [46]. Macrophages perform many important functions in inflammation: they help in antigen presentation to helper T cells via the MHC class II molecules [9.10]. Additionally, they release cytokines, chemokines, growth factors, enzymes and prostaglandins [47].They also secrete inflammatory mediators (such as IL-1, TNF-α and proteolytic enzymes) that interact with the extracellular matrix(ECM) and facilitate the accumulation of leukocytes into inflammatory site [48].

2.1 Role of macrophages in wound healing

The main inflammatory cells to appear in a wound in the first few hours of injury are neutrophils which arethen replaced by monocytes [49]. Monocytes move rapidly toward the wound site in response to many chemoattractant factors where they then differentiate into macrophages [49]. By day five of injury, macrophages represent the main inflammatory cell and have an important role in regulating subsequent events in the healing wound [49]. One of the main functions of macrophages is to remove cellular debris by phagocytosis. Macrophages also enhance fibrosis - which is important in re-building the extracellular matrix [3] - and help in the revascularization of the wounded area by releasing many growth and angiogenic factors [50,51]. Many studies have shown that the hypoxic environment of injured tissues stimulates macrophages to secrete many angiogenic and fibrogenic factors such as Vascular Endothelial Growth Factor (VEGF), fibroblast growth factor (FGF), and platelet derived growth factor (PDGF) [52, 53,54]. The role of macrophages in wound healing is summarized in figure 1.2.

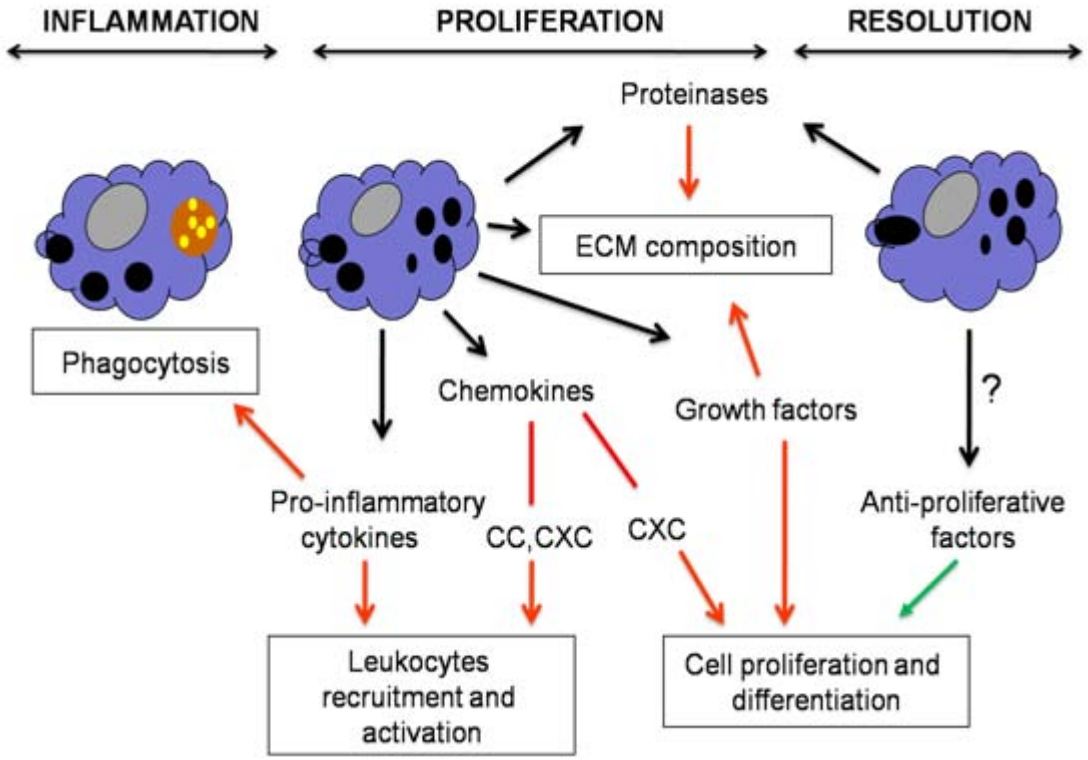

Figure 1.2: The role of macrophages in wound healing

Macrophages play an important role in all stages of wound healing including the early inflammatory stage, proliferation of cellular component of the wound and wound resolution. Macrophages promote the early inflammatory phase of the

wound by secreting pro-inflammatory cytokines which help in the accumulation of leukocytes. Macrophages also secrete growth factors that help in proliferation and differentiation of a wide range of cells in the wound. However, macrophages also then secrete anti-proliferative factors that help in the resolution phases of wound healing. Black arrows show synthesis of mediators. Red arrows show positive mediator effects. Green arrow indicates negative mediator effect. Redrawnfrom [49].

2.2 Role of macrophages in atherosclerosis

Atherosclerosis is a disease of larger and medium-sized arteries and is responsible for more than half of all deaths in the Western world. It is characterized by vascular inflammation and deposition of lipids, cholesterol, calcium and cellular debris within the intima of the blood vessel wall to form atheroma. As a result, atheroma causes acute and chronic lumen obstruction and decreases oxygen supply to target organs [55,56]. Lipid laden macrophages (foam cells) were detected in premature and advanced atherosclerotic lesions and are therefore thought to have an important role in the incidence and progression of atherosclerosis [57,58]. Early atherosclerotic lesions (fatty streaks) start with disruption of the endothelium followed by accumulation of monocytes and macrophages. MCP-1 secreted by the endothelial cells plays an important role in monocyte accumulation and macrophage retention in atherosclerotic lesions [59]. In 1998 Boring *et al.*demonstrated a decrease in atherosclerotic lesion size in mice deficient for the MCP-1 receptor, CCR-2. The number of macrophages and monocytes in the aortas of CCR-2-deficient mice was significantly low and the overall plasma cholesterol levels were unaffected by the CCR-2 genotype [60].As a potent chemoattractant for monocyte, CX3C also involved in the recruitment of monocytes into atherosclerotic plague [61] andCX3CR1 is required for vascular recruitment of inflammatory monocytes and development of macrophage-rich atherosclerotic lesions [62]. Recent studies showed that there are two different types of monocytes which have been identified in atherosclerotic lesion, $CCR2^{+}/CX3CR1^{+}$ and $CCR2^{-}/CX3CR1^{+}$ and both of them are involved in the pathogenesisof atherosclerotic lesion [63]. Macrophages in early atherosclerotic lesions accumulate cholesterol and triglyceride to form foam cells. More advanced lesions are formed by proliferating smooth muscle cells, foam macrophages and have a central lipid core [64]. Macrophages initiate and enhance atherosclerotic lesion by phagocytosis of oxidized low density lipoprotein (LDL) via scavenger receptor [65] and secretion of inflammatory mediators such as cytokines and ECM degrading enzymes [66]. The main cytokines secreted by foam macrophages in atherosclerotic plaques are PDGF, transforming growth factor-β (TGF-β), TNF-α, IL-1, IL-6, IL-8 and M-CSF [67,68,69,70,71]. Through these cytokines, macrophages promote smooth muscle cell infiltration and proliferation and also enhance lipoprotein oxidation [72,73]. Moreover, modification of ECM elements leads to retention of lipid in the blood vessel intema. The lipid content of foam cells is composed of a large amount of natural cholesterol derived from low density lipoprotein (LDL) and a small percentage of oxidized cholesterol (oxysterols). Recent studies have shown that the oxysterol content of foam macrophages impairs the export of cholesterol out of the foam macrophage. Therefore, the presence of foam macrophages in the atherosclerotic lesion can be maintained for long periods and promote disease progression [58]. The role of macrophages in atherosclerosis was confirmed by the inhibition of atherosclerosis in the M-CSF knockout mouse model (*op/op*) [74,75]. M-CSF is a growth factor that promotes the survival and differentiation of macrophages [76] so in these two studies, atherosclerosis was induced in the *op/op* mice either by crossing them with Apolipoprotein E (ApoE) knockout mice or by feeding them a high fat diet [74,75]. ApoE is a protein that is synthesized in the liver and has an anti-atherogenic role. Removal of *apoE*gene leads to severe hypercholesterolemia and spontaneous atherosclerosis even with a low fat diet [77]. Qiao *et al.,* 1997 and Smith *et al.,* 1995 showed that a lack of M-CSF markedly reduced atherogenesis in apoE null mice [74,75]. The role of macrophages in atherosclerosis can be summarized in three major points *(Figure 1.3):*

1) Continuous accumulation of foam macrophages into early and late atherosclerotic lesions.
2) Macrophages are an important source of cytokines that cause smooth muscle cell proliferation and ECM degradation.
3) Macrophages promote lipoprotein oxidation.

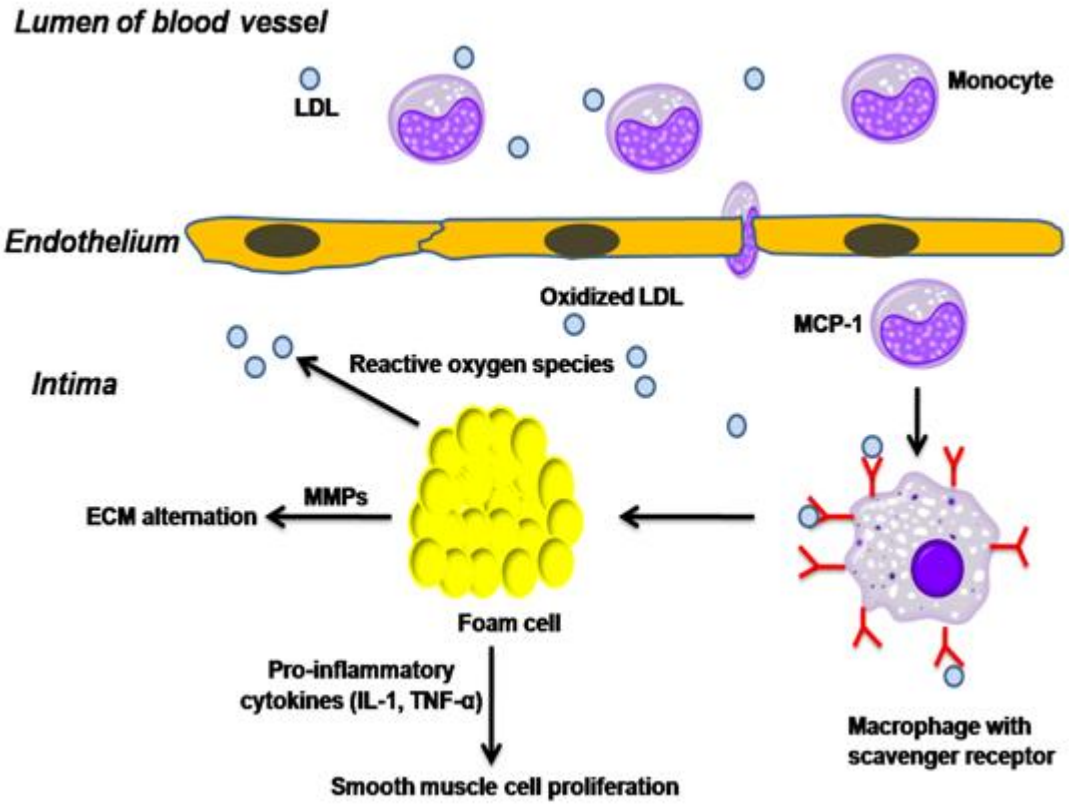

Figure 1.3: Role of macrophages inatherosclerosis

Macrophages participate in the development and progression of atherosclerosis. Monocyte recruitment into the atherosclerotic lesionis mediated by MCP-1 expressed by endothelial cells. Monocytes accumulate into the blood vessel intima where they differentiate into macrophages and express scavenger receptors. Through its scavenger receptors, macrophages engulf oxidized LDL to become foam cells. Once formed, foam cells secrete matrix metalloproteinases (MMPs) and pro-inflammatory cytokines (IL-1 and TNF-α) to enhance smooth muscle cell proliferation and ECM degradation. Foam cells are also an important source of reactive oxygen species that oxidize more LDLwhich is the main component of foam cells (modified from http://www.hdtforum.org/ktmlstandard/images/).

2.3 Role of macrophages in rheumatoid arthritis

Rheumatoid arthritis is characterized by chronic inflammation of joints[78]. Females are more commonly affected than males and also have a more severe clinical course [79]. Rheumatoid arthritis commonly affects middle aged people however people of any age can be affected[80].The inflamed joint contains a significant number of inflammatory cells such as B cells, T cells, plasma cells, mast cells and activated macrophages[81]. However,macrophages have an important role in rheumatoid arthritis as they accumulate in large numbers in the inflamed, hypoxic [82], synovial membrane [83,84]. Monocytes migrate into the rheumatic joint where they then differentiate into macrophages [85]. These activated macrophages secrete a large number of cytokines such as TNF-α, IL-1, IL-6, IL-8, IL12, IL-18 and CSF [86,87,88], among which, TNF-α plays an essential role in the pathogenesis of rheumatoid arthritis *(Figure 1.4)*. The binding of TNF-α to two different receptors, TNFR1 and TNFR2, activates two transcription factors, nuclear factor κB (NF-κB) and c-Jun which then allow the expression of genes that mediate different biological processes in rheumatoid arthritis [89,90]. TNF-α has the ability to enhance angiogenesis, activate chondrocytes and osteoclasts to cause the osteolytic lesions associated with the disease [91]. TNF-α also causes leukocyte accumulation [92]. Macrophages in the rheumatic joint also secrete a large amount of MCP-1 [93] and proteolytic enzymes such as elastase and collagenase [94]. All these mediators cause joint destruction and also lead to collagen and fibroblast accumulation. The role of macrophage in rheumatoid arthritis is highlighted by the regression of the disease when drugs directed toward macrophages mediators are used. e.g. administration of IL-4 and IL-13 decreases the production of TNF-α and IL-1 and hence reduce the severity of the disease [95]. Furthermore, Methotrexate and dexamethasone (drugs used for rheumatoid arthritis treatment) prevent monocyte accumulation and also decrease secretion of cytokines by activated macrophages [96,97]. Gold salts also decreases production of IL-8 and MCP-1 [98,99].

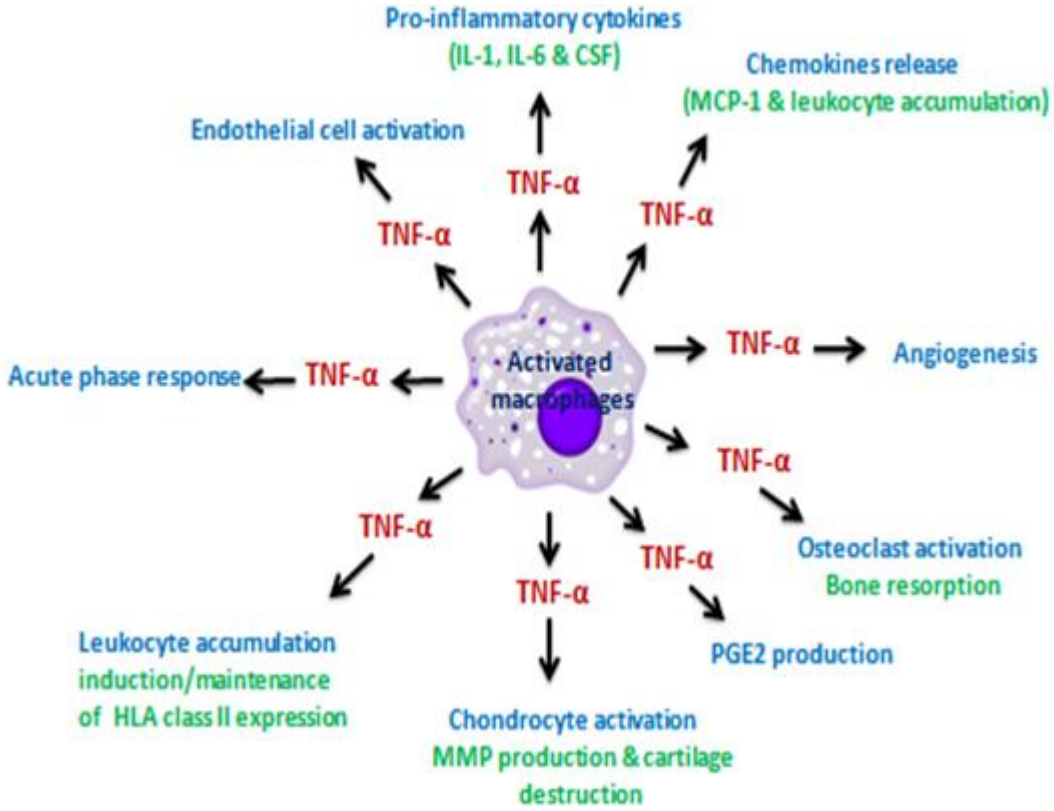

Figure 1.4: Role of macrophages in rheumatoid arthritis

TNF-α secreted by activated macrophages in rheumatoid joints plays an important role in disease pathogenesis. Through its binding to two different receptors, TNF-α activates transcription factors that mediate endothelial cell activation, promotion of angiogenesis and enhancement of the production of cytokines and chemokines that cause leukocyte accumulation. The activation of these transcription factors also mediates the destruction of bone and cartilage associated with rheumatoid arthritis. Redrawn from [83].

2.4 Role of macrophages in inflammatory bowel disease

Inflammatory bowel disease (IBD) (Chron's disease and Ulcerative colitis) is a chronic relapsing inflammatory disease of the gastrointestinal tract [100]. Macrophages also play an important role in the pathogenesis of the IBD ([101]. Many studies demonstrated that the accumulation of macrophages in lamina propria of small and large bowel is associated with increase expression of acid phosphatase and nonspecific esterase as well a change in the shape of the cells [102].Macrophages detected in the inflamed bowel also showed phenotype changes [103]. Furthermore, high level of cytokines such as tumour necrosis factor alpha (TNF-α) IL-6, 8, 10 and 12 was detected in active form of IBD where the ulceration is severe and involve a large segment of the bowel [104]. Peripheral blood monocytes from patient with IBD secret high level of IL-6 [105].

3. Role of Macrophages in Malignant Tumours

Following cardiovascular disease, malignant tumours arethe second most common cause of death worldwide,with lung malignancies alone contributing to 12% and breast cancer accounting for 10% of all cancer cases [106]. Other malignancies such as colorectal, stomach, liver, cervical, prostate, bladder, and non-Hodgkin's lymphoma (NHL) are also very common [106].

The majority of malignant tumours are composed of a complex multicellular population [107] and contain a large amount of leukocytic infiltration [108]. This leukocytic infiltration is formed mainly of macrophages [109] where they show a distinct phenotype and are called tumour associated macrophages (TAMs) [110,111,112]. Therefore, macrophages are a prominent cell type in most human and experimental tumours, for example TAMs represent up to 50% of the total cell population in breast carcinoma [113,114,115]. Chemoattractants produced by neoplastic cells such as CSF-1 [116,117], MCP-1 [118, 119, 120] and VEGF [121,122,123,124] are thought to enhance the accumulation of TAMs in tumours. Hypoxia also is an important stimulus for the attraction of TAMs to different tumours [127,128,129,130]also it enhances tumour proliferation and progression [125, 126]. It has been shown that TAMs accumulated in the hypoxic area of endometrial cancer [131], breast cancer [132] and ovarian tumours [133] and as tumour size increases, its centre becomes more hypoxic which leads to the accumulation of more TAMs [134,135].

Macrophages in healthy or inflamed tissue express a classically activated (or 'M1') phenotype that is activated by lipopolysaccharide (LPS) and interferon γ (INF-γ) and are capable of inhibiting tumour cell division through the secretion of IL-1 and TNF-α [112,136,137]. Macrophages can also bind tumour cells and lyse them by a process called macrophage-mediated tumour cytotoxicity. This isa non-phagocytic process which is selective for tumour cells and is also antibody independent [138]. Another process used by

the macrophage to lyse tumour cells is the antibody-dependent cellular toxicity process. In this process, macrophages lyse antibody-coated tumour cells [139]. In contrast, macrophages in primary and secondary tumours are often activated by tumour derived molecules and hypoxia to become alternatively activated (or 'M2' like) and enhance tumour growth and metastasis [112]. Although TAMs share several features with M2-activated macrophages, they have a variable phenotype depending upon tumour type, stage and their location in the tumour microenvironment and therefore, show different responses to treatments in different tumours [140,141,142].

Recent studies have suggested that macrophages promote tumour growth due to their ability to secrete a number of tumour mitogens including epidermal growth factor (EGF, a potent chemotactic factor for epithelial cells) [143,144,145], angiogenesis stimulating factors like VEGF [114,122,146,147,148,149,150,151,152], acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), PDGF [153], TNF-α, IL-1, and IL-8 [154,155,156,157,158]. Macrophages also play an important role in promoting tumour cells ability to metastasize [159,160,161,162]. The migration of tumour cells is enhanced by the expression of EGF in macrophages, the differentiation and survival of said macrophages are in turn promoted by CSF-1 secreted by the tumour cells [143,162,163] *(Figure 1.5)*.

Macrophages also stimulate resident cells such as fibroblasts and adipocytes to play a significant role in tumour growth and metastasis [164,165,166,167,168,169,170].In many human tumours, a high number of macrophage infiltration is associated with bad prognosis [47,171]and accumulation of macrophages in certain tumours can be used as an indication of relapse of the primary tumour [172]. Moreover, high levels of M-CSF, which promotes the survival and differentiation of macrophages [173], is also associated with poor prognosis [174, 175,176,177].Therefore transgenic mouse models that deplete macrophages with high efficiency have been used to assess the effect of macrophage depletion on tumour angiogenesis and progression[178,179].

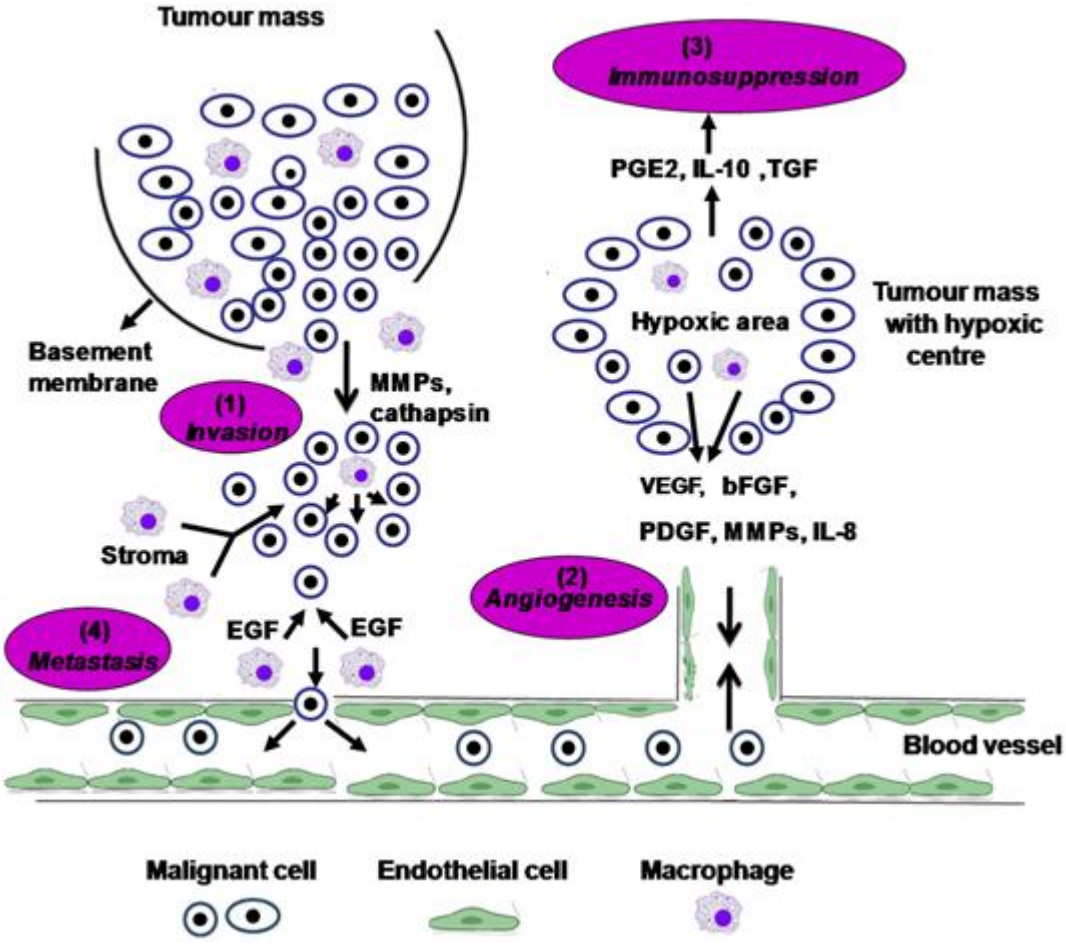

Figure 1.5: Role of TAMs in tumour progression

(1) Invasion: TAMs breakdown the basement membrane by secretion of a variety of proteases and attract tumour cells into surrounding stroma. (2) Angiogenesis: TAMs promote angiogenesis by secretion of angiogenic factors. (3) Immunosuppression: TAMs secrete immunosuppressive factors such as prostaglandin E2 (PGE2) and IL-10 that suppress the anti-tumour effects of other cells such as T cells. (4) Metastases: TAMs enhance tumour cell metastases through the secretion of EGF. Re-drawn from [180].

4. Concluding Remarks

The aim of this review has been to illustrate the potential importance of macrophages in benign and malignant lesions. Although, unequivocal evidence from both human and

murine diseases has certainly established a causative role for macrophages in certain diseases, yet, much is still to be learned about role of macrophages in these diseases.To further elucidate the role of macrophages in diseases, the use of macrophages depletion mouse model is recommended. And sincemost of the available models are either nonspecific, use toxic materials or are associated with severe developmental abnormalities, the use of inducible and specific models will be highly important. Mouse models that deplete more than 70% of macrophages will associated with a sever health problem and immune compression side effect in the mouse which will has a huge impact on the accuracy of any results, therefore, mouse model with moderate, about 50%, ablation will be more suitable [181]. The inducibility of the ablation also should be taking inconsideration as this may affect the study.

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References

[1] Ross, J. A. and M. J. Auger (2002). The biology of the macrophage. In; The Macrophages, **2nd edition**. Burke B & CE (Eds).Oxford University Press. . Oxford. UK, Oxford University.

[2] Van Furth, R. (1980). Cells of the mononuclear phagocyte system. Nomenclature in term of sites and conitions. In van Furth R (ed): Mononuclear Phagocytes: Functional Aspects. Part 1. The Huge Martins Nijhoff Publishers, 1980, pp1-30.

[3] Kovacs, E. J. and L. A. DiPietro (1994). Fibrogenic cytokines and connective tissue production. *Faseb J***8**(11): 854-61.

[4] Oflazoglu, E., I. J. Stone, L. Brown, K. A. Gordon, N. van Rooijen, M. Jonas, C. L. Law, I. S. Grewal and H. P. Gerber (2009). Macrophages and Fc-receptor interactions contribute to the antitumour activities of the anti-CD40 antibody SGN-40. *Br J Cancer***100**(1): 113-7.

[5] Bar, R. S., P. Gorden, J. Roth, C. R. Kahn and P. De Meyts (1976). Fluctuations in the affinity and concentration of insulin receptors on circulating monocytes of obese patients: effects of starvation, refeeding, and dieting. *J Clin Invest***58**(5): 1123-35.

[6] Thomas, D. W. and M. D. Hoffman (1984). Identification of macrophage receptors for angiotensin: a potential role in antigen uptake for T lymphocyte responses? *J Immunol***132**(6): 2807-12.

[7] Berken, A. and B. Benacerraf (1966). Properties of antibodies cytophilic for macrophages. *J Exp Med***123**(1): 119-44.

[8] Underhill, D. M. and A. Ozinsky (2002). Phagocytosis of microbes: complexity in action. *Annu Rev Immunol***20**: 825-52.

[9] Clausen, B. E., J. M. Waldburger, F. Schwenk, E. Barras, B. Mach, K. Rajewsky, I. Forster and W. Reith (1998). Residual MHC class II expression on mature dendritic cells and activated B cells in RFX5-deficient mice. *Immunity***8**(2): 143-55.

[10] Paglia, P. and C. MP (2002). Macrophages as antigen-presenting cells: relationship to dendritic cells and use in vaccination studies. In The Macrophage (2nd edition) 2002 Eds. Burke, B and Lewis, CE. Oxford University Press, Oxford, UK.

[11] Alberts, B., A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter (2002). Molecular Biology of the cell. **4th edition**, Garland Science. New york. USA.

[12] Goerdt, S. and C. E. Orfanos (1999). Other functions, other genes: alternative activation of antigen-presenting cells. *Immunity***10**(2): 137-42.

[13] Lin, E. Y., A. V. Nguyen, R. G. Russell and J. W. Pollard (2001). Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. *J Exp Med***193**(6): 727-40.

[14] Nathan, C. F. (1987). Secretory products of macrophages. *J Clin Invest***79**(2): 319-26.

[15] Gordon, S. and P. R. Taylor (2005). Monocyte and macrophage heterogeneity. *Nat Rev Immunol***5**(12): 953-64.

[16] Palframan, R. T., S. Jung, G. Cheng, W. Weninger, Y. Luo, M. Dorf, D. R. Littman, B. J. Rollins, H. Zweerink, A. Rot and U. H. von Andrian (2001). Inflammatory chemokine transport and presentation in HEV: a remote control mechanism for monocyte recruitment to lymph nodes in inflamed tissues. *J Exp Med***194**(9): 1361-73

[17] Geissmann, F., S. Jung and D. R. Littman (2003). Blood monocytes consist of two principal subsets with distinct migratory properties. *Immunity***19**(1): 71-82.

[18] Kuziel, W. A., S. J. Morgan, T. C. Dawson, S. Griffin, O. Smithies, K. Ley and N. Maeda (1997). Severe reduction in leukocyte adhesion and monocyte extravasation in mice deficient in CC chemokine receptor 2. *ProcNatlAcadSci U S A***94**(22): 12053-8.

[19] Heale, J. P. and D. P. Speert (2002). Macrophages in bacterial infection. In;The Macrophages, **2nd edition** . Burke B & CE (Eds).Oxford University Press. . Oxford.

[20] Kreutz, A., J. Fritsche and R. Andreesen (2002). Macrophages in tumour biology in The Macrophages. **2nd edition**, Burke B & CE. Oxford University Press. UK

[21] Ofek, I. and N. Sharon (1988). Lectinophagocytosis: a molecular mechanism of recognition between cell surface sugars and lectins in the phagocytosis of bacteria. *Infect Immun***56**(3): 539-47.

[22] Ebe, Y., G. Hasegawa, H. Takatsuka, H. Umezu, M. Mitsuyama, M. Arakawa, N. Mukaida and M. Naito (1999). The role of Kupffer cells and regulation of neutrophil migration into the liver by macrophage inflammatory protein-2 in primary listeriosis in mice. *PatholInt***49**(6): 519-32.

[23] Roh, M. S., L. Wang, C. Oyedeji, M. E. LeRoux, S. A. Curley, R. E. Pollock and J. Klostergaard (1990). Human Kupffer cells are cytotoxic against human colon adenocarcinoma. *Surgery***108**(2): 400-4; discussion 404-5.

[24] Song, E., J. Chen, N. Ouyang, M. Wang, M. S. Exton and U. Heemann (2001). Kupffer cells of cirrhotic rat livers sensitize colon cancer cells to Fas-mediated apoptosis. *Br J Cancer***84**(9): 1265-71.

[25] Nimmerjahn, A., F. Kirchhoff and F. Helmchen (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science***308**(5726): 1314-8.
[26] Perry, V. H. (2003). macrophages in the central and peripheral nervous system. In:The Macrophage as therapeutic target. Simon Gordon (Eds).Oxford University Press.
[27] Matyszak, M. K. and H. V. Perry (2002). Macrophages in the central nervous system. In;The Macrophages, **2nd edition**. Burke B & CE (Eds).Oxford University Press. Oxford, Oxford University.
[28] Miyamoto, T. and T. Suda (2003). Differentiation and function of osteoclasts. *Keio J Med***52**(1): 1-7.
[29] Jimi, E., I. Nakamura, H. Amano, Y. Taguchi, T. Tsurukai, M. Tamura, N. Takahashi and T. Suda (1996). Osteoclast function is activated by osteoblastic cells through a mechanism involving cell-to-cell contact. *Endocrinology***137**(5): 2187-90.
[30] Suzumoto, R., M. Takami and T. Sasaki (2005). Differentiation and function of osteoclasts cultured on bone and cartilage. *J Electron Microsc (Tokyo)***54**(6): 529-40.
[31] Chambers, J. T. (2003). The osteoclast. In:The macrophage as therapeutic target. Oxford. UK.
[32] Menetrier-Caux, C., G. Montmain, M. C. Dieu, C. Bain, M. C. Favrot, C. Caux and J. Y. Blay (1998). Inhibition of the differentiation of dendritic cells from CD34(+) progenitors by tumor cells: role of interleukin-6 and macrophage colony-stimulating factor. *Blood***92**(12): 4778-91.
[33] Satthaporn, S. and O. Eremin (2001). Dendritic cells (I): Biological functions. *J R Coll Surg Edinb***46**(1): 9-19.
[34] Kim, G. Y., K. H. Kim, S. H. Lee, M. S. Yoon, H. J. Lee, D. O. Moon, C. M. Lee, S. C. Ahn, Y. C. Park and Y. M. Park (2005). Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-kappa B as potential targets. *J Immunol***174**(12): 8116-24.
[35] Vuckovic, S. and J. N. D. Hart (2003). Dendritic cells versus macrophages as antigen-presenting cells:common and unique features. In:. Oxford. UK.
[36] Adamson, I. Y., H. Prieditis and L. Young (1997). Lung mesothelial cell and fibroblast responses to pleural and alveolar macrophage supernatants and to lavage fluids from crocidolite-exposed rats. *Am J Respir Cell MolBiol***16**(6): 650-6.
[37] Nakstad, B., T. Lyberg, F. Skjorten and N. P. Boye (1989). Subpopulations of human lung alveolar macrophages: ultrastructural features. *UltrastructPathol***13**(1): 1-13.
[38] Lindroos, P. M., P. G. Coin, A. Badgett, D. L. Morgan and J. C. Bonner (1997). Alveolar macrophages stimulated with titanium dioxide, chrysotile asbestos, and residual oil fly ash upregulate the PDGF receptor-alpha on lung fibroblasts through an IL-1beta-dependent mechanism. *Am J Respir Cell MolBiol***16**(3): 283-92
[39] Ballinger, M. N., L. L. Hubbard, T. R. McMillan, G. B. Toews, M. Peters-Golden, R. Paine Iii and B. B. Moore (2008). Paradoxical Role of Alveolar Macrophage-Derived Granulocyte Macrophage Colony Stimulating Factor in Pulmonary Host Defense post-Bone Marrow Transplantation. *Am J Physiol Lung Cell Mol Physiol*.
[40] Broug-Holub, E., G. B. Toews, J. F. van Iwaarden, R. M. Strieter, S. L. Kunkel, R. Paine, 3rd and T. J. Standiford (1997). Alveolar macrophages are required for protective pulmonary defenses in murine Klebsiella pneumonia: elimination of alveolar macrophages increases neutrophil recruitment but decreases bacterial clearance and survival. *Infect Immun***65**(4): 1139-46.
[41] Shapiro, S. D. (1999). The macrophage in chronic obstructive pulmonary disease. *Am J RespirCrit Care Med***160**(5 Pt 2): S29-32.
[42] Odegaard, J. I., D. Vats, L. Zhang, R. Ricardo-Gonzalez, K. L. Smith, D. B. Sykes, M. P. Kamps and A. Chawla (2007). Quantitative expansion of ES cell-derived myeloid progenitors capable of differentiating into macrophages. *J LeukocBiol***81**(3): 711-9.
[43] Pierce, G. F. (1990). Macrophages: important physiologic and pathologic sources of polypeptide growth factors. *Am J Respir Cell MolBiol***2**(3): 233-4.
[44] Duffield, J. S. (2003). The inflammatory macrophage: a story of Jekyll and Hyde. *ClinSci (Lond)***104**(1): 27-38.
[45] Pan, H., G. Mostoslavsky, E. Eruslanov, D. N. Kotton and I. Kramnik (2008). Dual-promoter lentiviral system allows inducible expression of noxious proteins in macrophages. *J Immunol Methods***329**(1-2): 31-44.
[46] Aliprantis, A. O., G. Diez-Roux, L. C. Mulder, A. Zychlinsky and R. A. Lang (1996). Do macrophages kill through apoptosis? *Immunol Today***17**(12): 573-6.
[47] Bingle, L., N. J. Brown and C. E. (2002). The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies. *J Pathol***196**(3): 254-65.
[48] Milano, S., F. Arcoleo, P. D'Agostino and E. Cillari (1997). Intraperitoneal injection of tetracyclines protects mice from lethal endotoxemiadownregulating inducible nitric oxide synthase in various organs and cytokine and nitrate secretion in blood. *Antimicrob Agents Chemother***41**(1): 117-21.
[49] DiPietro, L. A. (1995). Wound healing: the role of the macrophage and other immune cells. *Shock***4**(4): 233-40.
[50] Keane, M. P. and R. M. Strieter (1999). The role of CXC chemokines in the regulation of angiogenesis. *ChemImmunol***72**: 86-101.
[51] Sunderkotter, C., M. Goebeler, K. Schulze-Osthoff, R. Bhardwaj and C. Sorg (1991). Macrophage-derived angiogenesis factors. *PharmacolTher***51**(2): 195-216.
[52] Kivisaari, J. (1975). Oxygen and carbon dioxide tensions in healing tissue. *Acta ChirScand***141**(8): 693-6.
[53] Kuwabara, K., S. Ogawa, M. Matsumoto, S. Koga, M. Clauss, D. J. Pinsky, P. Lyn, J. Leavy, L. Witte, J. Joseph-Silverstein and *et al*. (1995). Hypoxia-mediated induction of acidic/basic fibroblast growth factor and platelet-derived growth factor in mononuclear phagocytes stimulates growth of hypoxic endothelial cells. *ProcNatlAcadSci U S A***92**(10): 4606-10.
[54] Xiong, M., G. Elson, D. Legarda and S. J. Leibovich (1998). Production of vascular endothelial growth factor by murine macrophages: regulation by hypoxia,

lactate, and the inducible nitric oxide synthase pathway. *Am J Pathol***153**(2): 587-98.

[55] Bjornheden, T., M. Levin, M. Evaldsson and O. Wiklund (1999). Evidence of hypoxic areas within the arterial wall in vivo. *ArterioscIerThrombVascBiol***19**(4): 870-6.

[56] Rossi, F. M. and H. M. Blau (1998). Recent advances in inducible gene expression systems. *CurrOpinBiotechnol***9**(5): 451-6.

[57] Moore, K. J., R. P. Fabunmi, L. P. Andersson and M. W. Freeman (1998). In vitro-differentiated embryonic stem cell macrophages: a model system for studying atherosclerosis-associated macrophage functions. *ArterioscIerThrombVascBiol***18**(10): 1647-5

[58] van Reyk, D. M. and W. Jessup (1999). The macrophage in atherosclerosis: modulation of cell function by sterols. *J LeukocBiol***66**(4): 557-61.

[59] Gu, L., Y. Okada, S. K. Clinton, C. Gerard, G. K. Sukhova, P. Libby and B. J. Rollins (1998). Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice. *Mol Cell***2**(2): 275-81.

[60] Boring, L., J. Gosling, M. Cleary and I. F. Charo (1998). Decreased lesion formation in CCR2-/- mice reveals a role for chemokines in the initiation of atherosclerosis. *Nature***394**(6696): 894-7.

[61] Lesnik, P., C. A. Haskell and I. F. Charo (2003). Decreased atherosclerosis in CX3CR1-/- mice reveals a role for fractalkine in atherogenesis. *J Clin Invest***111**(3): 333-40.

[62] Saederup, N., L. Chan, S. A. Lira and I. F. Charo (2008). Fractalkine deficiency markedly reduces macrophage accumulation and atherosclerotic lesion formation in CCR2-/- mice: evidence for independent chemokine functions in atherogenesis. *Circulation***117**(13): 1642-8.

[63] Tacke, F., D. Alvarez, T. J. Kaplan, C. Jakubzick, R. Spanbroek, J. Llodra, A. Garin, J. Liu, M. Mack, N. van Rooijen, S. A. Lira, A. J. Habenicht and G. J. Randolph (2007). Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J Clin Invest***117**(1): 185-94.

[64] Ross, R. and J. A. Glomset (1976). The pathogenesis of atherosclerosis (first of two parts). *N Engl J Med***295**(7): 369-77.

[65] Winyard, P. G., F. Tatzber, H. Esterbauer, M. L. Kus, D. R. Blake and C. J. Morris (1993). Presence of foam cells containing oxidised low density lipoprotein in the synovial membrane from patients with rheumatoid arthritis. *Ann Rheum Dis***52**(9): 677-80.

[66] Shibuya, K., M. Tajima, J. Yamate, T. Saitoh and T. Nunoya (1997). Carbon tetrachloride-induced hepatotoxicity enhances the development of pulmonary foam cells in rats fed a cholesterol-cholic acid diet. *ToxicolPathol***25**(5): 487-94.

[67] Apostolopoulos, J., P. Davenport and P. G. Tipping (1996). Interleukin-8 production by macrophages from atheromatous plaques. *ArterioscIerThrombVascBiol***16**(8): 1007-12

[68] Kishikawa, H., T. Shimokama and T. Watanabe (1993). Localization of T lymphocytes and macrophages expressing IL-1, IL-2 receptor, IL-6 and TNF in human aortic intima. Role of cell-mediated immunity in human atherogenesis. *Virchows Arch A PatholAnatHistopathol***423**(6): 433-42.

[69] Rayment, N. B., E. Moss, L. Faulkner, P. M. Brickell, M. J. Davies, N. Woolf and D. R. Katz (1996). Synthesis of TNF alpha and TGF beta mRNA in the different micro-environments within atheromatous plaques. *Cardiovasc Res***32**(6): 1123-30.

[70] Rosenfeld, M. E., S. Yla-Herttuala, B. A. Lipton, V. A. Ord, J. L. Witztum and D. Steinberg (1992). Macrophage colony-stimulating factor mRNA and protein in atherosclerotic lesions of rabbits and humans. *Am J Pathol***140**(2): 291-300.

[71] Tipping, P. G. and W. W. Hancock (1993). Production of tumor necrosis factor and interleukin-1 by macrophages from human atheromatous plaques. *Am J Pathol***142**(6): 1721-8.

[72] Campbell, J. H., R. E. Rennick, S. G. Kalevitch and G. R. Campbell (1992). Heparansulfate-degrading enzymes induce modulation of smooth muscle phenotype. *Exp Cell Res***200**(1): 156-67.

[73] Liu, Y., L. M. Hulten and O. Wiklund (1997). Macrophages isolated from human atherosclerotic plaques produce IL-8, and oxysterols may have a regulatory function for IL-8 production. *ArterioscIerThrombVascBiol***17**(2): 317-23.

[74] Qiao, J. H., J. Tripathi, N. K. Mishra, Y. Cai, S. Tripathi, X. P. Wang, S. Imes, M. C. Fishbein, S. K. Clinton, P. Libby, A. J. Lusis and T. B. Rajavashisth (1997). Role of macrophage colony-stimulating factor in atherosclerosis: studies of osteopetrotic mice. *Am J Pathol***150**(5): 1687-99.

[75] Smith, J. D., E. Trogan, M. Ginsberg, C. Grigaux, J. Tian and M. Miyata (1995). Decreased atherosclerosis in mice deficient in both macrophage colony-stimulating factor (op) and apolipoprotein E. *ProcNatlAcadSci U S A***92**(18): 8264-8.

[76] Stanley, E. R., L. J. Guilbert, R. J. Tushinski and S. H. Bartelmez (1983). CSF-1--a mononuclear phagocyte lineage-specific hemopoietic growth factor. *J Cell Biochem***21**(2): 151-9.

[77] Zadelaar, S., R. Kleemann, L. Verschuren, J. de Vries-Van der Weij, J. van der Hoorn, H. M. Princen and T. Kooistra (2007). Mouse models for atherosclerosis and pharmaceutical modifiers. *ArterioscIerThrombVascBiol***27**(8): 1706-21.

[78] Hirsch, R., J. P. Lin, W. W. Scott, Jr., L. D. Ma, S. R. Pillemer, D. L. Kastner, L. T. Jacobsson, D. A. Bloch, W. C. Knowler, P. H. Bennett and S. J. Bale (1998). Rheumatoid arthritis in the Pima Indians: the intersection of epidemiologic, demographic, and genealogic data. *Arthritis Rheum***41**(8): 1464-9.

[79] van Vollenhoven, R. F. (2009). Sex differences in rheumatoid arthritis: more than meets the eye. *BMC Med***7**: 12.

[80] Lawrence, R. C., C. G. Helmick, F. C. Arnett, R. A. Deyo, D. T. Felson, E. H. Giannini, S. P. Heyse, R. Hirsch, M. C. Hochberg, G. G. Hunder, M. H. Liang, S. R. Pillemer, V. D. Steen and F. Wolfe (1998). Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum***41**(5): 778-99.

[81] Szekanecz, Z. and A. E. Koch (2007). Macrophages and their products in rheumatoid arthritis. *CurrOpinRheumatol***19**(3): 289-95.
[82] Stevens, C. R., R. B. Williams, A. J. Farrell and D. R. Blake (1991). Hypoxia and inflammatory synovitis: observations and speculation. *Ann Rheum Dis***50**(2): 124-32.
[83] Brennan, F. M. and I. B. McInnes (2008). Evidence that cytokines play a role in rheumatoid arthritis. *J Clin Invest***118**(11): 3537-45.
[84] Pelegri, C., A. Franch, C. Castellote and M. Castell (1995). Immunohistochemical changes in synovial tissue during the course of adjuvant arthritis. *J Rheumatol***22**(1): 124-32.
[85] Ridley, M. G., G. Kingsley, C. Pitzalis and G. S. Panayi (1990). Monocyte activation in rheumatoid arthritis: evidence for in situ activation and differentiation in joints. *Br J Rheumatol***29**(2): 84-8.
[86] Firestein, G. S. and N. J. Zvaifler (1990). How important are T cells in chronic rheumatoid synovitis? *Arthritis Rheum***33**(6): 768-73.
[87] Gracie, J. A., R. J. Forsey, W. L. Chan, A. Gilmour, B. P. Leung, M. R. Greer, K. Kennedy, R. Carter, X. Q. Wei, D. Xu, M. Field, A. Foulis, F. Y. Liew and I. B. McInnes (1999). A proinflammatory role for IL-18 in rheumatoid arthritis. *J Clin Invest***104**(10): 1393-401.
[88] Remick, D. G., L. E. DeForge, J. F. Sullivan and H. J. Showell (1992). Profile of cytokines in synovial fluid specimens from patients with arthritis. Interleukin 8 (IL-8) and IL-6 correlate with inflammatory arthritides. *Immunol Invest***21**(4): 321-7.
[89] Beyaert, R., G. Van Loo, K. Heyninck and P. Vandenabeele (2002). Signaling to gene activation and cell death by tumor necrosis factor receptors and Fas. *Int Rev Cytol***214**: 225-72.
[90] Wallach, D., E. E. Varfolomeev, N. L. Malinin, Y. V. Goltsev, A. V. Kovalenko and M. P. Boldin (1999). Tumor necrosis factor receptor and Fas signaling mechanisms. *Annu Rev Immunol***17**: 331-67.
[91] Sattar, N., D. W. McCarey, H. Capell and I. B. McInnes (2003). Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation***108**(24): 2957-63.
[92] Feldmann, M. and R. N. Maini (2001). Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? *Annu Rev Immunol***19**: 163-96.
[93] Hachicha, M., P. Rathanaswami, T. J. Schall and S. R. McColl (1993). Production of monocyte chemotactic protein-1 in human type B synoviocytes. Synergistic effect of tumor necrosis factor alpha and interferon-gamma. *Arthritis Rheum***36**(1): 26-34.
[94] Tetlow, L. C., M. Lees, Y. Ogata, H. Nagase and D. E. Woolley (1993). Differential expression of gelatinase B (MMP-9) and stromelysin-1 (MMP-3) by rheumatoid synovial cells in vitro and in vivo. *RheumatolInt***13**(2): 53-9.
[95] Hart, P. H., M. J. Ahern, M. D. Smith and J. J. Finlay-Jones (1995). Regulatory effects of IL-13 on synovial fluid macrophages and blood monocytes from patients with inflammatory arthritis. *ClinExpImmunol***99**(3): 331-7.
[96] Loetscher, P., B. Dewald, M. Baggiolini and M. Seitz (1994). Monocyte chemoattractant protein 1 and interleukin 8 production by rheumatoid synoviocytes. Effects of anti-rheumatic drugs. *Cytokine***6**(2): 162-70.
[97] Seitz, M., P. Loetscher, B. Dewald, H. Towbin, C. Rordorf, H. Gallati, M. Baggiolini and N. J. Gerber (1995). Methotrexate action in rheumatoid arthritis: stimulation of cytokine inhibitor and inhibition of chemokine production by peripheral blood mononuclear cells. *Br J Rheumatol***34**(7): 602-9.
[98] Danis, V. A., A. J. Kulesz, D. S. Nelson and P. M. Brooks (1990). The effect of gold sodium thiomalate and auranofin on lipopolysaccharide-induced interleukin-1 production by blood monocytes in vitro: variation in healthy subjects and patients with arthritis. *ClinExpImmunol***79**(3): 335-40.
[99] Harth, M., P. A. Keown and J. F. Orange (1983). Monocyte dependent excited oxygen radical generation in rheumatoid arthritis: inhibition by gold sodium thiomalate. *J Rheumatol***10**(5): 701-7.
[100] Card, T., R. Hubbard and R. F. Logan (2003). Mortality in inflammatory bowel disease: a population-based cohort study. *Gastroenterology***125**(6): 1583-90.
[101] Grip, O., S. Janciauskiene and S. Lindgren (2003). Macrophages in inflammatory bowel disease. *Curr Drug Targets Inflamm Allergy***2**(2): 155-60.
[102] Selby, W. S., L. W. Poulter, S. Hobbs, D. P. Jewell and G. Janossy (1983). Heterogeneity of HLA-DR-positive histiocytes in human intestinal lamina propria: a combined histochemical and immunohistological analysis. *J ClinPathol***36**(4): 379-84.
[103] Mahida, Y. R. (2000). The key role of macrophages in the immunopathogenesis of inflammatory bowel disease. *Inflamm Bowel Dis***6**(1): 21-33.
[104] Grimm, M. C., S. K. Elsbury, P. Pavli and W. F. Doe (1996). Interleukin 8: cells of origin in inflammatory bowel disease. *Gut***38**(1): 90-8.
[105] Mazlam, M. Z. and H. J. Hodgson (1992). Peripheral blood monocyte cytokine production and acute phase response in inflammatory bowel disease. *Gut***33**(6): 773-8.
[106] Knowles, M. and P. Selby (2005). Introduction to the cellular and molecular biology of cancer.**4th edition**. Oxford university press.
[107] Leek, R. D., A. L. Harris and C. E. (1994). Cytokine networks in solid human tumors: regulation of angiogenesis. *J LeukocBiol***56**(4): 423-35.
[108] Silberstein, G. B. (2001). Tumour-stromal interactions. Role of the stroma in mammary development. *Breast Cancer Res***3**(4): 218-23.
[109] van RavenswaayClaasen, H. H., P. M. Kluin and G. J. Fleuren (1992). Tumor infiltrating cells in human cancer. On the possible role of CD16+ macrophages in antitumor cytotoxicity. *Lab Invest***67**(2): 166-74.
[110] Goerdt, S. and C. E. Orfanos (1999). Other functions, other genes: alternative activation of antigen-presenting cells. *Immunity***10**(2): 137-42.
[111] Mantovani, A., B. Bottazzi, F. Colotta, S. Sozzani and L. Ruco (1992). The origin and function of tumor-associated macrophages. *Immunol Today***13**(7): 265-70
[112] Mantovani, A., S. Sozzani, M. Locati, P. Allavena and A. Sica (2002). Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol***23**(11): 549-55.

[113] Kelly, P. M., R. S. Davison, E. Bliss and J. O. McGee (1988). Macrophages in human breast disease: a quantitative immunohistochemical study. *Br J Cancer***57**(2): 174-7.
[114] Mor, G., W. Yue, R. J. Santen, L. Gutierrez, M. Eliza, L. M. Berstein, N. Harada, J. Wang, J. Lysiak, S. Diano and F. Naftolin (1998). Macrophages, estrogen and the microenvironment of breast cancer. *J Steroid BiochemMolBiol***67**(5-6): 403-11.
[115] O'Sullivan, C. and C. E. (1994). Tumour-associated leucocytes: friends or foes in breast carcinoma. *J Pathol***172**(3): 229-35.
[116] Rambaldi, A., D. C. Young and J. D. Griffin (1987). Expression of the M-CSF (CSF-1) gene by human monocytes. *Blood***69**(5): 1409-13.
[117] Tang, R., F. Beuvon, M. Ojeda, V. Mosseri, P. Pouillart and S. Scholl (1992). M-CSF (monocyte colony stimulating factor) and M-CSF receptor expression by breast tumour cells: M-CSF mediated recruitment of tumour infiltrating monocytes? *J Cell Biochem***50**(4): 350-6.
[118] Roth, S. J., M. W. Carr and T. A. Springer (1995). C-C chemokines, but not the C-X-C chemokines interleukin-8 and interferon-gamma inducible protein-10, stimulate transendothelialchemotaxis of T lymphocytes. *Eur J Immunol***25**(12): 3482-8.
[119] Wong, M. P., K. N. Cheung, S. T. Yuen, K. H. Fu, A. S. Chan, S. Y. Leung and L. P. Chung (1998). Monocyte chemoattractant protein-1 (MCP-1) expression in primary lymphoepithelioma-like carcinomas (LELCs) of the lung. *J Pathol***186**(4): 372-7.
[120] Yoshimura, T., N. Yuhki, S. K. Moore, E. Appella, M. I. Lerman and E. J. Leonard (1989). Human monocyte chemoattractant protein-1 (MCP-1). Full-length cDNA cloning, expression in mitogen-stimulated blood mononuclear leukocytes, and sequence similarity to mouse competence gene JE. *FEBS Lett***244**(2): 487-93.
[121] Graves, D. T., R. Barnhill, T. Galanopoulos and H. N. Antoniades (1992). Expression of monocyte chemotactic protein-1 in human melanoma in vivo. *Am J Pathol***140**(1): 9-14.
[122] Leek, R. D. and A. L. Harris (2002). Tumor-associated macrophages in breast cancer. *J Mammary Gland Biol Neoplasia***7**(2): 177-89.
[123] Wahl, S. M., D. A. Hunt, L. M. Wakefield, N. McCartney-Francis, L. M. Wahl, A. B. Roberts and M. B. Sporn (1987). Transforming growth factor type beta induces monocyte chemotaxis and growth factor production. *ProcNatlAcadSci U S A***84**(16): 5788-92.
[124] Yoshimura, T., E. A. Robinson, S. Tanaka, E. Appella, J. Kuratsu and E. J. Leonard (1989). Purification and amino acid analysis of two human glioma-derived monocyte chemoattractants. *J Exp Med***169**(4): 1449-59.
[125] Vaupel, P., F. Kallinowski and P. Okunieff (1989). Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumors: a review. *Cancer Res***49**(23): 6449-65.
[126] Vaupel, P. (2004). The role of hypoxia-induced factors in tumor progression. *Oncologist***9 Suppl 5**: 10-7.
[127] Burke, B., N. Tang, K. P. Corke, D. Tazzyman, K. Ameri, M. Wells and C. E. (2002). Expression of HIF-1alpha by human macrophages: implications for the use of macrophages in hypoxia-regulated cancer gene therapy. *J Pathol***196**(2): 204-12.
[128] Burke, B., A. Giannoudis, K. P. Corke, D. Gill, M. Wells, L. Ziegler-Heitbrock and C. E. (2003). Hypoxia-induced gene expression in human macrophages: implications for ischemic tissues and hypoxia-regulated gene therapy. *Am J Pathol***163**(4): 1233-43.
[129] Lee, A. H., L. C. Happerfield, L. G. Bobrow and R. R. Millis (1997). Angiogenesis and inflammation in invasive carcinoma of the breast. *J ClinPathol***50**(8): 669-73.
[130] Talks, K. L., H. Turley, K. C. Gatter, P. H. Maxwell, C. W. Pugh, P. J. Ratcliffe and A. L. Harris (2000). The expression and distribution of the hypoxia-inducible factors HIF-1alpha and HIF-2alpha in normal human tissues, cancers, and tumor-associated macrophages. *Am J Pathol***157**(2): 411-21.
[131] Ohno, S., Y. Ohno, N. Suzuki, T. Kamei, K. Koike, H. Inagawa, C. Kohchi, G. Soma and M. Inoue (2004). Correlation of histological localization of tumor-associated macrophages with clinicopathological features in endometrial cancer. *Anticancer Res***24**(5C): 3335-42.
[132] Murdoch, C., A. Giannoudis and C. E. (2004). Mechanisms regulating the recruitment of macrophages into hypoxic areas of tumors and other ischemic tissues. *Blood***104**(8): 2224-34.
[133] Negus, R. P., G. W. Stamp, J. Hadley and F. R. Balkwill (1997). Quantitative assessment of the leukocyte infiltrate in ovarian cancer and its relationship to the expression of C-C chemokines. *Am J Pathol***150**(5): 1723-34.
[134] Collingridge, D. R., S. A. Hill and D. J. Chaplin (2001). Proportion of infiltrating IgG-binding immune cells predict for tumour hypoxia. *Br J Cancer***84**(5): 626-30.
[135] Stessels, F., G. Van den Eynden, I. Van der Auwera, R. Salgado, E. Van den Heuvel, A. L. Harris, D. G. Jackson, C. G. Colpaert, E. A. van Marck, L. Y. Dirix and P. B. Vermeulen (2004). Breast adenocarcinoma liver metastases, in contrast to colorectal cancer liver metastases, display a non-angiogenic growth pattern that preserves the stroma and lacks hypoxia. *Br J Cancer***90**(7): 1429-36.
[136] Mantovani, A., A. Sica, S. Sozzani, P. Allavena, A. Vecchi and M. Locati (2004). The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol***25**(12): 677-86.
[137] Mills, C. D., K. Kincaid, J. M. Alt, M. J. Heilman and A. M. Hill (2000). M-1/M-2 macrophages and the Th1/Th2 paradigm. *J Immunol***164**(12): 6166-73.
[138] Adams, D. O. and T. A. Hamilton (1988). Phagocytic cells. Cytotoxic activities of macrophages. In Galin, J.I, Goldstein, I.M and Snyderman, R. (ed), inflammation basic princible and clinical correlates. Raven Press, New York.
[139] Watanabe, M., P. K. Wallace, T. Keler, Y. M. Deo, C. Akewanlop and D. F. Hayes (1999). Antibody dependent cellular phagocytosis (ADCP) and antibody dependent cellular cytotoxicity (ADCC) of breast

cancer cells mediated by bispecific antibody, MDX-210. *Breast Cancer Res Treat***53**(3): 199-207.

[140] Biswas, S. K., L. Gangi, S. Paul, T. Schioppa, A. Saccani, M. Sironi, B. Bottazzi, A. Doni, B. Vincenzo, F. Pasqualini, L. Vago, M. Nebuloni, A. Mantovani and A. Sica (2006). A distinct and unique transcriptional program expressed by tumor-associated macrophages (defective NF-kappaB and enhanced IRF-3/STAT1 activation). *Blood***107**(5): 2112-22.

[141] Biswas, S. K., A. Sica and C. E. (2008). Plasticity of macrophage function during tumor progression: regulation by distinct molecular mechanisms. *J Immunol***180**(4): 2011-7.

[142] Sica, A. and V. Bronte (2007). Altered macrophage differentiation and immune dysfunction in tumor development. *J Clin Invest***117**(5): 1155-66.

[143] O'Sullivan, C., C. E. Lewis, A. L. Harris and J. O. McGee (1993). Secretion of epidermal growth factor by macrophages associated with breast carcinoma. *Lancet***342**(8864): 148-9.

[144] Segall, J. E., S. Tyerech, L. Boselli, S. Masseling, J. Helft, A. Chan, J. Jones and J. Condeelis (1996). EGF stimulates lamellipod extension in metastatic mammary adenocarcinoma cells by an actin-dependent mechanism. *ClinExp Metastasis***14**(1): 61-72.

[145] Wilson, S. E., Y. G. He, J. Weng, J. D. Zieske, J. V. Jester and G. S. Schultz (1994). Effect of epidermal growth factor, hepatocyte growth factor, and keratinocyte growth factor, on proliferation, motility and differentiation of human corneal epithelial cells. *Exp Eye Res***59**(6): 665-78.

[146] Bingle, L., C. E. Lewis, K. P. Corke, M. W. Reed and N. J. Brown (2006). Macrophages promote angiogenesis in human breast tumour spheroids in vivo. *Br J Cancer***94**(1): 101-7.

[147] Coffelt, S. B., R. Hughes and C. E. (2009). Tumor-associated macrophages: Effectors of angiogenesis and tumor progression. *BiochimBiophys Acta***1796**(1): 11-8.

[148] DeNardo, D. G., J. B. Barreto, P. Andreu, L. Vasquez, D. Tawfik, N. Kolhatkar and L. M. Coussens (2009). CD4(+) T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. *Cancer Cell***16**(2): 91-102.

[149] Leek, R. D., C. E. Lewis, R. Whitehouse, M. Greenall, J. Clarke and A. L. Harris (1996). Association of macrophage infiltration with angiogenesis and prognosis in invasive breast carcinoma. *Cancer Res***56**(20): 4625-9

[150] Lewis, C. E., R. Leek, A. Harris and J. O. McGee (1995). Cytokine regulation of angiogenesis in breast cancer: the role of tumor-associated macrophages. *J LeukocBiol***57**(5): 747-51.

[151] Molema, G., D. K. Meijer and L. F. de Leij (1998). Tumor vasculature targeted therapies: getting the players organized. *BiochemPharmacol***55**(12): 1939-45.

[152] Pardoll, D. (2009). Metastasis-promoting immunity: when T cells turn to the dark side. *Cancer Cell***16**(2): 81-2.

[153] Nagaoka, H., Y. Iino, H. Takei and Y. Morishita (1998). Platelet-derived endothelial cell growth factor/thymidine phosphorylase expression in macrophages correlates with tumor angiogenesis and prognosis in invasive breast cancer. *Int J Oncol***13**(3): 449-54.

[154] Crowther, M., N. J. Brown, E. T. Bishop and C. E. Lewis (2001). Microenvironmental influence on macrophage regulation of angiogenesis in wounds and malignant tumors. *J LeukocBiol***70**(4): 478-90.

[155] Folkman, J. (1990). What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst***82**(1): 4-6.

[156] Folkman, J. and P. A. D'Amore (1996). Blood vessel formation: what is its molecular basis? *Cell***87**(7): 1153-5.

[157] Folkman, J. (2000). Incipient angiogenesis. *J Natl Cancer Inst***92**(2): 94-5.

[158] O'Reilly, M. S., T. Boehm, Y. Shing, N. Fukai, G. Vasios, W. S. Lane, E. Flynn, J. R. Birkhead, B. R. Olsen and J. Folkman (1997). Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell***88**(2): 277-85.

[159] Coussens, L. M., W. W. Raymond, G. Bergers, M. Laig-Webster, O. Behrendtsen, Z. Werb, G. H. Caughey and D. Hanahan (1999). Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis. *Genes Dev***13**(11): 1382-97.

[160] Coussens, L. M., C. L. Tinkle, D. Hanahan and Z. Werb (2000). MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. *Cell***103**(3): 481-90.

[161] Li, L., T. A. Darden, C. R. Weinberg, A. J. Levine and L. G. Pedersen (2001). Gene assessment and sample classification for gene expression data using a genetic algorithm/k-nearest neighbor method. *Comb Chem High Throughput Screen***4**(8): 727-39.

[162] Qian, B., Y. Deng, J. H. Im, R. J. Muschel, Y. Zou, J. Li, R. A. Lang and J. W. Pollard (2009). A distinct macrophage population mediates metastatic breast cancer cell extravasation, establishment and growth. *PLoS One***4**(8): e6562.

[163] Pollard, J. W. (2004). Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer***4**(1): 71-8.

[164] Bhowmick, N. A., A. Chytil, D. Plieth, A. E. Gorska, N. Dumont, S. Shappell, M. K. Washington, E. G. Neilson and H. L. Moses (2004). TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. *Science***303**(5659): 848-51.

[165] Condeelis, J. and J. W. Pollard (2006). Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell***124**(2): 263-6.

[166] Iyengar, P., V. Espina, T. W. Williams, Y. Lin, D. Berry, L. A. Jelicks, H. Lee, K. Temple, R. Graves, J. Pollard, N. Chopra, R. G. Russell, R. Sasisekharan, B. J. Trock, M. Lippman, V. S. Calvert, E. F. Petricoin, 3rd, L. Liotta, E. Dadachova, R. G. Pestell, M. P. Lisanti, P. Bonaldo and P. E. Scherer (2005). Adipocyte-derived collagen VI affects early mammary tumor progression in vivo, demonstrating a critical interaction in the tumor/stroma microenvironment. *J Clin Invest***115**(5): 1163-76.

[167] DeVisser, K. E., A. Eichten and L. M. Coussens (2006). Paradoxical roles of the immunesystem during cancer development. *Nat Rev Cancer***6**(1): 24-37.

[168] Joyce, J. A. and J. W. Pollard (2009). Microenvironmental regulation of metastasis. *Nat Rev Cancer***9**(4): 239-52.

[169] Wyckoff, J., W. Wang, E. Y. Lin, Y. Wang, F. Pixley, E. R. Stanley, T. Graf, J. W. Pollard, J. Segall and J. Condeelis (2004). A paracrine loop between tumor cells and macrophages is required for tumor cell migration in mammary tumors. *Cancer Res***64**(19): 7022-9.

[170] Lucy Ireland, Almudena Santos, Muhammad S. Ahmed, Carolyn Rainer, Sebastian R. Nielsen, Valeria Quaranta, Ulrike Weyer-Czernilofsky, Danielle D. Engle, Pedro A. Perez-Mancera, Sarah E. Coupland, AzzamTaktak, Thomas Bogenrieder, David A. Tuveson, Fiona Campbell, Michael C. Schmid and AinhoaMielgo. Chemoresistance in pancreatic cancer is driven by stroma-derived insulin-like growth factors. (2016). *Cancer Res* **76**(23): 6851-6863.

[171] Goede, V., L. Brogelli, M. Ziche and H. G. Augustin (1999). Induction of inflammatory angiogenesis by monocyte chemoattractant protein-1. *Int J Cancer***82**(5): 765-70.

[172] Toi, M., T. Ueno, H. Matsumoto, H. Saji, N. Funata, M. Koike and T. Tominaga (1999). Significance of thymidine phosphorylase as a marker of protumor monocytes in breast cancer. *Clin Cancer Res***5**(5): 1131-7.

[173] Stanley, E. R., L. J. Guilbert, R. J. Tushinski and S. H. Bartelmez (1983). CSF-1--a mononuclear phagocyte lineage-specific hemopoietic growth factor. *J Cell Biochem***21**(2): 151-9.

[174] Chambers, S. K., Y. Wang, R. E. Gertz and B. M. Kacinski (1995). Macrophage colony-stimulating factor mediates invasion of ovarian cancer cells through urokinase. *Cancer Res***55**(7): 1578-85.

[175] Chambers, S. K., B. M. Kacinski, C. M. Ivins and M. L. Carcangiu (1997). Overexpression of epithelial macrophage colony-stimulating factor (CSF-1) and CSF-1 receptor: a poor prognostic factor in epithelial ovarian cancer, contrasted with a protective effect of stromal CSF-1. *Clin Cancer Res***3**(6): 999-1007.

[176] Scholl, S. M., C. Pallud, F. Beuvon, K. Hacene, E. R. Stanley, L. Rohrschneider, R. Tang, P. Pouillart and R. Lidereau (1994). Anti-colony-stimulating factor-1 antibody staining in primary breast adenocarcinomas correlates with marked inflammatory cell infiltrates and prognosis. *J Natl Cancer Inst***86**(2): 120-6.

[177] Scholl, S. M., R. Lidereau, A. de la Rochefordiere, C. C. Le-Nir, V. Mosseri, C. Nogues, P. Pouillart and F. R. Stanley (1996). Circulating levels of the macrophage colony stimulating factor CSF-1 in primary and metastatic breast cancer patients. A pilot study. *Breast Cancer Res Treat***39**(3): 275-83.

[178] Lin, E. Y., A. V. Nguyen, R. G. Russell and J. W. Pollard (2001). Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. *J Exp Med***193**(6): 727-40.

[179] Lin, E. Y., J. F. Li, L. Gnatovskiy, Y. Deng, L. Zhu, D. A. Grzesik, H. Qian, X. N. Xue and J. W. Pollard (2006). Macrophages regulate the angiogenic switch in a mouse model of breast cancer. *Cancer Res***66**(23): 11238-46.

[180] Lewis, C. E. and J. W. Pollard (2006). Distinct role of macrophages in different tumor microenvironments. *Cancer Res***66**(2): 605-1

[181] Gheryani N, Coffelt SB, Gartland A, Rumney RMH, Kiss-Toth E, Lewis CE, Tozer GM, Greaves DR, Dear TN and Miller G. (2012). Generation of a Novel Mouse Model for the Inducible Depletion of Macrophages In Vivo. genesis: The Journal of Genetics and Development. PMID: 2292712.