REVIEW

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The possible mechanisms of tumor progression *via* CSF-1/CSF-1R pathway activation

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Abstract

CSF-1/CSF-1R (colony-stimulating factor-1/colony-stimulating factor-1 receptor) is the primary growth factor regulating the survival, proliferation, and differentiation of cells of the mononuclear phagocytic lineage. Multiple studies have demonstrated that CSF-1/CSF-1R plays a certain role in tumor tissues. CSF-1 binding to CSF-1R through the class III RTKs leads to a series of signal molecules responding to CSF-1 *via* various signaling pathway. Through these pathways, all signal molecules would promote development of tumor directly or contribute to progress of various cancers indirectly by increasing tumor-associated macrophages, for instance promoting tumor growth, angiogenesis, extracellular matrix breakdown, invasion, and metastasis. Thus, in this paper, we analysis multiple experimental results comprehensively, making a review about the mechanism of CSF-1/CSF-1R promoting tumor progression.

Keywords: CSF-1/CSF-1R, tumor, angiogenesis, cell microenvironment, invasion and metastasis.

Introduction

The complex relationship between tumor and the immune system has been widely studied. Studies show that tumor cells are responded to the host immune through expressing tumor-associated antigens [1, 2]. Related response in immune system will further influence the development of tumor. Colony-stimulating factor-1 receptor (CSF-1R), encoded by the c-fms proto-oncogene, is traditionally recognized as one of the most significant substances to affect macrophage physiology in immune system. CSF-1R is a primary growth factor regulating the survival, proliferation, and differentiation of cells of the mononuclear phagocytic lineage [3–6]. In order to activate monocytes and macrophages, CSF-1/CSF-1R signaling enhances their cytotoxicity, phagocytosis, chemotaxis, and cytokine production in immune response and inflammation [7].

Recently, it has been demonstrated that they play not only a critical physiological role. Furthermore, CSF-1/CSF-1R dependent macrophages have also been identified to promote disease progression in various conditions ranging from cancer [8] to atherosclerosis [7] and arthritis [9]. Various studies have shown that CSF-1/CSF-1R has been abnormally highly expressed in tumor tissues, and is also closely related with tumor progression [10–13]. On one hand, CSF-1/CSF-1R effects tumor cells directly, on the other hand, it promote the development of tumor indirectly through mobilizing and adjusting the immune system responding to activate mononuclear scavenger system, which is the most significant aspect for CSF-1/CSF-1R to promote tumor progression. The two ways cooperatively lead to proliferation, differentiation, invasion and metastasis, of tumor cells.

Tumor associated macrophages (TAMs) led by CSF-1/CSF-1R have a wide range of activities like promoting tumor growth, angiogenesis, extracellular matrix breakdown, invasion, metastasis [10, 14], and are usually related to more poor prognosis [15]. Allavena and Mantovani *e.g.* found that TAMs most frequently promote pro-tumor functions at tumor tissues early [16]. They are skillful in activation of the neoangiogenic switch and suppression of adaptive immunity, which is usually protective and limits tumor progression [14]. TAMs also have been correlated with the secretion of soluble factors, which support the proliferation of and invasion of malignant cells, and even be resistant to apoptotic stimuli of tumor cells [17, 18]. Moreover, study [19] shows that tumor-associated macrophages and mammary carcinoma cells migrate away from the primary tumor in the case of enhancement of tumor invasion [12]. Thus, in the development of tumor, CSF-1-induced motility of macrophage function is likely to be a significant factor.

Many experiments have provided the basis for us to show that CSF-1/CSF-1R play an irreplaceable role in tumor progression. The mechanism is complex and unknown. It is worthy of our in-depth discussion, and so as to put forward new proposals for the diagnosis and treatment of tumor. Therefore, this review demonstrates our current understanding of the function of CSF-1/CSF-1R in tumor.

CSF-1 and CSF-1R

CSF-1 is secreted by macrophages, epithelial and fibroblasts cells and tumor cells [7]. The growth factor and its receptor play vital roles in normal development. Beyond promoting cell differentiation and maturation, they often appear as mediators of intercellular communication by diffusible molecules [20]. Regulation for mononuclear phagocytic lineage cells is especially important, and this is the basis of many diseases [7–9]. It can promote monocyte differentiating into macrophage, and support its survival and proliferation.

CSF-1 belongs to a small group of short-chain four-helix bundle, RTK-binding cytokines (Figure 1) [6]. The core receptor-binding domains of these three cytokines all have a similar head-to-head dimer structure [21, 22]. Effects of CSF-1 on the target cells are mediated by the CSF-1 receptor (CSF-1R) [23], a ~165 kDa glycoprotein encoded by the c-fms proto-oncogene. Evidence shows that CSF-1 expression is significantly correlated with that of CSF-1R [12]. The CSF-1R belongs to the class III RTK subfamily. Binding of ligands to the class III RTKs is considered to induce receptor (CSF-1R) dimerization, CSF-1 intermolecular autophosphorylation and kinase domain activation. Then make its effect protein phosphorylation of tyrosine residues, and transform the biological activity of the effector [24].

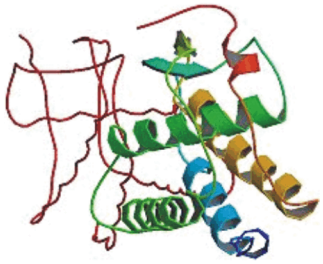

Figure 1 – ***Structure of the M-CSF: short-chain 4-helix bundle.***

Accumulating evidences from mouse models and human drug response suggests that initiation and maintenance of tumor require signals emanating, which comes from the activated tyrosine kinase domain of growth factor receptors [25–27]. Virtually, all epithelial tumors, phosphorylation of tyrosine residues deregulates growth factor receptor activity, which would activate the driving oncogene through leading to activating mutations, genomic amplification, and autocrine loops [28, 29]. What tumor cell survival depended upon is the driving oncogene [27, 30, 31].

As a result, we assume that if we targeted control CSF-1, that may affect its combination with CSF-1R, and affect the proliferation, growth and survival of cancer cells.

The possible mechanisms of tumors led to by CSF-1/CSF-1R

Multiple studies [11–13, 32] have demonstrated that CSF-1/CSF-1R in tumor tissues are highly expressed. At present, it is shown that CSF-1/CSF-1R is highly expressed in obvious tumor tissue, like breast cancer [19], prostate cancer [33], head and neck cancer [34], ovarian cancer [12], leiomyosarcoma [10], colon cancer [35], skin melanoma, testicular cancer, bladder cancer, etc. However, most studies based on mice more than human. Table 1 is about the expression of CSF-1/CSF-1R in human tissues. Kirma *et al.* uses transgenic technology to make the CSF-1 over expressed in breast tissue, and the result shows that the breast duct branch increase, hyperplasia, dysplasia and other precancerous lesions appear, suggesting that the CSF-1 promotes cell dysplasia, which can promote the growth of tumor [36]. According to the existing study, function of CSF-1/CSF-1R resulting in progression of tumor basically has the following several aspects of the possible mechanism (Figure 2).

Table 1 – ***The expression of CSF-1/CSF-1R in cancer and human normal sample***

Study	Method	Expression of CSF-1/CSF-1R (sample size)		
		Test group (cancer tissue)	Control group (normal tissue)	*P* value
Ovarian cancer [12]	IHC	50% (47)	20% (48)	0.005
Prostate cancer [33]	IHC	74% (59)	40% (59)	<0.0001
Head and neck cancer [34]	ELISA	565 pg/mL (59)	447 pg/mL (59)	0.002
Colorectal cancer [35]	ELISA	874 pg/mL (70)	453 pg/mL (40)	<0.05
Prostate cancer [37]	ELISA	508.61± 62.33 pg/mL (37)	302.01± 57.25 pg/mL (30)	<0.05
Pancreatic cancer [38]	ELISA	877 ng/L (47)	430 ng/L (35)	<0.05

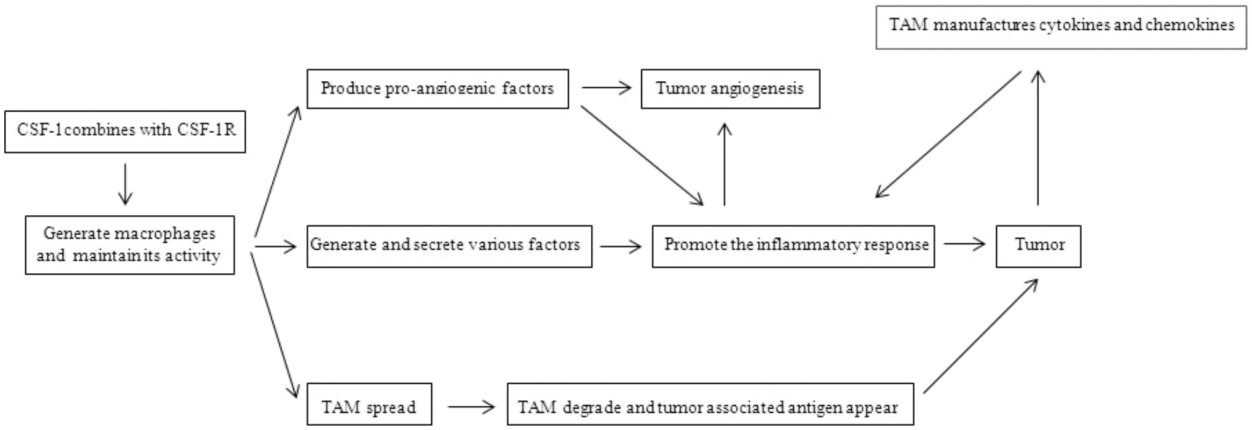

Figure 2 – ***The possible mechanisms of tumors led to by CSF-1/CSF-1R.***

CSF-1/CSF-1R promotes angiogenesis

The growth of tumor cells cannot depart from the support of blood supply. Therefore, the formation of new blood vessels of tumor is critical [6, 39]. TAMs have been shown to increase tumor angiogenesis. There are studies [10] revealing that CSF-1 high expression combines with high microvessel density (MVD). MVD has a stronger relevance with expression of CSF-1. This suggests that CSF-1 may mediate an angiogenic phenotype. Another laboratory-evidence [40] proves that CSF-1 signature-positive cases clearly have increased tumor vascularity more than CSF-1 signature-negative cases. And there is a significant positive correlation exist between

the mRNA levels of CD34 and CSF-1 after performing pairwise Pearson correlations between CSF-1, CD34, and VEGF genes on mRNA levels, while no significant or negative correlations between CD34 and VEGF. These results further suggest that in pathological tumor vascularization, CSF-1 plays a very important role.

After combining with CSF-1R, CSF-1 promote the proliferation of TAMs and support it to produce a number of various pro-angiogenic factors including vascular endothelial growth factor, basic fibroblast growth factor, tumor necrosis factor-α, and others. These release various growth factors and cytokines activating fibroblasts, and further promote the formation of microvascular of tumor [41–43]. In addition, it was shown that depletion of CSF-1 leads to the suppression of tumor angiogenesis in a mouse model [32] of osteosarcoma, which highlights the potential significance of this molecule in mediating angiogenesis of tumors.

Recent years, accumulation of evidences [44–46] has demonstrated a relationship between the numbers of CSF-1/CSF-1R related TAM and the failure of antitumor therapies. Increasing TAM cells in tumors generate them refractory to angiogenic blockade by VEGF antibodies [47]. Furthermore, pharmacological inhibition or depletion of TEMs in tumor-bearing mice considerably increases the efficacy of therapeutic treatment with a vascular-disrupting agent. Overall, these data make it clear that TAM, which related by CSF-1/CSF-1R, markedly increase the development of tumor [16, 48, 49]. Therefore, it is worthy for us to consider to inhibit the expression of CSF-1/CSF-1R to prevent TAM.

Altogether, these findings largely suggest an important role for CSF-1/CSF-1R as well as the resulting TAM infiltration in the pathological neovascularization of tumors and provide a rationale for CSF-1/CSF-1R targeted therapies.

CSF-1/CSF-1R changes the cell micro-environment

CSF-1/CSF-1R can influence the generation of various factors and adjust their secretion, like VEGF, EGF, FGF, PDGF and TGF-β, which encourage the pro-tumor functions of TAM. The tumor microenvironment consisted by these growth factors plays a critical role in the regulation and control of cancer progression by fostering a benefit conformation for tumor cells, while restraining normal cells.

Nature of the molecular and cellular in the tumor immune microenvironment turn the balance of suppressive *versus* cytotoxic responses in the vicinity of the tumor to influences disease outcome. Several important components make up the tumor microenvironment, including the tumor parenchyma cells, mesenchymal cells, fibroblasts, blood, and lymph vessels, as well as tumor infiltrating immune cells, chemokines, and cytokines [50]. The immune system is a significant determinant of the tumor microenvironment and cancer-related inflammation is now recognized as a hallmark of cancer [51, 52]. Effective tumor surveillance of the host immune system protects body against diseases, but long-term chronic inflammation contributes to disease progression and tumor cell is a good editor to modify the immunization program, which would provide profitable conditions for tumor.

As major producers of inflammatory mediators, CSF-1/CSF-1R related TAM is the key initiators of the chronic inflammation subtle present in the tumor microenvironment. Studies show that CSF-1/CSF-1R related TAM are a major source of proteolytic enzymes degrading the ECM that supports the release of matrix-bound growth factors further promoting the inflammatory response [16, 53, 54]. Conditions of persistent inflammation generated by CSF-1/CSF-1R related TAM predispose to carcinogenesis in tissues, and even accelerate tumor development in established malignancies [53, 55, 56]. Several experimental studies [57–60] have demonstrated that CSF-1/CSF-1R inducing nuclear factor (NF)-κB activation in TAM is required for tumor promotion in inflammation-induced murine tumor models. Moreover, the inflammatory factors not only promote the proliferation directly, but also increase tumor cells resistance to apoptotic stimuli [53, 61]. In turn, activated TAM manufactures cytokines and chemokines, which perpetuate and amplify the inflammatory cascade [53].

Besides promoting the happen and independent of inflammatory indirectly by influencing the survival, proliferation and differentiation of TAM, CSF-1/CSF-1R affects the inflammatory cascade directly. Studies [7] show that the increased microglial expression of CSF-1/CSF-1R augments the microglial inflammation responsible for the diabetic microenvironment. CSF-1/CSF-1R is studied as a key cytokine in the regulation of inflammatory responses. Similar patterns of CSF-1/CSF-1R expression have also been reported in the tumor environment [5]. Accumulating evidences [62] suggest *in vitro*, CSF-1R overexpresses, meanwhile, phagocytosis of tumor augments and the inflammatory response is more active. This suggests CSF-1/CSF-1R plays a critical role in the inflammatory pathogenesis of several lesions including tumor.

CSF-1/CSF-1R promote the invasion and metastasis

CSF-1 is a powerful chemotactic and chemokines factors for macrophages. CSF-1 stimulated macrophage migration has recently been demonstrated in several diseases, including tumor invasion and metastasis [63], inflammatory arthritis [64] and atherosclerosis [65, 66].

Eugene P. Toy [12, 67] confirmed that overexpression of CSF-1/CSF-1R can obviously enhance invasiveness of ovarian cancer cells. Clinical specimens arising from ovarian cancer metastases present strong immunostaining for both CSF-1 and its receptor, while benign ovarian tissue show expression of little CSF-1/CSF-1R. *In vivo*, Bix3 ascitic human ovarian cancer cells which transfected with CSF-1 cDNA sequences seem to increase the expression of CSF-1 in the Bix3T8.2 cells and lead to a highly significant increase in the invasiveness, adhesion, and motility observed [68, 69]. If giving a therapeutic intervention at the mRNA and protein levels of expression, CSF-1-induced transformation of macrophage cells should be inhibited and both invasiveness and metastatic potential would be diminished [70]. Therefore, we could manipulate gene expression to affect tumor phenotype.

Studies [71] have further shown that the characteristics of dependence on CSF-1 for survival and proliferation and a pleomorphic but adherent phenotype have been

retained in the BAC1.2F5 mouse macrophage cells. However, with the starvation of CSF-1, BAC1.2F5 macrophage cells round up, retract their pseudopodia, and eventually die. However, when adding CSF-1 to quiescent cells, CSF-1R is rapidly activated, eliciting receptor autophosphorylation and tyrosine phosphorylation of a large amount of cytoskeletal proteins and cytoplasmic proteins related with signaling cells, like tumor cells, macrophages [72, 73]. Morphological changes of macrophage are also effected rapidly, with extension of lamellipodia and formation of ruffles on the cell surface and macrophage spreading, followed by cell polarization and increased motility. As the degradation of the macrophages which localized in the distance, tumor-associated antigen would appear, and the risk of cancer is greatly increased [19, 74]. Meanwhile, CSF-1/CSF-1R promotes the carcinoma cells undergoing morphological changes, which promote adhesion molecule E-cadherin dissociation from the cytoskeleton protein, release the tumor cell connections between compound, which damage the cell connections, and reduce adhesion ability of the tumor cell to other tumor cells surface, make it easy for cancer cells away from the original site for the ability of movement and proliferation [12, 75, 76]. From this a series of changes, it is not hard to guess that under the induction of CSF-1/CSF-1R, tumor progress will accelerate greatly.

In addition, the CSF-1/CSF-1R has been proved to [67] exist in tumor metastases. Through inducing the fibronectin in tumor cells, CSF-1/CSF-1R passes through the membrane and invades distant tissue. This fully shows that CSF-1/CSF-1R of the tumor cells can also induce and enhance the chemotaxis and migration ability of macrophage through autocrine loop. This improves the invasiveness of cancer tissues and promotes the tumor invasion and metastasis, and further stimulates the secretion of CSF-1, form a circle. But, Eugene P. Toy [12] shown an inhibition in the invasive and metastatic phenotype of ovarian cancer cells, which would be led to decreases of CSF-1 protein secretion, and bodies prevent the transformation of otherwise ovarian cancer cells by disruption of CSF-1/CSF-1R autocrine loop provides additional steps. Antisense targeting of the CSF-1R disrupts this autocrine loop, which established by the endogenous secretion of CSF-1/CSF-1R from the ovarian cancer cells transfectants, leading to a great inhibition of the highly aggressive ovarian cancer phenotype. This suggests that the tumor cells can also control the secretion of CSF-1/CSF-1R except through autocrine loop and we suspect that it is the paracrine form, which can also further affect the progress of tumor.

Self-contribution and foreseen therapeutic applications of the CSF-1/CSF-1R

Last year, we have used DNA chips what can detects 14112 human genes to test 12 radiotherapy resisted nasopharyngeal carcinoma patients and eight radiotherapy sensitive nasopharyngeal carcinoma patients, and found 111 genes expression in radiotherapy resisted patients significantly differ from radiotherapy sensitive patients [77]. The expression difference of CSF-1R is the most significant. The expression of CSF-1R is much higher in patients with radiation resistance, and the trend of the expression of CSF-1R trend is stable. This difference greatly inspires us. Therefore, we select CSF-1R/CSF-1R as focus for further study.

At present, CSF-1 has been applied as a hematopoietic growth factor for bone marrow transplant patients to improve the granulocyte function and the survival rate [78]. However, there is no doubt for the patient with definite inflammatory diseases that it will raise the spread of inflammatory diseases. Recent studies have shown that M279, as a monoclonal anti-CSF-1R antibody, it may selectively remove tissue macrophage populations in prolonged treatment [79]. We also look forward to verify the treatment role of anti-CSF-1R antibody in the further study in cancer.

Conclusions and future perspectives

It is now clear that CSF-1/CSF-1R contribute great in the process of tumor development. On one hand, CSF-1/CSF-1R induce mononuclear cells to develop into macrophages and further play an irreplaceable role in regulating the macrophages in tumor development, like increasing the tumor new capillaries, building sustained inflammatory microenvironment, inducing migration of tumor cell to the distance, etc. On the other hand, CSF-1/CSF-1R directly promotes tumor cells to release inflammatory mediators to respond inflammation cascade, supporting the continued progress of tumor cells. These two aspects depend on the excessive expression of CSF-1/CSF-1R. Under the conditions of CSF-1/CSF-1R overexpression, the combination of CSF-1 and CSF-1R promotes its effector tyrosine residues phosphorylation, and then produces a series of signal molecules to produce the effector molecular activity enhancement, which changes internal environment to promote the development of tumor. As a result, we could cut the way of tumor development through regulating the expression of CSF-1/CSF-1R. At the same time, preventing CSF-1/CSF-1R to promote the differentiation and activation of macrophage can also improve the condition of tumor development in theory. What's more, regulation of the secretion of CSF-1, prevention the CSF-1 autocrine and paracrine form is another target of blocking tumor progression.

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