The critical role of macrophages in ovarian cancer treatment

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Abstract

The occurrence of and poor prognosis associated with ovarian cancer (OC) pose a serious threat to the health of middle-aged and elderly women. Thus, there is an urgent need to understand the pathogenesis of OC and establish effective therapeutic measures. The OC microenvironment is thought to facilitate malignancy, as well as close relationships among several types of cells. Macrophages are known to be present in the OC microenvironment. They are usually the M1 pro-inflammatory or M2 anti-inflammatory subtype and contribute to the microenvironment via secreting cytokines. The poor prognosis associated with OC is closely related to the negative regulation of M2 macrophage polarization, which contributes to the immune escape of tumor cells and maintains the malignant growth and distant metastasis of OC cells. In this review, we have focused on the involvement of macrophages in OC during the aging process and the macrophage-based therapeutic strategies for OC.

Keywords: Ovarian cancer, macrophage polarization, ageing, tumour associated micro-environment

Introduction

Ovarian cancer (OC) is the most lethal type of malignant tumor of the female reproductive system [1]. The malignant progression of OC is associated with multiple elements, including gene mutation, ovulation frequency, an abnormal host immune response, oncogene activation and silencing of tumor suppressor genes, and interaction of tumor cells with growth factors and cytokines in the tumor-associated microenvironment [2, 3]. Patients with OC have lower progression-free survival (PFS) and overall survival (OS) rates due to the lack of effective methods for early diagnosis. Cytoreductive surgery (CRS) and chemotherapy with paclitaxel/platinum are the most common therapeutic treatments; however, 70% of OC patients are at risk of recurrence and chemotherapy resistance [4]. Among the many cytological mechanisms involved in the malignant progression of OC, macrophage polarization is widely considered an important component.

Macrophages are a class of natural immune cells with a variety of physiological functions [5]. Upon stimulation, macrophages can be polarized into the M1 and M2 phenotypes. The characteristics of several subtypes of macrophages are displayed in Table 1 [6-20]. The tumor-associated macrophages (TAMs) found in malignant tumor microenvironments are typically M2 macrophages, and these regulate tumor growth, migration, and angiogenesis by producing a large number of cytokines, growth factors, extracellular matrix remodeling molecules, and other molecules [21]. Previous studies have found that M2 macrophage polarization is closely correlated with the malignant progression of colon cancer [22], prostate cancer [23], liver cancer [24], thyroid cancer [25], craniocerebral tumors [26], pancreatic cancer [27], and other tumors. Therefore, regulating the activity and phenotype conversion of macrophages [28-29] is a potential therapeutic strategy for OC that could improve the poor prognosis associated with OC. This review focuses on the role macrophage polarization plays in OC during aging and treatment strategies based on macrophage modulation.

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The role of macrophages in the poor prognosis associated with ovarian cancer (OC)

OC has the highest mortality rate of all the malignant tumors of the female reproductive system. Macrophages play important roles in the OC microenvironment; they af-

fect the host's ability to defend against microbes, viruses, and parasites, as well as against tumor cells. OC TAMs are generally the M2 phenotype, contributing to the occurrence, development, distant metastasis, and angiogenesis of malignant tumors and hence the poor prognosis associated with OC [30]. It has been demonstrated that large proportions of CD163+ M2 macrophages are present in epithelial OCs and are related to poor prognosis [31]. In addition, a high M1 to M2 macrophage ratio in OC tissue is associated with early diagnosis and long survival of tumor patients [32]; and the reverse has also been shown [33].

larization in the tumor microenvironment through CCL2/ Monocyte Chemotactic Protein 1 (MCP-1) signaling [40]. It has also been shown that TNF-α, CCL22, and Chemokine (C-X-C motif) ligand 12 (CXCL12) secreted by OC cells induce polarization of M0 macrophages (monocyte) into M2 macrophages in the tumor microenvironment [41]. In addition, the expression of the transmembrane protein semaphorin 4D (SEMA4D) was found to be higher in an OC cell line and the cell culture supernatant than in normal human ovarian cells and the cell culture supernatant, and peripheral blood mononuclear cells (PBMCs) were found to tend to differentiate into M2 macrophages when

Table 1. The differences among several subtypes of macrophages.

	Inducers	Cell expression markers	Cytokine and chemokine production	References
M1a **M1b**	IFNc, LPS, TNF	Common markers: CD80, CD86, CD68, MHC-II, IL-1R, TLR-2, TLR-4, iNOS, IL10, IL-12; M1a subtype without CD206 or MGL-1, M1b subtype with CD206 and MGL-1	TNF-α, IL-1β, IL-6, IL-12, IL-23, IL-27, CXCL9, CXCL10, CXCL11, CXCL16, CCL5, Arg-2, iNOS, ROS	[5-10]
M2a	IL-4, IL-13	MR, AMACI, MHCII, ArgI, IL-1Ra, IL-1R II, FIZZ1, Ym1/2	TGFβ, IL-10, IL-Ra, CCL17, CCL22, CCL18, CCL22, CCL24	[11-15]
M2b	IC, TLR, IL-1R ligands, IL-1β	MR, MHCII, CD86	IL-1β, IL-6, TNFα, IL-10, IL-12, CCL1	[9, 13]
M2c	IL-10, Glucocorticoids, TGFβ	MR, CD163, TLR-1, TLR-8, ArgI	IL-10, TGFβ, CCL16, CCL18, CXCL13	[16, 17]
M2d	TLR+A2R ligands, adenosine receptor ligands	VEGF, TNFα, IL-12, IL-10	IL-10, IL-12, VEGF, TNFα	[18, 19]
M3		Arg1, Chi3l3, Ccr2, Cx3cr1, Ccr1, Ccr9; without CD11c or CD206		[20]

Potential mechanisms involving M2 macrophages that facilitate OC progression

M2 macrophages promote the immune escape of tumor cells by releasing immunosuppressive factors in the OC microenvironment. For example, during the progression of a malignant tumor, macrophages that are stimulated with interleukin (IL)-4, IL-10, and IL-13 polarize into the M2 phenotype and secrete IL-4, IL-5, and IL-6, which in turn induce the progression of angiogenesis, immunosuppression, and matrix remodeling [34]. TAMs regulate tumor-cell migration in the microenvironment by modulating the secretion of and interactions between epithelial growth factor (EGF), tumor necrosis factor alpha (TNF-α), and colony stimulating factor-1 (CSF-1) [35]. In the OC microenvironment, TAMs promote cell invasion by enhancing the activity of c-Jun and (Nuclear Factor-kappa B) NF-κB and the upregulation of SR-A [36, 37]. The cytokines and chemokines secreted by OC cells can increase macrophage recruitment and polarization [38]. For example, it has been shown that leukemia inhibitory factor (LIF) and IL-6 secreted by OC cells promote the differentiation of macrophages into the M2 phenotype [39]. In another study, CCL2 released by epithelial OC cells was found to increase the recruitment of macrophages and M2 po-

stimulated by recombinant soluble SEMA4D [42]. It is also likely that Cyclooxygenase-2 (COX-2) derived from OC stem cells affects M2 macrophage polarization via activation of the Janus kinase (JAK) and COX-2/ prostaglandin E2 (PGE2) signaling pathways [43-45].

Effects of macrophages on the malignant progression of different forms of OC

Macrophages play different roles in several types of histologically classified OC. TAM infiltration is most common in serous and mucinous OC, and the infiltration of M2 macrophages predicts a poor prognosis for serous OC cases [46]. Serous OC accounts for more than 70% of all epithelial OCs. Ciucci *et al*. found that patients with low-grade serous OC had less infiltrating CD68+ macrophages and M2 CD163+ macrophages in tumor tissues than patients with high-grade serous OC [47]. These results suggest that the differentiation activity of M2 macrophages is related to the occurrence, development, and metastasis of different types of histologically classified OC [48].

In women, smoking can activate nicotinic receptors, and this activation has been shown to polarize macrophages into the M2 phenotype, thereby increasing the risk of mucinous OC [49]. However, the relationship between smoking, macrophage polarization, and the risk of mucinous

OC needs to be further investigated.

Endometrioid carcinoma and clear cell carcinoma of the ovary are mostly caused by endometriosis [50]. A study suggested that CDC42^{+} macrophages may inhibit endometriosis in endometrioid carcinoma and clear cell carcinoma of the ovary and thus play a role in alleviating malignant progression [51]. It has also been shown that glypican-3 (GPC3), which is specifically expressed in ovarian clear cell carcinoma, can inhibit ovarian tumor growth in mice by enhancing the proportion of M1 macrophages [52]. Furthermore, B7-H4 is expressed on the surface of OC cells and is associated with the infiltration of T cells and CD14^{+} macrophages in ovarian clear cell carcinoma but not in serous OC and ovarian endometrioid carcinoma [53].

Despite several studies having shown that M1 macrophages have significant anti-tumor effects, Untack Cho *et al.* found that M1 macrophages could promote OC cell metastasis by activating the NF-κB signaling pathway [54].

Together, these findings suggest that TAMs play important roles in the development and progression of OC. Hence, the effects of macrophages in different polarization states on the malignant progression of different histological subtypes of OC must be further explored.

Macrophages can affect ovarian function during aging

Immune dysregulation associated with aging affects the balance between immune cell subtypes and their relevant functions, resulting in the occurrence and progression of cancer [55]. Several characteristics of the aging process, such as non-infectious low-grade chronic inflammation, contribute considerably to age-related pathological changes [56] and functional decline [57]. It has also been shown that aging stimulates higher expression of a large number of innate immune system macromolecules, cytokines, and multi-protein complexes [58]. In addition to their beneficial roles, IL-1β and IL-18 also contribute to the occurrence and progression of disease during aging [59].

Ovarian aging is a natural process characterized by follicular depletion and a reduction in oocyte quality, which result in loss of ovarian function, cycle irregularity, and eventually infertility and menopause [60]. Ovarian aging can also involve ovarian myocyte inflammation and the gradual development of OC [61]. In cases of OC-related inflammation, it is critical to maintain the balance between the macrophage phenotypes so that it is in favor of protection against OC rather than in favor of malignant progression.

Macrophages have the ability to modulate ovarian function during the aging process due to their roles in follicle growth regulation, tissue remodeling during ovulation, and corpus luteum formation and regression [62]. Interestingly, in cases where there is poor progression of OC, the increased number of macrophages present may indicate the critical role these immune cells play during the aging

process [63]. Additionally, M2 macrophages are the main source of inducers in the tumor-associated microenvironment and contribute to the regulation of tumor metastasis, tumor invasion, and other malignant behaviors [62]. Negatively modulating M2 macrophage polarization and reducing the proportion of macrophages could delay OC progression.

Therapeutic strategies for OC that involve modulating macrophages during the aging process

The occurrence and development of tumors can trigger a series of inflammatory reactions that can serve as therapeutic targets. On the one hand, it has been found that inflammatory microenvironments can promote drug resistance and gene instability in tumor epithelial cells and affect the infiltration and colonization of immune cells, such as macrophages [64, 65]. On the other hand, TAMs act as a 'bridge' between the anti-tumor immune response and tumor cells during the occurrence and development of malignant tumors. At present, there are four therapeutic approaches that target TAMs: inhibition of the growth of TAMs, prevention of the recruitment of macrophages, repolarization of M2-like TAMs into M1 macrophages, and nanoparticle- and liposome-based delivery of anti-tumor drugs [66].

Studies have shown that human recombinant antibody single-chain variable fragments (scFv) can be used to prevent the binding of mesothelin and macrophages, thus inhibiting the polarization of M0 macrophages into TAMs [67]. Several therapeutic drugs that target TAMs are being investigated or have been used in clinical practice. For example, trabectedin can interfere with the survival of TAMs [68], and alemtuzumab reduces the number and activity of TAMs by targeting surface proteins [69]. Nanoparticles loaded with cisplatin can be endocytosed by TAMs and thus affect tumor cells and play a role in targeted therapy [70]. Histidine-rich glycoprotein (HRG) has been found to regulate the repolarization of M2-like TAMs into M1 macrophages; hence, it could be used to inhibit the proliferation and metastasis of malignant tumors and promote an anti-tumor immune response [71]. Paclitaxel, an anti-tumor drug used in the treatment of OC, can regulate the repolarization of M2 macrophages into M1 macrophages through the Toll Like Receptor 4 (TLR4)-dependent pathway, thereby inhibiting tumor growth [72]. Studies have also indicated that the relationship between macrophage polarization and OC can be affected by cisplatin. In cisplatin-sensitive tumor cells, macrophages promote the epithelial-mesenchymal transition (EMT) process and EMT-related gene expression, while such effects cannot be found in cisplatin-resistant tumor cells, suggesting that macrophage polarization plays a significant role in malignant tumor progression [73].

Some plant extracts have been found to inhibit tumor growth by altering macrophage polarization. For example, in OC, neferine affects angiogenesis by regulating the po-

larization of TAMs, thus exerting anti-tumor effects [74]. In other research, deoxyschizandrin extracted from berries has been found to inhibit the activity of M2 macrophages, and onionin A has been found to have a cytotoxic effect on OC cells and restrain the activity of M2 macrophages [75, 76]. Thus, these findings indicate that targeting macrophage polarization is an effective strategy for inhibiting the malignant progression of OC.

Discussion and perspective

OC is considered the most malignant gynecological tumor type because it has atypical clinical symptoms, is difficult to diagnose early, and gradually develops chemotherapy resistance during treatment. Also, there is no effective treatment for high-grade recurrent OC, and aging is a major factor in the occurrence and progression of OC. Therefore, there is an urgent need to understand the molecular mechanisms involved in the malignant progression of OC and to develop effective therapeutic drugs.

The tumor microenvironment is a complex network of cytokines, exosomes secreted by different cells, immune cells, fibroblasts, and mesenchymal stem cells. To maintain a suitable tumor microenvironment, several cytokines are released by different types of immune cells during aging. Hence, the occurrence and development of tumors are largely affected by the innate and adaptive immune responses.

A growing number of studies are showing that suppressing and eliminating tumor cells by activating the innate immune system is an effective tumor treatment strategy. Macrophages are part of the infiltrating immune cell population in the tumor microenvironment and are involved in regulating the malignant progression of OC. In most cases, M1 macrophages have an anti-tumor effect, while M2-like TAMs support immunosuppression and tumor immune escape. Among all the infiltrating immune cells in the tumor microenvironment, TAMs are typically the most abundant cell type. By initiating fibrosis, TAMs regulate the tumor microenvironment, thereby inhibiting immune defense and facilitating angiogenesis. In various tumor types, the number of M2 macrophages in tumors is negatively correlated with patient survival and positively correlated with tumorigenesis. Hence, alteration of the M1 to M2 macrophage ratio is a potential strategy for treating OC and improving the associated prognosis.

Declarations

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