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Cancer Macrophages are Present in Endometrial Cancers: A Mini Review

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Abstract

The complex tumour microenvironment is a crucial regulator of anti-tumor immune responses in gynecologic cancers. How cancer cells interact with the diverse population of immune effector cells has a substantial impact on the efficacy of traditional chemotherapy and cutting-edge immunotherapy methods. In this study, we focus specifically on the role of macrophages in ovarian, endometrial, and cervical cancers. We discuss the evolution of macrophages and how their polarisation status is influenced by the stimuli in their surroundings. By fostering tumour growth and controlling immune-suppression, tumor-associated macrophages (TAMs) in the tumour microenvironment affect treatment outcomes. We outline clinical strategies that particularly target TAMs, such as limiting macrophage differentiation, blocking immunological checkpoints, reducing monocyte recruitment to the tumour, and preventing immune checkpoint blockade.

Keywords: Cancer • Tumor-associated macrophages • Gynecological cancer

Introduction

Intriguing new therapeutic approaches have been developed as a result of recent advances in our understanding of the relationship between the immune system and cancer. Immunotherapy increases the immune system's ability to recognise and destroy cancer cells rather than focusing on the processes or signalling pathways inside the cancer cell. The complex microenvironment of gynecologic malignancies, which contains a variety of immune effector cells, regulates how well immunotherapies and other anti-neoplastic treatments work. The development of cutting-edge therapy strategies with significant potential for improving the prognosis of patients with gynecologic malignancies has been facilitated by a deeper understanding of the many components of this microenvironment and their interactions.

Inflammation plays a significant role during several stages of carcinogenesis, from the emergence of the primary tumour to the spread of metastatic illness. An important stage in the course of tumour growth is the emergence of an immunosuppressive environment that prevents the immune system from efficiently combating the tumour. The several levels of immunosuppression prevalent in the tumour microenvironment, including T cell exhaustion and insufficient dendritic cell antigen presentation, have an effect on both the innate and adaptive immune systems.

The landscape of myeloidderived suppressor cells (MDSCs), which control immune suppression to promote the growth and spread of tumours, is diverse [1]. Based on a variety of morphological and behavioural characteristics, they are divided into two main subsets: polymorphonuclear MDSCs (pMN-MDSCs) and monocytic MDSCs (m-MDSCs). In the tumour microenvironment, m-MDSCs specialise and develop into tumor-associated macrophages (TAMs) via modulating the expression of a number of cell-surface markers. TAMs carry out a variety of activities, including immunological ones including the phagocytosis of cancer cells and immunosuppression. TAMs release a variety of chemicals, including VEGF for angiogenesis that support the growth of tumours.

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Literature Review

Macrophages those are tissue-resident

Tissue-resident macrophages, which can support themselves and have a long lifespan, are produced by an embryo's yolk sac. Recent research on developmental mapping and ontogeny has revealed a critical and distinctive role for tissue-resident macrophages. Depending on the tissue, tissue-resident macrophages have different phenotypes and functions. These macrophages play a key role in modulating immune inflammatory responses and controlling metabolism [2]. Although they all play comparable duties, the liver's Kupffer cells, the brain's microglia, the lung's alveolar macrophages, and the bone osteoclasts are all very well adapted to their particular organ-specific functions.

Each tissue-resident macrophage phenotype is maintained by local cues that activate a particular transcriptional programme, such as cytokines or metabolites originating from the tissue. One of the most important components is colony stimulating factor 1 (CSF-1), which is required for macrophage survival and proliferation. Peritoneal macrophages in mice respond to omentum-derived retinoic acid by activating the transcription factor GATA6, which causes peritoneal-specific localization, polarisation, and regulation of gut IgA synthesis by peritoneal B-1 cells (RA). The omentum serves as a source of retinoic acid to maintain the resident phenotype of the peritoneal macrophage tissue and is an early and favoured site of ovarian cancer metastasis. Leukocytes gather to form immunological clusters, often known as "milky patches," in the perivascular area of the omentum. The proliferation of monocytes in early postnatal mice and their presence in milky areas lend credence to the idea that omental macrophages are descended from embryonic omental precursor cells. The creation of macrophage colony stimulating factor (CSF-1) by cells in milky areas and the repopulation of macrophages after depletion support the theory of local macrophage differentiation.

Swarm of macrophages

In contrast to tissue-resident macrophages, infiltrating macrophages are derived from bone marrow. Due to their limited lifespan, they are frequently replaced by circulating monocytes. Monocytes from blood arteries are drawn into various tissues by growth factors and certain chemokines, such as CCL2 and CCL5 [3]. Similar to tissue-resident macrophages, infiltrating macrophages

can detect cues in the local environment and develop into specialised macrophage populations to support tissue homeostasis, immunology, and inflammation.

Macrophages and the tissue environment: The immunological phenotype of macrophages is extremely changeable and is regulated by inputs from the immediate tissue environment. Macrophages must be exposed to bacterial lipopolysaccharides (LPS) and/or inflammatory cytokines produced by Th1 cells, such as tumour necrosis factor (TNF) and interferon, in order to become "classically activated" or M1 macrophages (IFN-). Nuclear factor B (NFB) heterodimer (p50-p65), hypoxia-inducible factor one, and members of the interferon-regulatory factor/signal transducer and activator of transcription (IRF/STAT) family (IRF3, IRF5, STAT1, and STAT5) collaborate to activate a cascade of transcription factors that results in the M1 phenotype (HIF1).

Because of this, the conventional M1 or M2 description of macrophage polarisation state, while useful for identifying extreme conditions, is unable to capture the dynamics of macrophage function as a whole. The complexity of macrophage activation states in vivo further limits our ability to predict the biological effects of targeting a specific macrophage subtype, notwithstanding the advances. It will be very helpful to define these macrophages in the context of health and disease using next-generation sequencing.

Macrophages and prognosis: The role of tumor-associated macrophages as a prognostic predictor in gynecologic malignancies has been examined in a number of studies. The presence of macrophages in tumour tissue has been investigated using a number of histological markers, including CD68, a pan-macrophage marker, HLA-DR+ and iNOS+ for M1 macrophages, and CD163 or CD206 for the M2-macrophage population. M2-macrophages are frequently associated with a poor prognosis, as shown for breast, gastric, endometrial, cervical, and ovarian malignancies as well as other cancers [4].

Ovarian epithelial carcinoma and TAMs: Numerous studies have demonstrated that TAMs have a major tumor-promoting role in epithelial ovarian cancer. A high density of CD163+ M2 TAMs was linked to an advanced stage and a poor outcome for the patient in a study on epithelial ovarian cancer. Other studies have uncovered crucial details about the impact of TAMs on immunological checkpoints such B7-H4 and PD-1/PD-L1 in ovarian cancer. These immunological checkpoints function as inhibitory mechanisms to maintain the immune system in a self-tolerant state and control the duration and strength of an immune response. Cancer cells can take advantage of immune checkpoint pathways and evade immune surveillance by overexpressing B7-H4 and PD-L1. On T cells, a transmembrane protein known as B7-H4 has an undiscovered ligand. PD-L1, a ligand for PD-1 on T cells, encourages T cell fatigue and suppresses cytotoxic T cell responses. The ability of TAMs to express PD-L1 and B7-H4, which exacerbates an immunosuppressive environment, is interesting to highlight.

TAMs and endometrial cancer: TAMs' involvement in the promotion of endometrial cancer tumours has been supported by similar discoveries. In both the epithelial and stromal compartments, endometrial carcinomas exhibit a greater CD68+ macrophage density than healthy endometrium [5,6]. It's noteworthy that TAMs seem to support oestrogen and progesterone's endometrial cancer-related effects. For instance, Jiang et al. showed that a rise in TAMs in endometrial cancer was associated with a decrease in the expression of the progesterone receptor. It's interesting to note that Ning et al. demonstrated that macrophages can modify endometrial cancer cells' oestrogen sensitivity, hence encouraging the growth of estrogen-dependent tumours.

Phagocytosis of macrophages

The majority of current immunotherapy methods focus on disabling immune checkpoints on B and T cells, which are the adaptive immune system's building blocks. In the innate arm, the CD47/SIRP interaction triggers a similar immune checkpoint. An integrin-associated protein known as CD47 was demonstrated to be a tumour antigen in human ovarian cancer in the 1980s [7]. Cancer cells exhibit an overexpression of CD47. By binding to the signal-regulatory protein alpha (SIRP) that is found on macrophages, CD47 prevents macrophage-mediated phagocytosis. Downstream signalling activates tyrosine phosphatase, and submembrane assembly at the phagocytic synapse inhibits myosin accumulation.

TAMs and anti-cancer drugs

Numerous investigations have shown that some anti-neoplastic medications used to treat ovarian cancer can modify TAM activity and number in the tumour microenvironment [8]. For instance, the chemical trabectedin destroys DNA in tumour cells by intercalating with the minor groove. Trabectedin interacts with DNA-binding proteins to change the expression of genes for inflammatory chemokines and angiogenic factors.

Conclusion

TAMs have important pro- and anti-tumor functions in the microenvironment of gynecologic malignancies. Understanding how TAMs affect important pathways of tumour growth, metastasis, and current anti-neoplastic therapy is a substantial scientific challenge in this extremely dynamic cell type. It is exciting to examine TAMs as targets for novel immunotherapy approaches with great potential to considerably prolong survival in gynecologic cancer patients.

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