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Review Article

Tumor associated macrophages in gynecologic cancers

Venkatesh Krishnan [a], Bruce Schaar [a], Supreeti Tallapragada [a], Oliver Dorigo [a,b,*]

[a] Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Stanford University School of Medicine, Stanford, CA, USA.
[b] Stanford Women's Cancer Center, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, USA

HIGHLIGHTS

- Presence of TAMs correlates with poor prognosis in gynecologic cancers.
- TAMs are likely to express both M1 and M2 markers in the tissue microenvironment.
- TAMs can promote metastasis, angiogenesis and inhibit anti-tumor immune responses.
- Current therapeutic strategies for targeting TAMs are reviewed.

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ABSTRACT

The complex tumor microenvironment in gynecologic cancers plays a major role in modulating anti-tumor immune responses. The interaction of cancer cells with the diverse spectrum of immune effector cells has an important impact on the efficacy of standard chemotherapy and novel immunotherapy approaches. In this review, we specifically focus on the role of macrophages in ovarian, endometrial and cervical cancers. We discuss the origins of macrophages and their polarization state dictated by the microenvironment's cues. Within the tumor niche, tumor-associated macrophages (TAMs) promote tumor growth and mediate immune-suppression thereby effecting treatment responses. We outline clinical strategies that directly target TAMs, including inhibition of macrophage differentiation, prevention of the recruitment of monocytes to the tumor, enhancement of phagocytosis and immune checkpoint blockade.

Contents

* Corresponding author.
E-mail addresses: vkrishnan@stanford.edu (V. Krishnan), bschaar@stanford.edu (B. Schaar), supreeti@stanford.edu (S. Tallapragada), odorigo@stanford.edu (O. Dorigo).

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1. Introduction

Recent advances in our understanding of the interactions between the immune system and cancer have led to promising new therapeutic approaches [1]. Immunotherapy augments the immune system's ability to recognize and destroy cancer cells rather than targeting processes or signaling pathways within the cancer cell. The response to anti-neoplastic therapies including immunotherapies is regulated by the complex microenvironment in gynecologic cancers, which encompasses a diverse spectrum of immune effector cells. In-depth insights into the various components of this microenvironment and its interactions have led to the development of novel therapeutic strategies that bear great potential for improving the outcomes of patients with gynecologic cancers.

Inflammation plays a major role at different stages of carcinogenesis, from primary tumor initiation to metastatic spread. A key event that is essential to the progression of tumor growth is the establishment of an immunosuppressive milieu that prevents an effective attack by the immune system on the tumor. Multiple layers of immunosuppression in the tumor microenvironment affect both the adaptive and innate immune system including T cell exhaustion and poor antigen presentation by dendritic cells [2].

The tumor microenvironment has a diverse landscape of myeloid-derived suppressor cells (MDSCs) that mediate immune suppression to promote tumor growth and metastasis. Based on their different phenotypic and morphological characteristics they are divided into two main subsets, polymorphonuclear MDSCs (pMN-MDSCs) and monocytic MDSCs (m-MDSCs) [3]. In the tumor niche, m-MDSCs differentiate and develop into tumor-associated macrophages (TAMs) by regulating the expression of a range of cell-surface markers. TAMs have various functions that include immune responses such as phagocytosis of cancer cells and immunosuppression. TAMs secrete various factors that support tumor growth including VEGF for angiogenesis [1].

1.1. TAM Ontogeny

There are two separate origins for macrophages that contribute to tissue homeostasis as well as to the pathophysiology of immune-related diseases such as cancer: tissue-resident macrophages and infiltrating macrophages (Fig. 1).

2. Tissue-resident macrophages

Tissue-resident macrophages are embryonically derived (yolk sac), capable of self-maintenance and are long-lived. Recent ontogeny and developmental mapping studies have revealed an important and distinct role for tissue-resident macrophages [4]. Tissue-resident macrophages are heterogeneous and adopt a tissue-specific phenotype and function. These macrophages play a prominent role in regulating metabolism and mediating immune inflammatory responses. Bone osteoclasts, brain microglia, Kupffer cells in the liver, and lung alveolar macrophages share common functions but are also highly adapted to their organ-specific purposes [5]. Recent next-generation sequencing studies have revealed unique transcription signatures of these tissue-specific macrophages such as GATA6 for peritoneal macrophages [6].

Each tissue-resident macrophage phenotype is maintained by local signals such as tissue-derived cytokines or metabolites that induce a specific transcriptional program. One of the most important factors is colony stimulating factor 1 (CSF-1) which is required for macrophage survival and proliferation. In mice, peritoneal macrophages respond to omentum-derived retinoic acid (RA) by expressing the transcription

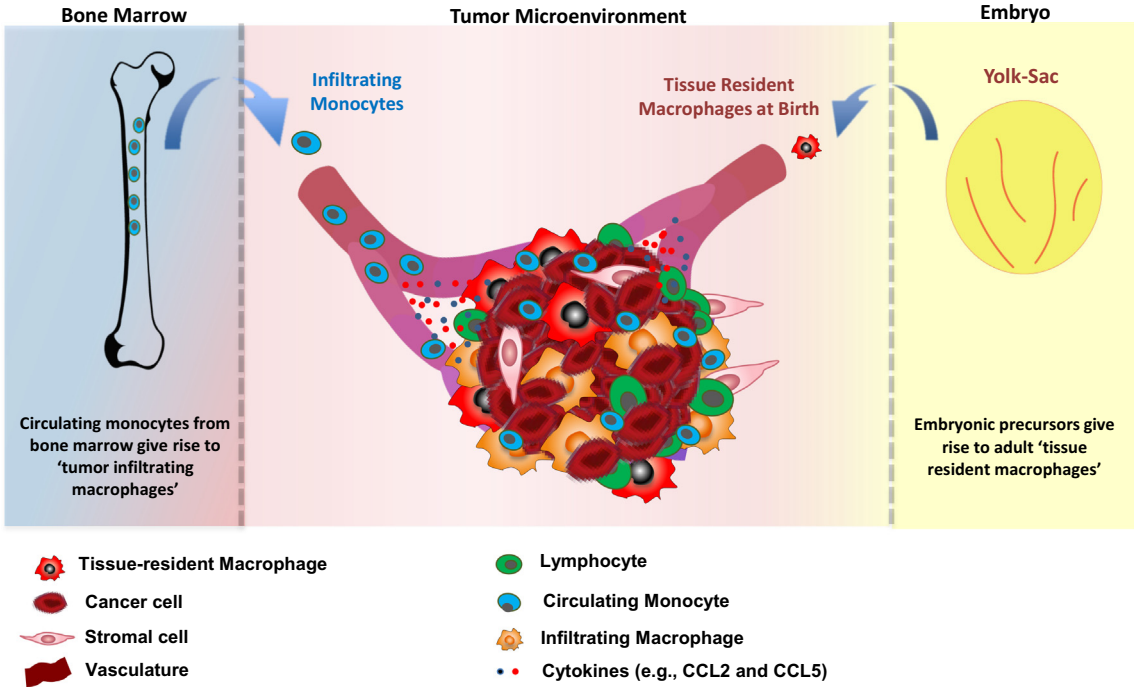

Fig. 1. Macrophage ontogeny: Macrophages originate either from circulating monocytes derived from bone marrow or from embryonic precursors that seed peripheral locations and self-sustain over the lifetime of the host. In the tumor microenvironment, TAMs constitute a mixed population that includes resident cells of embryonic origin present at the time of birth and infiltrating monocytes/macrophages attracted to the site through chemokines (such as CCL2, CCL5, and CSF-1) secreted by cancer cells and stromal cells. The delineation of the role of each macrophage origin in tumor progression remains an open question.

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