

Introduction to the Tumour Microenvironment Review Series

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Guest Editor



For many years, cancer researchers focused on the attributes of tumour cells that lead to life-threatening malignancy. These studies have provided a comprehensive understanding of the role of oncogenes and tumour suppressor genes, as well as their associated signal transduction pathways, in cancer [1]. In recent years, it has become clear that a complete understanding of the many steps and processes that occur during cancer progression must include the response of the tissues in the immediate vicinity of the tumour, as well as the systemic changes that occur in the bone marrow, circulation and sites of metastasis. Tumours are complex tissues that contain extracellular matrix (ECM), activated fibroblasts, immune cells, pericytes, adipocytes, epithelial cells, glial cells and vascular and lymphatic endothelial cells. Collectively, this tissue is referred to as the tumour microenvironment (TME). The tumour stroma has been likened to the granulation tissue that forms during wound healing [2]. This process involves the temporal orchestration of resident and surrounding uninjured cells, the coagulation system and the immune system, as well as the recruitment of various types of cells that produce and remodel the ECM. Whereas wounds usually heal with time, the signals that initiate the formation of the tumour stroma persist, leading to the description of tumours as 'wounds that do not heal' [2].

It has become clear that the non-cancerous cells that comprise the TME are not innocent bystanders; rather, they are conscripted to promote tumour progression. The TME contains multiple types of immune cells, which are recruited or activated by the chemokines and cytokines that are secreted by tumour cells [3]. In addition, cell death and necrosis drive the recruitment and activation of macrophages in the TME. Tumour-associated macrophages are a rich source of pro-angiogenic factors and they have been shown to promote metastasis [4, 5]. Various types of immune cells also facilitate tumour cell intravasation and promote the formation of premetastatic niches [6]. Cancer-associated fibroblasts (CAFs) also promote primary tumour growth and metastasis

[7–9]. Multiple origins of CAFs have been proposed, including adjacent tissue, the bone marrow and endothelial cells [10, 11]. These cells express markers that are associated with an activated phenotype, such as stromal cell-derived factor-1 (SDF-1), fibroblast activation protein and α -smooth muscle actin [7–9].

Vascular and lymphatic endothelial cells are recruited to the TME by the members of the VEGF family that are secreted by tumour and stromal cells [12]. In 1975, Judah Folkman proposed that tumours cannot grow beyond a relatively small size without stimulating a vascular system to supply them with nutrients [13]. Subsequent studies have validated this hypothesis and have identified key stimulators and inhibitors of angiogenesis. The data indicate that the relative concentrations of the stimulators and inhibitors determine endothelial cell phenotype, with the change from a quiescent to angiogenic phenotype being referred to as the 'angiogenic switch' [14]. This switch corresponds to the transition of a poorly vascularized tumour to one that is well vascularized. Thus, the presence of endogenous inhibitors of angiogenesis in the TME is probably central to tumour dormancy [15]. Of the endogenous inhibitors, thrombospondin-1 (TSP-1) is highly expressed in the TME by stromal fibroblasts and immune cells [16]. The importance of TSP-1 is underscored by the fact that oncogenes suppress TSP-1, whereas tumour suppressor genes stimulate TSP-1 [17, 18]. Tumour cells have also been reported to instruct stromal cells to decrease their expression of TSP-1, thus, further decreasing the local barriers to angiogenesis [19]. This type of cross-talk between the tumour cells and stromal cells may facilitate co-evolution of the various cell types that comprise tumour tissue.

The ECM is a key component of the TME that has both positive and negative effects on tumour growth. Many of the endogenous inhibitors of angiogenesis are derived from ECM proteins [20]. However, the components of the ECM, including its associated growth factors and the cellular proteases that modify structure

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and function of the ECM, also promote tumour growth and metastasis [21–23]. Through its interaction with integrins, proteoglycans and other receptors, the ECM serves to support cytoskeletal organization, and cell adhesion, migration and invasion [24, 25].

Taken together, the data support the hypothesis that dynamic and reciprocal interactions between the tumours cells and their neighbouring stromal cells within the TME determine the course of tumour progression. These studies also indicate that the constituents of the TME are central to metastasis. In this review series, we will explore the function of the various cellular and protein constituents of the TME. This journey will begin with a discussion of the role of lymphangiogenesis and cancer metastasis.

Mumprecht and Detmar summarize data showing that the members of the VEGF family stimulate lymphangiogenesis within tumour tissue and distant lymph nodes. Expansion of the lymphatic vasculature in sentinel lymph nodes creates a premetastatic niche that favours future tumour cell growth. Subsequent reviews will discuss the role of CAFs, vascular endothelial cells, pericytes, immune cells, adipocytes, glial cells and ECM in the TME. They will also explore exciting new therapeutic opportunities that target the constituents and processes that are essential to TME structure and function. In this context, anti-angiogenic therapeutics, such as Avastin, are already demonstrating significant efficacy [26].

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