Tumor Macroenvironment and Metabolism

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In this review we introduce the concept of the tumor macroenvironment and explore it in the context of metabolism. Tumor cells interact with the tumor microenvironment including immune cells. Blood and lymph vessels are the critical components that deliver nutrients to the tumor and also connect the tumor to the macroenvironment. Several factors are then released from the tumor itself but potentially also from the tumor microenvironment, influencing the metabolism of distant tissues and organs. Amino acids, and distinct lipid and lipoprotein species can be essential for further tumor growth. The role of glucose in tumor metabolism has been studied extensively. Cancer-associated cachexia is the most important tumor-associated systemic syndrome and not only affects the quality of life of patients with various malignancies but is estimated to be the cause of death in 15%–20% of all cancer patients. On the other hand, systemic metabolic diseases such as obesity and diabetes are known to influence tumor development. Furthermore, the clinical implications of the tumor macroenvironment are explored in the context of the patient's outcome with special consideration for pediatric tumors. Finally, ways to target the tumor macroenvironment that will provide new approaches for therapeutic concepts are described.
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Complications of a malignant tumor can be either (1) local due to direct effects of the primary tumor or metastatic lesions on the surrounding tissues, or (2) systemic. Tumors may cause systemic effects by releasing soluble factors into blood or lymph vessels[1] or via immune reactions caused by cross-reactivity between cancer cells and normal tissues.[2] Some of these systemic complications can be categorized under the well-known paraneoplastic syndromes.[2] Perhaps the most common effect tumors exert on their macroenvironment is cancer-associated cachexia. Other systemic changes, though pathological, are subclinical and might not only be beneficial as clinical markers for prognosis and therapy prediction[3] but also may help to understand the mechanisms causing systematic complications.

With recent advances in cancer therapy, patients live longer and, therefore, it is of utmost importance to improve the quality of life during this time. In this context, addressing systemic complications as a target for intensive research and development of treatment options is imperative. This review aims to introduce the concept of tumor macroenvironment, explore it in the context of the tumor microenvironment, and discuss the clinical and therapeutic implications of this concept.

TUMOR MICROENVIRONMENT

Before discussing a definition of the tumor macroenvironment, we will briefly explore the cellular elements of the tumor microenvironment and consider their local and systemic interactions.

Tumor-Associated Inflammation and Angiogenesis

As early as 1863 Rudolf Virchow observed that tumor tissues are infiltrated by immune cells; he was

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also the first to hypothesize a direct link between inflammation and cancer.[4] This hypothesis is now widely accepted and a large body of research supports this fact. About 15% of human cancers are estimated to arise from sites of infection or chronic inflammation.[5] Moreover, the majority of solid tumors exhibit infiltration by immune cells and release pathological levels of cytokines into the surrounding tissue and/or into the bloodstream.

The local effect of cytokines released into the tumor microenvironment has been reviewed extensively.[6] The interaction between these cytokines and the tumor microenvironment affects tumor growth and remodeling of the tumor microenvironment. Critical components of the tumor microenvironment are newly synthesized blood and lymph vessels, which represent key events in tumor growth that are driven by the metabolic needs of proliferating cells, including oxygen and nutrients, and are mediated by pro-inflammatory cytokines. A key event that initiates or enhances the angiogenic process is stabilization of hypoxia inducible factor 1-alpha (HIF1α) in the hypoxic tumor microenvironment.[7] Interleukin-1 beta (IL-1β) is an important mediator of tumor angiogenesis.[8] Together with prostaglandin E2 (PGE2), IL-1β upregulates HIF1α protein levels and activates vascular endothelial growth factor (VEGF), a reaction that is mainly mediated by the nuclear factor κB (NFκB) pathway.[9] This cascade of gene activation illustrates one important example of a mechanistic explanation for the role of inflammation in tumor development. Other mechanisms supporting angiogenesis have been reviewed elsewhere.[10] The newly synthesized blood and lymph vessels not only contribute to delivery of oxygen and nutrients to tumor cells thereby supporting tumor growth[10] but also allow tumor cells to release a wide range of soluble factors into the bloodstream. Mechanistically, this represents the key event connecting the tumor microenvironment with the whole body of the patient exerting systemic biological effects. We suggest using the term "tumor macroenvironment" to define the pathological interaction between the tumor cells, as well as the tumor microenvironment with other organs and systems of the body.

TUMOR MACROENVIRONMENT VERSUS TUMOR MICROENVIRONMENT

Unlike in normal tissue, cellular proliferation in tumors is an uncontrolled process. During the early stages of tumorigenesis, two main signaling types dominate in the tumor microenvironment to support tumor cell proliferation. The first type of signaling increasing proliferation constitutes autocrine stimulation among tumor cells themselves. Tumor cells may release growth factor ligands that bind to receptors on the surface of tumor cells, thereby stimulating proliferation.[11] The second type of signaling constitutes paracrine interaction between tumor cells and other components of the microenvironment. Factors released from tumor cells can stimulate normal cells to produce growth factors to which tumor cells respond subsequently.[12] When the size of the tumor reaches the oxygen and nutrient diffusion limit, tumor cells encounter not only a profound metabolic challenge but also hypoxia and nutrient deprivation.[13]

To survive in this hostile environment, tumor cells deregulate their intrinsic metabolic machinery and, via paracrine signaling, remodel the tumor microenvironment to activate tumor-associated angiogenesis. Though tumor cells are master regulators of the tumor microenvironment, each type of cell in this environment may interact with other neighboring cells.[14] Soluble factors released, such as chemokines, cytokines, and growth factors, (1) recruit inflammatory cells, fibroblasts, and myeloid cells; (2) reshape the extracellular matrix; and (3) initiate and support neo-vascularization. On the one hand, tumor-induced angiogenesis supports tumor growth, but on the other hand the newly formed blood vessels are tortuous and leaky. This, again, results in a hostile microenvironment that may induce even more aggressive properties of cancer cells. The imperfectly formed network of newly formed blood vessels in close proximity to tumor cells and inflammatory cells results in accumulation and/or release of soluble factors from the tumor microenvironment into the circulation at high levels. This leads to pathological endocrine effects and interaction between the tumor microenvironment and the patient's organs and systems, resulting in the development of cancer-associated systemic syndromes in the tumor macroenvironment (Figure 1).

METABOLISM OF THE TUMOR MACROENVIRONMENT

Protein and Amino Acid Metabolism

Increased whole-body protein turnover is often associated with tumor growth. This has been well documented in cachectic[15] and non-cachectic cancer patients.[16] The decrease in protein synthesis[17] and the increase in muscle protein degradation in cancer patients[18] imply that tumors are able to mobilize muscle proteins. Indeed, several studies demonstrated a direct relationship between tumor growth and host protein metabolism. The concept of tumors as "nitrogen traps" was described as early as in 1951 by Mider.[19] Nitrogen mobilized from tissues represents a potential source of building blocks for