

Review

A Bloody Conspiracy. Blood Vessels and Immune Cells in the Tumor Microenvironment

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Simple Summary: The tumor microenvironment has risen over the last years as a significant contributor to the failure of antitumoral strategies due to its numerous pro-tumorigenic activities. In this review, we focused on two features of this microenvironment, namely angiogenesis and immunity, which have been the targets of therapies to tackle tumors via its microenvironmental part over the last decade. Increasing our knowledge of the complex interactions within this ecosystem is mandatory to optimize these therapeutic approaches. The development of innovative experimental models is of great help in reaching this goal.

Abstract: Cancer progression occurs in concomitance with a profound remodeling of the cellular microenvironment. Far from being a mere passive event, the re-orchestration of interactions between the various cell types surrounding tumors highly contributes to the progression of the latter. Tumors notably recruit and stimulate the sprouting of new blood vessels through a process called neo-angiogenesis. Beyond helping the tumor cope with an increased metabolic demand associated with rapid growth, this also controls the metastatic dissemination of cancer cells and the infiltration of immune cells in the tumor microenvironment. To decipher this critical interplay for the clinical progression of tumors, the research community has developed several valuable models in the last decades. This review offers an overview of the various instrumental solutions currently available, including microfluidic chips, co-culture models, and the recent rise of organoids. We highlight the advantages of each technique and the specific questions they can address to better understand the tumor immuno-angiogenic ecosystem. Finally, we discuss this development field's fundamental and applied perspectives.

Keywords: tumor; angiogenesis; immunity; infiltration; paracrine; microenvironment; chips; microfluidics; organoids

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1. The Tumor Microenvironment: The Octopus Spreading Its Tentacles

1.1. The Tumor Vascularization, a Key Partner in the Malignant Progression

Cancers represent a major health issue, accounting for nearly 10 million deaths in 2020, according to the World Health Organization [1]. Concomitantly with the identification of the intrinsic genetic drivers of tumorigenesis, the research community has evidenced over the last decades the critical importance of the tumor microenvironment in the evolution of the pathology.

Tumors progress in concert with their neighbors and orchestrate a kind of conspiracy to promote their malignant development [2]. Among these “partners in crime”, the vasculature plays a key role, notably by providing the tumors with nutrients and oxygen required for their sustained growth, and an angiogenic switch is typical during malignant progression. Almost half a century ago, Judah Folkman introduced this concept of tumor

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