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Review Article

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Tumour Microenvironment (TME) as a Target for Future Therapies

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Abstract

Cancer biology, a dynamic and rapidly evolving field, continues to unveil novel insights into the complex mechanisms underlying tumorigenesis and disease progression. This article highlights some of the emerging trends that are shaping our understanding of cancer biology. Advances in genomics and single-cell sequencing have enabled a comprehensive exploration of tumour heterogeneity and clonal evolution, shedding light on the development of therapy resistance and the identification of potential therapeutic targets. The integration of multi-omics data, including genomics, transcriptomics, proteomics, and epigenomics, is providing a holistic view of cancer molecular landscapes, aiding in the discovery of biomarkers for early detection and personalized treatment strategies. The intricate interplay between the tumour microenvironment, immune system, and cancer cells has led to the development of immunotherapies that harness the body's immune response to effectively target and eliminate cancer cells. Moreover, the rise of organoid and 3D culture models has enabled more accurate recapitulation of tumour behaviour in vitro, facilitating drug screening and the study of tumour-stroma interactions. Overall, these emerging trends underscore the increasing complexity of cancer biology and hold promise for driving the development of innovative diagnostic tools and targeted therapies, ultimately aiming to improve patient outcomes and quality of life.

Keywords: Cancer Biology, Tumour-Microenvironment, Targeted Therapy, Epigenomics, Omics Data, Diagnosis, Micro RNA.

Introduction

Solid tumours, characterized by the abnormal growth of cells within a localized mass, pose substantial challenges in the field of oncology. As one of the leading causes of mortality worldwide, the diagnosis and treatment of solid tumours have been focal points of extensive research and clinical efforts [1]. However, the landscape of solid tumour research is constantly evolving, unveiling new trends that have the potential to reshape our understanding and approach to cancer management. reported six hallmarks of cancer development that are responsible for the generation of TME by lateral communication/signalling [2]. These hallmarks include continuous proliferation signaling, escape from cell death pathways, induction of neovasculature (angiogenesis), avoiding growth suppressors, activation of metastasis, and replicative immortality.

Understanding the tumour microenvironment (TME) is essential for developing targeted therapies and improving cancer treatment outcomes [3]. This refers to the cellular and non-cellular components present within and around a tumour. It plays a crucial role in tumour development, progression, and response to treatment. Understanding the complexity of the TME is the focus of this study for finding strategic treatment options.

In this article we delve into these emerging trends in solid tumours and its microenvironment, exploring their implications for diagnostics, treatment strategies, and patient outcomes. By examining the latest findings in the context of these trends, we aim to contribute to a deeper understanding of the ongoing advancements in the field of oncology.

Tumour Microenvironment

Tumours develop in complex tissue environments, which they depend on for sustained growth, invasion and metastasis. This is referred as tumour microenvironment (TME) it consists of complex and dynamic cellular and non-cellular surroundings in which a tumour grows and exists. TME plays a crucial role in tumour development, progression, and response to therapy. TME is composed of various components, including immune cells, blood vessels, fibroblasts, extracellular matrix (ECM), and signaling molecules. The interactions and crosstalk between these components influence tumour behavior and treatment outcomes [4, 5].

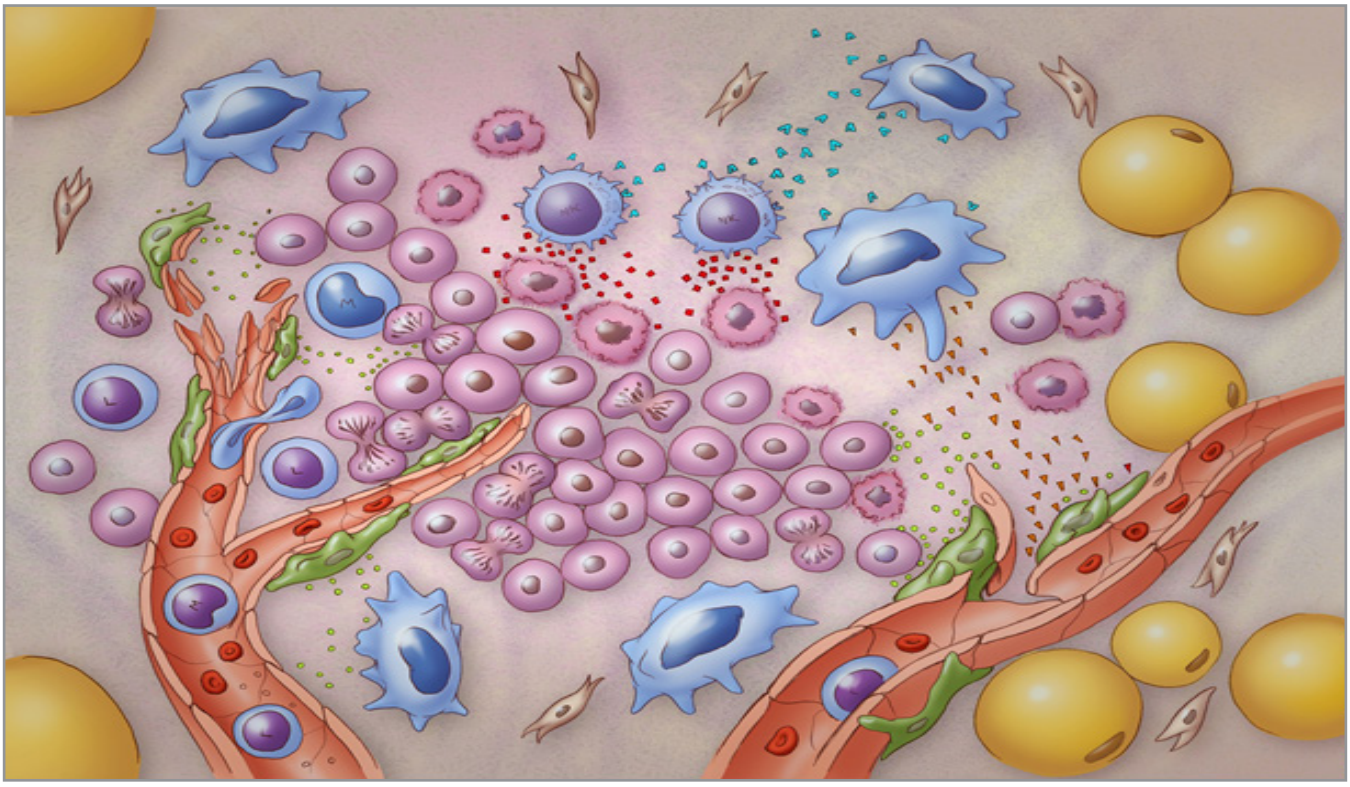

Figure 1: showing tumour microenvironment (poster diagram created by S.F.Borgogno)

Key components of the tumour microenvironment include:
Immune Cells: Immune cells like T cells, B cells, natural killer (NK) cells, macrophages, and dendritic cells are present within the TME. These cells can have both tumour-promoting and tumour-suppressing effects. Tumour cells often evolve strategies to evade immune surveillance, but immunotherapy approaches seek to harness the immune system's power to target and destroy cancer cells.

Blood Vessels: Tumours require a blood supply to receive nutrients and oxygen, and this is facilitated by the formation of new blood vessels, a process known as angiogenesis. The quality and density of blood vessels in the TME can affect tumour growth and metastasis.

Fibroblasts: These are connective tissue cells that play a role in tissue repair and wound healing. In the TME, cancer-associated fibroblasts (CAFs) are often activated and can contribute to tumour growth, invasion, and therapy resistance through ECM remodeling and secretion of various signaling molecules.

Extracellular Matrix (ECM): The ECM is a complex network of proteins and carbohydrates that provide structural support to tissues. In the TME, the ECM composition and stiffness can influence tumour cell behavior, migration, and response to therapy.

Signaling Molecules: Various signaling molecules such as cytokines, growth factors, and chemokines are produced by different cell types in the TME. These molecules can influence cell growth, migration, and immune responses.

Hypoxia: Tumours often grow faster than the surrounding blood vessels can supply them with oxygen, leading to areas of low oxygen (hypoxia) within the tumour. Hypoxic conditions can promote aggressive tumour behavior and resistance to therapies.

Metabolic Changes: Tumour cells often have altered metabolic pathways compared to normal cells. The TME can influence these metabolic changes and contribute to tumour survival and growth.

Understanding the tumour microenvironment is crucial for developing effective cancer treatments. Therapies targeting the TME aim to disrupt the supportive environment that enables tumour growth and progression. For instance, immunotherapies like immune checkpoint inhibitors aim to enhance the immune system's ability to recognize and attack cancer cells. Additionally, anti-angiogenic drugs target the blood vessel formation process, reducing the tumour's nutrient supply.

Tumour Cells are the central players in cancers, they are supported by the TME and interact with various other components that plays a pivotal role in cancer biology, and targeting its various components holds promise for improving cancer treatment strategies.

Over the last two decades, research in TME has progressed significantly and advances were made in understanding the role of the TME components and their impact on responses to various treatment strategies, including immunotherapies. TME is made up of several important components as mentioned above including the tumour parenchyma cells, fibro-

blasts, mesenchymal cells, blood, and lymph vessels, as well as tumour infiltrating immune cells, chemokines, and cytokines.

Among the nonimmune components, tumour-associated fibroblasts are responsible for the formation and remodeling of the extracellular matrix and constitute a source of growth factor which promotes the growth of carcinoma cells

How does the TME help in Tumour Development?

The tumour microenvironment (TME) is a complex and dynamic ecosystem that surrounds and interacts with tumour cells within solid tumours. It consists of a variety of components, including immune cells, stromal cells, blood vessels, extracellular matrix (ECM), signaling molecules, and more. The interactions and cross-talks within this microenvironment play a crucial role in tumour development and progression [6, 7]. The contributions of the tumour microenvironment to these processes are presented below:

(i) Angiogenesis and Nutrient Supply: Tumours require a continuous supply of nutrients and oxygen to grow. The TME helps facilitate this by promoting angiogenesis, the formation of new blood vessels. Hypoxia (low oxygen levels) within the tumour triggers the release of pro-angiogenic factors like vascular endothelial growth factor (VEGF). New blood vessels that form as a result supply the tumour with nutrients and oxygen, aiding in its growth.

(ii) Immune Suppression and Evasion: Immune cells within the TME play a dual role – they can either recognize and destroy cancer cells (immunosurveillance) or be manipulated by the tumour to promote its survival (immune evasion). Tumour cells can secrete factors that suppress the immune response, making it difficult for immune cells to target the cancer cells effectively. This allows the tumour to evade the body's natural defence mechanisms.

(iii) Inflammatory Response: Chronic inflammation within the TME is often observed in many types of tumours. Inflammation can provide a supportive environment for tumour growth and progression by promoting cell proliferation, angiogenesis, and tissue remodeling. Inflammatory cells and cytokines present in the TME contribute to a pro-tumorigenic environment.

(iv) Extracellular Matrix Remodeling: The ECM is a network of proteins and carbohydrates that provides structural support to tissues. In the TME, the ECM undergoes changes that can promote tumour cell invasion and metastasis. Tumour cells and stromal cells produce enzymes that degrade the ECM, allowing cancer cells to invade surrounding tissues and potentially spread to distant sites.

(v) Cancer-Associated Fibroblasts (CAFs): CAFs are stromal cells present in the TME that interact with tumour cells. They can secrete growth factors, cytokines, and ECM-modifying enzymes that enhance tumour growth, invasion, and metastasis. CAFs can also contribute to immune suppression and angiogenesis.

(vi) Exosome Signaling: Tumour cells release small vesicles called exosomes into the TME. These exosomes contain signaling molecules, genetic material, and proteins that can influence nearby cells. They can help in preparing distant sites for metastasis, promoting angiogenesis, and modulating the immune response.

(vii) Metabolic Adaptation: The TME can undergo metabolic changes to support tumour growth. Cancer cells often have altered metabolic pathways that allow them to thrive even in nutrient-poor environments. By altering the metabolism of both tumour and stromal cells, the TME can create conditions that favour tumour progression.

(viii) Cellular Cross-Talk: The various components of the TME communicate with each other through direct interactions and the secretion of signaling molecules. Crosstalk between tumour cells, immune cells, stromal cells, and other components can influence the behaviour of these cells, either promoting or inhibiting tumour development and progression.

With this information there has come a paradigm shift in cancer treatment from traditional chemotherapy to new strategies which target cancer cells within the TME. The first-generation therapy was antibody based, targeting Immune check-point blockade (ICB) in TME. This worked by dulling T-cell activation and blocking receptor-ligand interaction (eg CTLA4 and PD1) some patients responded to this therapy [8]. However, identification of relevant biomarkers is required to recognize patients who are expected to benefit from immune check-point blockade therapy (Anderson and Simon -2020).

TME an Arena for Targeted Therapies

Understanding the complexity of the tumour microenvironment is essential for developing targeted therapies [9, 10]. By targeting specific components or interactions within the TME, researchers and clinicians aim to disrupt the supportive environment that enables tumour growth and metastasis, ultimately improving the effectiveness of cancer treatments [5]. These are the new strategies that have emerged in recent times to mitigate cancer development, as TME is known to regulate tumour progression. The tumour microenvironment (TME) includes the cellular and non-cellular components present within and around a tumour which play a crucial role in tumour development, progression, and response to treatment. It is now recognized that the TME can differ quite profoundly from one organ to another (such as breast cancer, lung cancer, prostate cancer, or head and neck cancer) and thus we cannot simply extrapolate findings between different tumour types. Considering the different types of cells and secretions within TME can eliminate cancer cells and inhibit tumour growth more effectively [5]. We must additionally examine the patient as a whole, and not just focus on the tumour in isolation since the morphology and functionality of every TME is different. Cancer immunotherapy can recognize and kill cancer cells by regulating the body's immune system. An important component of tumour immunosuppress is the programmed death ligand-1/programmed death-1 (PD-L1/PD-1) signalling pathway, which can inhibit the activation of T-lymphocytes and enhance the immune tolerance of tumour cells, thereby achieving tumour immune escape. Therefore, targeting the PD-L1/PD-1 pathway is an attractive strategy for cancer treatment; however, the therapeutic effectiveness of PD-L1/PD-1 is still undergoing clinical trials. Thus, the TME field will inevitably continue to focus its efforts on developing

strategies to relieve immune-suppressive mechanisms and look for a common denominator, to activate antitumour immunity and/or boost the efficacy of immune-targeted agents have also endorsed that Immunotherapy holds the promise for improving the prognosis and quality of life for patients with solid tumours by harnessing the body's immune system to target and eliminate tumour cells [8, 11]. Precision medicine, another key trend, emphasizes tailoring treatment strategies based on individual patient characteristics, such as genetic mutations and molecular profiles.

Nanoparticle Strategies to Target the Cellular TME

Another novel area in cancer treatment strategy is the use of Nano-medicine [12]. Most recently nanoparticle approaches have been reported to target cancer cells in TME. The procedure is that the nano-medicine designed to target the cells will lead to nutrient deprivation of cancer cells along with exposure of these cells to various destruction mechanisms. Thus, targeting TME conditions can provide the formulation-scientist with an advantage of utilizing the conditions present to specifically target cancer cells. In this regard [13, 14]. reported that formulation of nanoparticles, can be triggered by a dual approach, i.e., acidic pH and upregulated matrix metalloproteinase-2 in TME.

Future Drug Development Considering Tumour Microenvironment (TME)

Multifunctional nanoparticle development based on TME conditions can be focused in the future, which can, at the same time, provide spatial and temporal drug/gene release. Efforts are on in this direction and research in this area has been shifted toward these multifunctional targeted nanoparticles, but it is not easy and more hard work is needed. Researchers are focusing on universal nanoparticles that are compatible with the incorporation of drug/gene separately for new treatment strategies.

In conclusion it is seen that Tumour microenvironment plays an important role in the initiation and progression of tumours. Generally, the microenvironment of early-stage tumours tends to exert antimalignancy functions, whereas that of late-stage tumours tends to exert promalignancy functions. There is a bidirectional, dynamic, and intricate complex of interactions between the stromal and cancer cells, in which tumour cells contribute to the generation and modification of the tumour microenvironment. The tumour microenvironment (TME) does play a significant role as a target for future therapies. The TME consists of non-cancerous host cells and non-cellular components surrounding the tumour. It has been recognized that the TME influences tumour growth, progression, and response to therapy. Targeting the TME can help disrupt the supportive environment that promotes tumour growth and metastasis. For example, therapies aimed at modulating the tumour stroma, such as targeting cancer-associated fibroblasts (CAFs), have shown promise in improving cancer therapy outcomes. Additionally, understanding the changes in the TME after radiotherapy can provide insights into mechanisms that can be targeted to enhance treatment efficacy. Therefore, targeting the tumour microenvironment holds great potential for the development of future therapies in cancer treatment [15, 16].

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