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Review

Physical oncology: New targets for nanomedicine

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ABSTRACT

Physical oncology is an emerging paradigm which recognizes tissue mechanics, *per se*, as an active modulator of tumorigenesis, treatment resistance and clinical outcome, mediated by mechanosignaling pathways, matrix remodeling and physical barriers to drugs. The tumor microenvironment displays abnormal physical properties in comparison to healthy tissue which contribute to cancer progression and resistance to current treatments. Physical aberrancies comprise the chaotic organization of tumor vasculature, an increased interstitial pressure, an increased solid stress, hypoxia, an abundant extracellular matrix and a progressive stiffening of solid tumors. The physical barriers in tumors are of critical importance, as tissue mechanics compromises drug delivery, reduces immune cell infiltration and promotes disease aggressiveness. All these physical hallmarks of cancer, although not fully understood, are inspiring new anticancer strategies aiming to target and normalize the physical anomalies of solid tumors, particularly in the field of nanomedicine. Here we summarize the recent paradigm shift of physical oncology and review some of the proposed strategies using nanomaterials to tackle the tumor microenvironment and its aberrant physical properties. Nanomedicine might harness the features of the tumor microenvironment in order to improve nanoparticle and drug delivery, or propose nano-agents that can be activated on demand to achieve a tailored spatio-temporal modulation of the tumor microenvironment, reduce tumor pressure and stiffness and alleviate the resistance to current treatments.

1. -Introduction

The tumor microenvironment (TME) is not only an anatomically supporting tissue, but dynamically contributes to cancer onset, progression and resistance to treatment. Over the past decades, an increasing number of publications have highlighted the crucial influence of the physical and mechanical properties of the tumor comprising rigidity, cell rheology, internal pressure, chaotic vascularization and hypoxia on cancer initiation, progression, metabolism, resistance to therapy and metastastic spread [1–7]. Since then, the physical abnormality of cancer has driven to the emergence of a new discipline: physical oncology.

In most solid tumors which represent 90% of human tumors including carcinomas and sarcomas, cell proliferation is followed by a progressive rigidification of the tissue, eventually becoming stiffer than healthy tissue. This phenomenon explains why tumors are frequently detected through physical palpation as they appear as a rigid mass residing from a healthy compliant tissue. Ultrasound imaging (shear wave elastography) and magnetic resonance elastography allows the mapping of the rigidity/stiffness at the tissue level and thus have led to the improvement of non-invasive diagnosis of solid tumors, in particular in breast, hepatic and pancreatic cancer [8–10]. This aberrant tumor stiffness highlights the importance of the tumor microenvironment in cancer progression. The tumor microenvironment is composed of the extracellular matrix (ECM), as well as a large cohort of non-tumoral stromal cells and their derived extracellular vesicles that collectively participate in tumor growth and progression: fibroblasts, the major producers and regulators of the ECM components among which collagen and hyaluronic acid; endothelial cells and pericytes that are the building blocks and regulators of the tumor blood vessels and a variety of immune cells which further control the tumor ecosystem (Fig. 1). An aberrant production and organization of the ECM, associated with a high level of fibrosis, are hallmarks of cancer characterized by a desmoplastic reaction [11]. The transformation of fibroblasts into myofibroblasts or cancer-associated fibroblasts (CAF) results in

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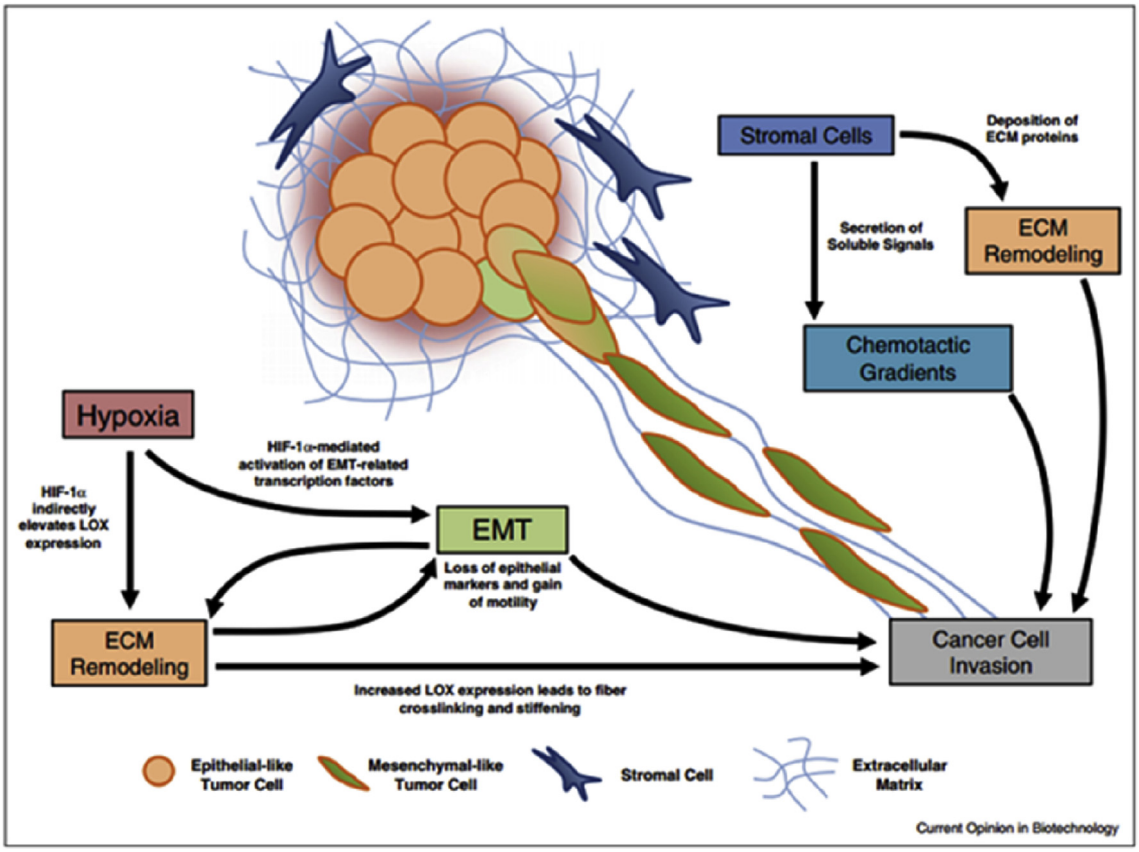

Fig. 1. The complex behavior of the tumor microenvironment is characterized by a tight dynamic interplay between tumor cells, stromal cells and soluble factors that induces ECM remodeling and favors migration and invasiveness of cancer cells (adapted from Ref. [4]).

collagen deposition in response to the transforming growth factor β (TGF-β) as well as mechanical forces [12,13]. TGF-β also regulates the production of enzymes that remodel the ECM such as matrix metalloproteinases (MMPs) or lysyl oxidase (LOX). The linear, long and highly reticulated collagen networks contribute to the aberrant rigidification of the tumor ECM [14]. In turn, tissue stiffness and solid stress cause the contraction of the myofibroblasts that further activate TGF-β production [15]. Concomitantly, cancer cells modify their mechanical properties, both adhesion and contractility, to adapt to the TME and become invasive and metastatic [16,17]. The dynamical behavior of the TME and the active crosstalk of its components not only heightens the complexity of cancer, but also inspire new strategies to tackle the TME and its physical properties as part of therapeutic options. In this review, we will first describe the physical aberrancies of cancer and their importance for the disease progression and resistance to the standard-of-care treatments. Second, we will focus on the recent approaches in nanomedicine with the potential to modulate the tumor microenvironment with a spatial-temporal control or to exploit its specificities with the aim to improve drug delivery, to overcome treatment resistance and to achieve better clinical outcome. Additionally, we lay out opportunities of cancer nanotherapies to tailor fine-tuned priming of the TME in order to optimize the efficacy of subsequent conventional treatments in stratified patients.

2. The physical aberrancy of cancer and the importance of tissue stiffness for tumor progression

Cancer is characterized by a disruption of the mechanical homeostasis that regulates the dynamical interplay between cells and their extracellular matrix. Mechanical modifications can be observed at different scales by means of biophysical methods that allow measuring the diverse forces in living tissue. While palpation readily reveals the enhanced rigidity of breast tumors compared to surrounding tissue, the quantification and mapping of stiffness can be achieved through non-invasive imaging techniques such as ultrasound or magnetic resonance elastography (Fig. 2A) [8,9,18]. Stiffening of progressing tumors is mainly due to ECM deposition, crosslinking and reorganization. However, paradoxically, single-cell mechanical studies revealed that cancer cells are softer than non-malignant ones due to alterations in their cytoskeletal architecture [16,17]. In contrast, metastatic cells are even more compliant, suggesting that metastasis and resistance to shear flow in the vasculature might be promoted by cell compliance [16,17,19]. Reconciling the tissue-level and single-cell measurements, atomic force microscopy (AFM) with micrometer spatial resolution has unveiled the biomechanical heterogeneity of tumor tissue by uniquely distinguishing the softer cancer cells [20] within the stiff tumor ECM in patient biopsies of breast cancer [21], hepatocellular carcinoma [22] and brain tumors [23] in line with their histological appearance (Fig. 2B–C). AFM nanomechanical profiles revealed the mechanical heterogeneity of malignant tissues in comparison to benign counterparts, with lower elasticity peak representative of cancer cells that can serve as a mechanical fingerprint to define the stages of progression of liver, brain and breast cancer [21–23]. Moreover, a direct link was established between cancer cell softening in the primary tumor biopsies and metastatic spreading, mediated by an upregulation of the Rho family-related pathways [21–23]. Ex vivo AFM as well as *in vivo* MRE may also give insights on dissipative viscous forces, with particular interest in the