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Biomaterials to suppress cancer stem cells and disrupt their tumoral niche

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ABSTRACT

Lack of improvement in the treatment options of several types of cancer can largely be attributed to the presence of a subpopulation of cancer cells with stem cell signatures and to the tumoral niche that supports and protects these cells. This review analyses the main strategies that specifically modulate or suppress cancer stem cells (CSCs) and the tumoral niche (TN), focusing on the role of biomaterials (i.e. implants, nanomedicines, etc.) in these therapies. In the case of CSCs, we discuss differentiation therapies and the disruption of critical cellular signaling networks. For the TN, we analyze diverse strategies to modulate tumor hypervascularization and hypoxia, tumor extracellular matrix, and the inflammatory and tumor immunosuppressive environment. Due to their capacity to control drug disposition and integrate diverse functionalities, biomaterial-based therapies can provide important benefits in these strategies. We illustrate this by providing case studies where biomaterial-based therapies either show CSC suppression and TN disruption or improved delivery of major modulators of these features. Finally, we discuss the future of these technologies in the framework of these emerging therapeutic concepts.

1. Introduction

Conventional cancer treatment is based on two premises: first, that cancer cells are a homogeneous population that displays a distinct phenotype as compared to healthy cells, and that medicines can take advantage of these differences to eliminate the disease (Clevers, 2011). The second premise is that the tumoral niche is a clinically advantageous feature, at least for nanomedicine-based therapies, since its enhances permeability to macromolecules and nanocarriers and promotes their accumulation in the tumor (Schätzlein, 2006). Nowadays, there is growing evidence demonstrating that these two premises are incorrect or at least incomplete.

Tumor cell heterogeneity is now a widely accepted feature of cancer and can be discussed at the genetic and developmental levels, being both of these tightly connected. At the genetic level, tumor cells present intrinsic genetic variability, which results in several cancer subclones that evolve following Darwinian processes in an attempt to adapt towards the environment. This process leads to an enrichment of cells presenting advantageous mutations and more aggressive phenotype (Greaves and Maley, 2012). At the developmental level, it has been confirmed that tumor initiation and relapse is driven by a selected tumor cell subpopulation that has high resistance towards conventional therapies and that takes advantage of stem cell-specific features (Farrar, 2009; Marotta and Polyak, 2009). Antitumorals are designed to target rapidly cycling cells such as those from the tumor bulk, but will spare the quiescent (but deadly) cancer stem cells (CSCs) that will generate tumor relapse and metastasis (Clevers, 2011).

Abbreviations: ALDH, aldehyde dehydrogenase; APL, acute promyelocytic leukemia; ATRA, all trans retinoic acid; BBB, blood-brain-barrier; b-FGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; CSC, cancer stem cells; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EPR, enhanced permeation and retention; GM-CSF, granulocyte macrophage colony stimulating factor; IFN, interferon; IL, interleukins; HIF, hypoxia inducible factor; HPMA, *N*-(2-hydroxypropyl)methacrylamide; LOX, lysyl oxidase; LPS, lipopolysaccharide; MSCs, mesenchymal stem cells; PAGA, poly[α-(4-aminobutyl)-L-glycolic acid]; PCL, poly (ε-caprolactone); PEDF, pigment epithelium-derived factor; PEG, poly(ethylene glycol); PEI, polyethyleneimine; PGA, poly-glutamic acid; PLA, poly-lactic acid; PLGA, poly(lactic-*co*-glycolic acid); PMDS, poly(*N*-methyldietheneamine sebacate); PVP, polyvinyl pyrrolidone; ROS, reactive oxygen species; TAM, tumor associated-macrophages; TGF-*beta*, transforming growth factor-*beta*; TLR, toll-like receptor; TICs, tumor initiating cells; TN, tumor niche; TNF-α, tumor necrosis factor-alpha; TRP2, tyrosine related protein 2; VEGF, vascular endothelial growth factor; VHL, Von Hippel–Lindau.

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Tumor niche (TN) refers to the microenvironment that interacts with tumor cells and regulates their fate. TN has been revealed as a critical barrier for cancer treatment and it is analyzed in this manuscript through four different features: the vascular niche, the inflammatory and immunosuppresive niche, the hypoxic niche and the extracellular matrix, all of which are closely related among themselves, with the CSC phenotype (Fig. 1). The tumor microenvironment was mostly seen as an advantage in the past, since it enhances the permeability and retention of the nano-sized drugs in the tumor (i.e. the EPR effect). However, tumor vasculature is highly irregular and could be tight in some regions, while being leaky in others. This irregular growth of tumor vasculature also generates non-functional branches, leading to poorly irrigated regions that cannot be easily accessed with chemotherapy (Jain, 2005). Besides, the accumulation of stroma in the tumor and the high intratumoral pressure also prevent drug transport to the inner regions. A recent survey of the literature has indicated that only a 0.7% of the nanocarrier dose is delivered to solid tumors (Wilhelm et al., 2016), a results that suggests the failure of the overall concept of passive targeting as it is understood nowadays.

Besides its barrier effect to drug delivery, the tumor niche also provides important signaling, often related to the cancer stem cell phenotype, that promotes tumor spreading and protection. CSCs and their niche have been recognized as critical features of cancer progression in the last years, and are currently in the focus of intense programs for drug development. Indeed, some prototypes have been developed to the stage of clinical implementation or are in advanced clinical trials (Fig. 2). Most of the programs, however, are still focusing on separate aspects of CSCs and the TN, and as it will be illustrated in this review, those features are tightly interconnected (Fig. 1) and might not be effectively addressed separately.

The field of biomaterials and drug delivery, mostly in tissue engineering, has focused on pulsing important cell signaling routes, particularly those related to stem cell development, and understanding and mimicking the biological substrate (the "niche"). Concretely, scaffolds and other tissue engineering devices are frequently used to: (i) induce stem differentiation (Prabhakaran et al., 2009), (ii) deliver cell-cycle modulators (Nayab et al., 2007), (iii) modulate the inflammatory niche (Lisignoli et al., 2006), (iv) modulate tissue vasculature (Stegemann and Nerem, 2003) and (v) induce extracellular matrix remodeling (Schneider et al., 2010). This spectrum of biological activity fits perfectly the requirements of a new generation of antitumorals capable of modulating CSCs and their niche.

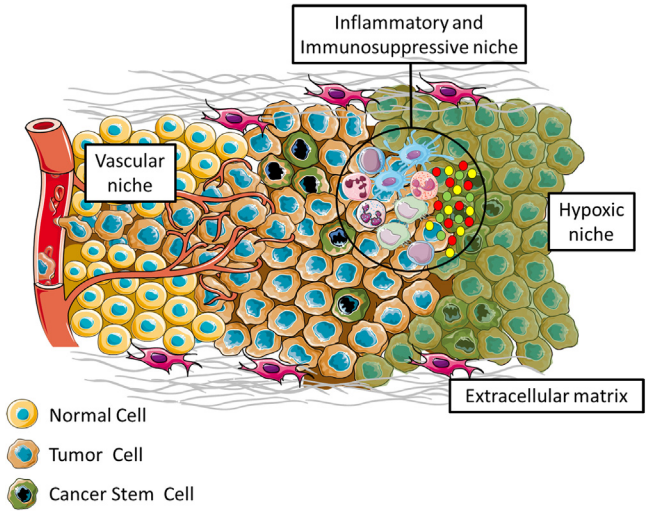

Fig. 1. General overview of the organization of cancer stem cells (CSCs) and their tumor niche (TN). CSCs dwell in complex colonies together with differentiated cancer cells and other non-tumoral cell types. The tumoral niche presents several features that are critical for CSC physiology and relevant for the design of new therapies. These are: (i) a disorganized and hypertrophic vascular niche, (ii) a highly dynamic, remodeled extracellular matrix, (iii) the formation of hypoxic regions and (iv) the generation of an inflammatory microenvironment.

The objective of this review is to analyze the properties and implications of the CSC phenotype and the TN, and to cover the main therapies designed to address these characteristics, focusing on the potential role of biomaterial-based technologies (i.e. implants, nanomedicines, etc.) in such therapies.

2. Cancer stem cells

Cancer stem cells (CSCs) have been defined as a cell subpopulation in the tumor bulk that possesses stem cell capacities. CSCs may be derived from adult stem cells or progenitor cells, but also from terminally differentiated cells that undergo epigenetic changes (Marotta and Polyak, 2009; Hermann et al., 2010). In any case, malignant cells take advantage of stem cell-specific signaling to drive tumor development.

CSCs were isolated for the first time in the 1990′s in acute myeloid leukemia, and were named "tumor initiating cells" (TICs) because they were able to start by themselves a tumor. Later, CSCs were isolated in several types of solid tumors (colon, glioma, pancreatic, lung, breast etc.). The fundamental traits of CSCs can be listed as: (i) ability for self-renewal and tumor reactivation, even in the absence of growth signals; (ii) evasion of apoptosis by secreted factors; (iii) increased activity of drug efflux transporters that enhances their resistance to chemotherapy and radiation; (iv) quiescence; (v) capacity to differentiate into any cell of the tumor population; (vi) ability to migrate and metastasize to other tissues, and (vii) increased capacity for DNA repair (Wicha et al., 2006; Kaiser, 2015). From a molecular biology perspective, CSC traits are driven by the activation of specific signaling pathways (Table 1), many of them present also on non-pathological stem cells.

The key implication of CSCs is that a reduced number of these cells have the capacity to regenerate the tumor. Therefore, any therapy that aims at successfully increasing survival needs to be effective in fully eliminating these cells, which are more resistant to conventional cytotoxic drugs. A corollary to this is that tumor reduction is only informative on the capacity of the drug to eliminate the bulk tumor cells, and might not correlate with medium or long-term survival. There are, however, some drugs that treat specifically CSCs, as described in seminal works in oncology (Clement et al., 2007; Visvader and Lindeman, 2008; Hambardzumyan et al., 2008; Zhao et al., 2009; Wang et al., 2010; Singh and Settleman, 2010; Merchant and Matsui, 2010; Takebe et al., 2011, 2015, 2015; Yu et al., 2012; Pattabiraman and Weinberg, 2014; Skvortsov et al., 2015). Although some overlapping is admitted, for clarity, we classify these CSCs-specific therapies by two action mechanisms: (i) CSC differentiation and (ii) targeting CSC signaling pathways. The most studied drugs that act by these two mechanisms are presented in the following sections, together with biomaterial-based systems that have shown the capacity to enhance their activity in cancer models or at least improve their delivery profile.

2.1. Differentiation therapy

2.1.1. Retinoid derivatives

Since cancer stem cells take advantage of specific cell programs to boost their malignancy, the CSC pool can be depleted by inducing differentiation towards a mature phenotype (Fig. 3). The use of differentiation therapies is intrinsically linked with the discovery of CSCs in hematopoietic cancers, where the most