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Review article

Translational aspects in targeting the stromal tumour microenvironment: From bench to bedside

R. Bhome [a,b,*], H.A. Al Saihati [a], R.W. Goh [a,c], M.D. Bullock [a,b], J.N. Primrose [b], G.J. Thomas [a], A.E. Sayan [a], A.H. Mirnezami [a,b,*]

[a] Cancer Sciences, Faculty of Medicine, University of Southampton, Somers Cancer Research Building, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
[b] University Surgery, South Academic Block, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
[c] School of Medicine, University of Southampton, University Road, Southampton SO17 1BJ, UK

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ABSTRACT

Solid tumours comprise, not only malignant cells but also a variety of stromal cells and extracellular matrix proteins. These components interact via an array of signalling pathways to create an adaptable network that may act to promote or suppress cancer progression. To date, the majority of anti-tumour chemotherapeutic agents have principally sought to target the cancer cell. Consequently, resistance develops because of clonal evolution, as a result of selection pressure during tumour expansion. The concept of activating or inhibiting other cell types within the tumour microenvironment is relatively novel and has the advantage of targeting cells which are genetically stable and less likely to develop resistance. This review outlines key players in the stromal tumour microenvironment and discusses potential targeting strategies that may offer therapeutic benefit.

Focal points:

- Benchside
  - The tumour stroma consists of mesenchymal, immune and vascular cells housed in an extracellular matrix. Stromal cells and extracellular matrix proteins represent genetically stable targets which can be exploited in cancer treatment. Numerous *in vitro* and animal studies support the concept of stromal-directed treatment.
- Bedside
  - Several therapeutic strategies have been developed or repurposed to target the stroma. The anti-angiogenic agent bevacizumab was one of the first specific stromal-targeting agents to be licensed for cancer treatment over a decade ago. More recently, immune modulation of the stroma has become a hugely successful strategy, with novel drugs such as checkpoint inhibitors set to re-volutionise cancer treatment.
- Governments
  - Funding bodies should continue to acknowledge the pivotal role that the stroma plays in cancer progression, in parallel with cancer cell itself. Undoubtedly, the most successful treatment regimens of the future will address both the “seed” and the “soil”.

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Abbreviations: TME, tumour microenvironment; MSC, mesenchymal stem cell; NK, natural killer; APC, antigen presenting cell; EC, endothelial cell; ECM, extracellular matrix; CAF, cancer-associated fibroblast; EMT, epithelial–mesenchymal transition; αSMA, alpha smooth muscle actin; LOX, lysyl oxidase; LOX-L, lysyl oxidase-like protein; BAPN, beta-aminopropionitrile; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; Th, helper T cell; Treg, regulatory T cell; TIL, tumour infiltrating lymphocyte; IFN, interferon; CTLA-4, cytotoxic T lymphocyte-associated protein-4; PD-1, programmed cell death protein-1; PD-L1, PD-1 ligand; NSCLC, non-small cell lung cancer; TAM, tumour associated macrophage; CSFR-1, colony stimulating factor receptor-1; PBMC, peripheral blood mononuclear cell; PDGF-β, platelet-derived growth factor-β; VDA, vascular damaging agent; CA4P, combretastatin A4 phosphate; HIF, hypoxia inducible factors; MMP, matrix metalloprotease

* Corresponding author at: Cancer Sciences, Faculty of Medicine, University of Southampton, Somers Cancer Research Building, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK.

E-mail addresses: r.bhome@soton.ac.uk (R. Bhome), haas1e11@soton.ac.uk (H.A. Al Saihati), rg12g10@soton.ac.uk (R.W. Goh), m.bullock@soton.ac.uk (M.D. Bullock), j.n.primrose@soton.ac.uk (J.N. Primrose), g.j.thomas@soton.ac.uk (G.J. Thomas), a.e.sayan@soton.ac.uk (A.E. Sayan), a.h.mirnezami@soton.ac.uk (A.H. Mirnezami).

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Contents

1. Introduction

Paget [1] first highlighted the importance of the tumour microenvironment (TME) over a century ago when he described his 'seed and soil' hypothesis. The concept that cancer cells (seeds) require a specific TME (soil) in order to establish or propagate a tumour is just as valid today and is indeed recognised as the first key milestone, in a series of articles by the journal Nature, highlighting the most influential discoveries in the field of cancer [2].

The microenvironment of solid tumours consists of a diverse network of cellular and acellular components [3]. A histological categorisation is to divide these elements into cancer and stromal compartments, with the stromal compartment further divided into a cellular component and the extracellular matrix. Cancer cells and cancer stem cells [4] form the cancer compartment. Stromal cells can be sub-classified into: mesenchymal (fibroblasts and mesenchymal stem cells (MSCs)), immune (T cells, macrophages, natural killer (NK) cells and antigen presenting cells (APCs)) and vascular (endothelial cells (ECs) and pericytes). Of these, vascular cells are permanently located in the TME, immune cells are transient, and mesenchymal cells may be permanent or transient [5]. The extracellular matrix (ECM) is a biologically active three-dimensional scaffold for cancer and stromal cells, comprising proteoglycans and fibrous molecules [6]. By its cellular interactions it permits tumour expansion, invasion and dissemination [7]. Fig. 1 summarises key components of the TME.

Malignant cells accrue mutations which can allow escape from regulatory mechanisms [8]. We can think of these cells as genetically unstable and highly plastic [9]. One of the effects of chemotherapy is to apply selection pressure to these heterogeneous cells, allowing expansion of resistant clones. In contrast, stromal cells are not mutated [10], turnover more slowly [11] and are therefore genetically more stable. These cells are less likely to develop chemotherapeutic drug resistance. The stroma is therefore an appealing target for novel cancer therapies.

Cancer is characterised by a misregulation of genes such as those encoding oncogenic, tumour suppressor and DNA repair proteins [12]. As a result, there are certain key signalling pathways which are commonly altered across many cancer types, underpinning the hallmarks of cancer [13]. Notably, microRNAs (miRs) are master regulators of gene expression and signalling pathways, with an estimated one-third of all genes under miR control [14]. As a consequence, there has been much interest in modulating oncogenic and tumour-suppressing miRs for therapeutic benefit.

In this review, we outline existing and potential targets for novel chemotherapeutic agents in the stroma with an introduction to miR targeting strategies.

2. The mesenchymal stroma

Fibroblasts are mesenchymal cells which secrete ECM components [15]. Cancer-associated fibroblasts (CAFs) are variably defined in the literature. It is best to consider them as any fibroblast adjacent to the tumour, rather than by their expression profile or cell of origin [16]. CAFs may originate from resident fibroblasts [17], bone marrow-derived MSCs [18] and epithelial cells (including cancer cells and endothelial cells) through the process of epithelial-mesenchymal transition (EMT; [19],[20],[21]). Spindle shaped myofibroblasts expressing alpha smooth muscle actin (αSMA) and vimentin, with typical ultrastructural appearances [22] are a subpopulation of CAFs which are associated with tumorigenesis and cancer progression [23,24] but it is important to note that not all CAFs are myofibroblasts. Nonetheless, αSMA positivity is most commonly used to denote the 'activated' CAF phenotype [25] and TGF-β is widely accepted as the main cancer cell-secreted factor which activates CAFs [26,17].

CAFs, like other fibroblasts, regulate the integrity of the ECM through their secretory function. In normal physiology, myofibroblasts are capable of closing a wound. Cancer is considered to be a 'wound that does not heal' [27] and in this context, myofibroblastic CAFs are thought to remain persistently activated [28]. Activated CAFs have been shown to alter the morphology of epithelial cells [29] and drive tumorigenesis [30].

CAFs express the enzyme lysyl oxidase (LOX) and lysyl oxidase-like proteins (LOX-L) 1–4 which allow crosslinking of ECM substrates such as collagen with elastin. This stiffens the ECM and stimulates integrin-dependent mechanotransduction pathways which promote invasion [31]. LOX/LOX-L expression correlates with worse prognosis in head and neck, lung, ovarian and breast cancers [32]. LOX inhibitors such as beta-aminopropionitrile (BAPN) have been shown to reduce breast cancer cell motility *in vitro* [33]. In cervical cancer models, the same drug was shown to reduce hypoxia-induced EMT, invasion and migration [34]. Bondareva et al. [35] showed that BAPN reduced metastasis of MDA-231 breast cancer cells only if given at the same time or prior to systemic injection of tumour cells. This suggests that LOX inhibition is important in preventing extravasation of tumour cells from the circulation. Nonetheless, this class of drug has not been carried forward into human trials as yet. Inevitably, with collagen

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