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New approaches to targeting the bone marrow microenvironment in multiple myeloma

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Multiple myeloma is a tumour with a remarkably destructive effect on its host organ, the bone marrow. Through expression or secretion of adhesion molecules, growth factors, exosomes, miRNAs, chemokines and inhibitors, the tumour substantially alters its microenvironment, promoting both tumour survival and osteolytic bone disease. This altered niche is ideally suited to the sustenance of its proliferating compartment and the protection and immune evasion of its dormant, drug resistant fraction. The possibility of deepening response to a drug treatment regime, maintaining remission or even eradicating resistant stem cells by pharmacologically manipulating the tumour's interactions with this niche is a major driving force in current myeloma research. Examples of promising therapies include CXCR4 antagonists, RANKL inhibitors, HIF1α pathway inhibitors, and inhibitors of Notch, Wnt and TGFβ family pathways.

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Introduction

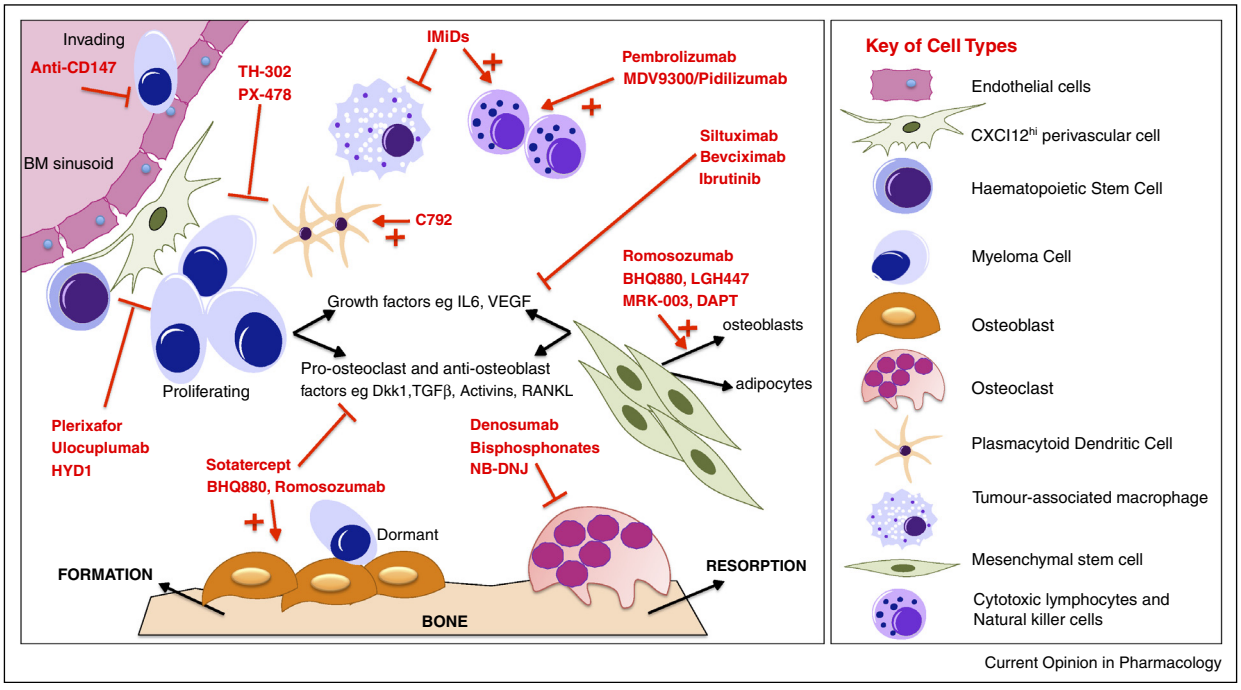
As the cradle of the haematopoietic system, the bone marrow (BM) has evolved to support the growth of rapidly dividing cells. It is a mixed but highly spatially organized tissue comprising bone and fibrous extracellular matrices, mesenchymal stem cells, fibroblasts, cells committed to osteoblast or adipocyte fate, mature osteoblasts, adipocytes and osteocytes, as well as dense vascularity with adapted endothelial cells and innervation, cells of haematopoietic origin including macrophages, osteoclasts, and T cells. It is therefore unsurprising that a tumour cell with a capacity for clonal renewal would have a survival advantage upon arrival in such a niche. To effectively hijack such an environment to maximum capacity however, mere proliferation is insufficient; the tumour must also suppress the features that keep normal checks on the proliferation and differentiation of the haematopoietic system usually nursed here, the cells whose role it is to control growth, maintain quiescence or exert immune-mediated control. Therefore tumours destroy where haematopoiesis does not; bone matrix is lysed or laid down inefficiently; normal haematopoietic development is suppressed and immune mediation disrupted. Abnormal angiogenesis disrupts oxygen tension gradients and stromal components are harnessed to proliferate, apoptose, or alter their expression patterns. We examine here the example of multiple myeloma, because its irreversible alteration in function of microenvironment components is the root of many of its well-studied pathological features. The lytic bone disease and hypercalcaemia are caused by disruption of bone homeostasis; the anaemia, fatigue and weight loss are due to high levels of inflammatory cytokines and haematopoietic suppression; recurrent infections are due to immunosuppression. All result from a manipulated bone marrow niche.

A tumour that metastasizes through bone has usually been rendered incurable. This niche affords drug resistance [1] and protection for stem cell quiescence, whilst still encouraging outgrowth of the bulk. The immense pharmacological potential held in tumour–niche interactions and signalling networks lies in causing their disruption to a degree where a survival advantage is no longer afforded; thereby exposing protected dormant cells, restoring chemosensitivity and precipitating immune-mediated destruction, whilst allowing functional haematopoiesis to continue (Figure 1).

Homing/metastasizing to the niche

Maturing B cells accurately home to the bone marrow, there completing their maturation to plasma cells, to reside long term. This residency, as that of haematopoetic stem cells (HSCs) [2,3,4], is dependent on CXCL12 signalling from specialized stromal cells [5]. Plasma cells without the CXCL12 receptor CXCR4 cannot home [6], and continue to require contact with marrow CXCL12^{hi} reticular cells for survival, although other cell types are also required [7]. In keeping with their cell of origin, myeloma cells express high levels of CXCR4 and require stromal expression of CXCL12 for homing and niche maintenance [8]. There is accumulating evidence for

Figure 1



The cellular interactions of the bone marrow niche and myeloma, showing currently developed drugs and their target cellular interactions. Drugs labelled in red with indication of site of action.

the potential of targeting CXCR4. A CXCR4 antagonist plerixafor (AMD3100), clinically used for HSC mobilization, has been proposed as a means of inducing chemosensitivity in myeloma [9], and is under clinical trial (NCT00903968). In addition, the CXCR4-neutralising antibody ulocuplumab has been shown to reduce disease dissemination in mice [10] and has activity in Phase 1b trials [11]. Recent evidence suggests however that there may be a subtle difference in the precise niche of the dormant (possibly the 'cancer-initiating') myeloma fraction when compared to that of pluripotent haematopoietic stem cells (HSCs) or healthy plasma cells, with non-dividing myeloma cells being located on the endosteal surface, in contact with mature osteoblasts which have relatively lower CXCL12 expression [12,13••]. It could be argued that either pharmacological mobilization (to enhance chemosensitivity) or protection (to maintain dormancy) of these quiescent cells could have clinical benefit. A further host of adhesion molecules mediate the binding of myeloma cells to the niche, including VCAM-1, VLA-4 and CD44. Another drug candidate for mobilization–sensitization is the CD44-blocking small molecule HYD1, which has shown efficacy in overcoming chemoresistance *in vitro* and reducing disease burden *in vivo* [14]. The interaction between bone marrow endothelial cell eCyPA and CD147 on myeloma cells has also recently been proposed as a key homing mechanism in myeloma, with an antibody to CD147 recently shown in murine models to abrogate homing, and have anti-myeloma activity [15••].

Niche benefits to tumour

The importance of bone marrow stromal cells (BMSCs) in disease pathogenesis is exemplified by recent studies demonstrating their ability to modify the bone marrow microenvironment to render it permissive for myeloma development [16]. BMSCs promote growth in adherent myeloma cells through expression or secretion of adhesion molecules, chemokines, growth factors, exosomes and miRNAs, which has been extensively reviewed elsewhere [17]. This results in enhanced proliferation and reduced apoptosis of tumour. Growth factor-blockade targets include IL6, although neutralizing antibody siltuximab has recently not improved outcome in a combination therapy trial [18]. A trial in smouldering myeloma is ongoing (NCT01484275). Anti-VEGF bevacizumab has reached phase 2 trials [19], but also showed no benefit. Bone marrow adipocytes and secreted adipokines may also support myeloma growth, based on the observation that a high-fat diet created a myeloma-permissive microenvironment reminiscent of MGUS [20]. This is supported by clinical data showing obesity is linked to a higher incidence of myeloma.

The bone marrow has long been presumed to be hypoxic, due to low perfusion and activation of hypoxia pathways,