The bone-marrow niche in MDS and MGUS: implications for AML and MM

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Abstract | Several haematological malignancies, including multiple myeloma (MM) and acute myeloid leukaemia (AML), have well-defined precursor states that precede the development of overt cancer. MM is almost always preceded by monoclonal gammopathy of undetermined significance (MGUS), and at least a quarter of all patients with myelodysplastic syndromes (MDS) have disease that evolves into AML. In turn, MDS are frequently anteceded by clonal haematopoiesis of indeterminate potential (CHIP). The acquisition of additional genetic and epigenetic alterations over time clearly influences the increasingly unstable and aggressive behaviour of neoplastic haematopoietic clones; however, perturbations in the bone-marrow microenvironment are increasingly recognized to have key roles in initiating and supporting oncogenesis. In this Review, we focus on the concept that the haematopoietic neoplasia–microenvironment relationship is an intimate rapport between two partners, provide an overview of the evidence supporting a role for the bone-marrow niche in promoting neoplasia, and discuss the potential for niche-specific therapeutic targets.

Myelodysplastic syndromes (MDS) encompass a group of clonal haematological disorders characterized by ineffective haematopoiesis that lead to various cytopenias and the presence of blood cells with an abnormal (dysplastic) morphology[1]. Cytogenetic abnormalities can be detected using metaphase karyotyping in about 50% of patients with MDS, whereas recurrent somatic mutations, across more than 40 different genes, are detectable in >90% of patients[1,2]. Overall, about a quarter of patients with MDS eventually develop acute myeloid leukaemia (AML) — 10% of those with the lowest-risk forms of MDS and >50% for those with the highest-risk forms, with risk defined by number and degree of cytopenias, karyotype, and proportion of bone-marrow blasts at diagnosis[3].

A clonal haematopoiesis phenotype associated with somatic mutations — but not with the criteria defining haematological malignancy — has, in turn, been recognized as an antecedent of MDS or overt haematological cancer and is termed 'clonal haematopoiesis of indeterminate potential' (CHIP)[4]. When CHIP is defined by a variant allele frequency of the associated somatic mutation of ≥2%, patients with CHIP develop a haematological malignancy, most commonly MDS or AML (annual incidence: approximately 0.5–1% of patients)[5]. Early stage, low-risk MDS is characterized by excessive intramedullary apoptosis of haematopoietic cells and accompanying biochemical changes, resulting in bone-marrow failure[6]. Over time, additional somatic genetic events are commonly detected as MDS progresses to a higher-risk stage, in which immature blast cells begin to accumulate in the bone marrow and the rate of intramedullary apoptosis decreases[7]. Further clonal expansion of haematopoietic cells and acquisition of additional defects that impair differentiation results in AML, which is currently defined — somewhat arbitrarily — by a myeloblast frequency of ≥20% in the bone marrow or blood, or by one of a small number of karyotypes that define AML regardless of blast proportion, such as t(8;21), inv(16), or t(15;17)[8].

Whereas less than one-third of AML cases are preceded by a diagnosed MDS stage[9–11], overt symptomatic multiple myeloma (MM) almost always results from progression of MGUS (which is not always clinically diagnosed), often via an intermediate stage of smouldering MM (SMM)[12,13]. This sequential progression supports the idea that clonal evolution of cancer cells occurs between the original stages of neoplasia and the time of symptomatic disease[14–16]; however, many of the chromosomal alterations and single-nucleotide variants present in MM tumour specimens are also detectable at lower frequencies in MGUS and SMM samples[17]. Thus, progression to MM is probably attributable to the expansion of subclones that arise in the early stages of MGUS or SMM[17].

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Key points

- Multiple myeloma is almost always preceded by monoclonal gammopathy of undetermined significance, and at least one-quarter of all patients with myelodysplastic syndromes (MDS) have disease that evolves into acute myeloid leukaemia; in turn, MDS are frequently anteceded by clonal haematopoiesis of indeterminate potential
- The bone-marrow microenvironment has been recognized to be a vibrant and complex living tissue that can aid and abet neoplastic disease processes
- Neoplastic clones can transform the local bone-marrow microenvironment to favour their own growth at the expense of nonmalignant haematopoietic cells
- An intricate and dynamic relationship between stem cell 'seeds' and the niche 'soil' helps to determine whether healthy haematopoiesis or an overgrowth of haematological malignancies occurs within the bone marrow
- Targeting microenvironment-specific alterations might not only prevent disease progression from precursor states but also enhance the effectiveness of available therapies for the overt malignancies once progression has occurred

For many years, the bone-marrow microenvironment was considered — if it was considered at all — to be little more than an inert scaffold, providing structure for the much more interesting haematopoietic stem and progenitor cell (HSPC) activity contained within. In the past decade, however, the bone-marrow microenvironment has been recognized to be a vibrant and complex living tissue that, in addition to important homeostatic roles in haematopoiesis, can aid and abet neoplastic disease processes[18–21]. Moreover, evidence indicates that neoplastic clones can transform the local bone-marrow microenvironment to favour their own growth at the expense of nonmalignant haematopoietic cells[18–21]. Hence, an intricate and dynamic relationship between haematopoietic stem cell 'seeds' and the niche 'soil' helps to determine whether the end product of haematopoiesis will be a healthy, physiologically useful crop of mature blood cells or instead an overgrowth of developmentally stunted, immature, dysfunctional dysplastic blasts — akin to haematological 'weeds' (REF. 22).

The risk of progression from MGUS or SMM to MM, and CHIP to MDS to AML, is heterogeneous despite the fact that the precursor states of both MM and AML are associated with mutations conferring a clonal advantage. Therefore, the probability of transformation might be dependent on the surrounding microenvironmental cells that are either permissive of or inhibit further clonal expansion[23–33]. In the context of MGUS, one of the most recent studies that provides proof of principle that the tumour microenvironment regulates disease progression involved the development of a genetically humanized mouse model that permitted the progressive growth of bone-marrow mononuclear cells from patients with MGUS and asymptomatic myeloma *in vivo*, contrary to findings in control mice[34]. This observation suggested that the clinical stability of these lesions might be reflect, in part, the effects of growth controls extrinsic to tumour cells[34]. Similarly, investigators have made many provocative observations, primarily using animal models, concerning the abnormal behaviour of the cellular components of the bone-marrow niche and disordered signalling pathways in MDS and AML[35,36]. Herein, we use the examples of MM and AML, two clonal diseases with well-defined precursor stages, to discuss the known and diverse roles of the bone-marrow microenvironment in supporting the progression of haematological malignancies. This comparative approach could aid in the discovery of potential niche-based targets for therapeutic intervention.

Normal composition of the marrow niche

The bone-marrow niche is composed of many cellular and noncellular components (that is, the extracellular matrix and soluble factors) that collectively participate in haematopoiesis[37–39]. The cellular compartment includes endothelial cells, osteolineage cells, osteoclasts, osteocytes, adipocytes, sympathetic neurons, nonmyelinating Schwann cells, mesenchymal stem cells (MSCs; also known as mesenchymal stem and progenitor cells (MSPCs)), C-X-C motif chemokine 12 (CXCL12)-abundant reticular cells, macrophages, and megakaryocytes[39]. Osteolineage cells passage through distinct developmental stages, including primitive MSPCs, osteoprogenitors, bone-forming osteoblasts, periosteal cells (bone-lining cells that are situated adjacent to osteoids comprising new, unmineralized bone tissue), and terminally differentiated osteocytes located within the lacunae of fully formed, calcified bone. Collectively, these diverse cell types orchestrate the localization, proliferation, and differentiation of nonmalignant HSPCs (FIG. 1).

Investigators have engaged in a lively debate about the possible distinct roles of different bone-marrow niches, such as the osteoblastic–endosteal versus vascular niches, in various aspects of homeostatic haematopoiesis[37–39]. Indeed, the self-renewal and differentiation of HSPCs are regulated by the distinct microenvironmental factors and conditions within the osteoblastic–endosteal and the vascular niche, respectively. The vascular niche refers to regions within the bone marrow that contain the largest numbers of blood vessels (predominantly consisting of endothelial cells and pericytes), which creates a unique microenvironment that directly influences the behaviour of HSPCs[37–39]. Specifically, the vascular niche is the site of HSPC mobilization, proliferation, and differentiation. Thus, this niche is the origin of particular blood cell lineages generated by the expansion of a specific set of $CD48^-/CD150^+$ HSPCs[37–39]. By contrast, the osteoblastic–endosteal niche, localized at the inner surface of the bone cavity, is the preferential site of HSPC homing for long-term retention in a quiescent state, with cells also undergoing self-renewal[37–39]. Together, these two niches act to maintain haematopoietic homeostasis. A description of the roles of each type of microenvironmental component within these niches in the regulation of haematopoiesis is beyond the scope of this Review, and several publications have described the current understanding of this process in more detail[37–39].

Influence of the tumour microenvironment

The results of several studies have shown that stromal cells, including fibroblasts, are critical for the establishment of a premetastatic niche that supports

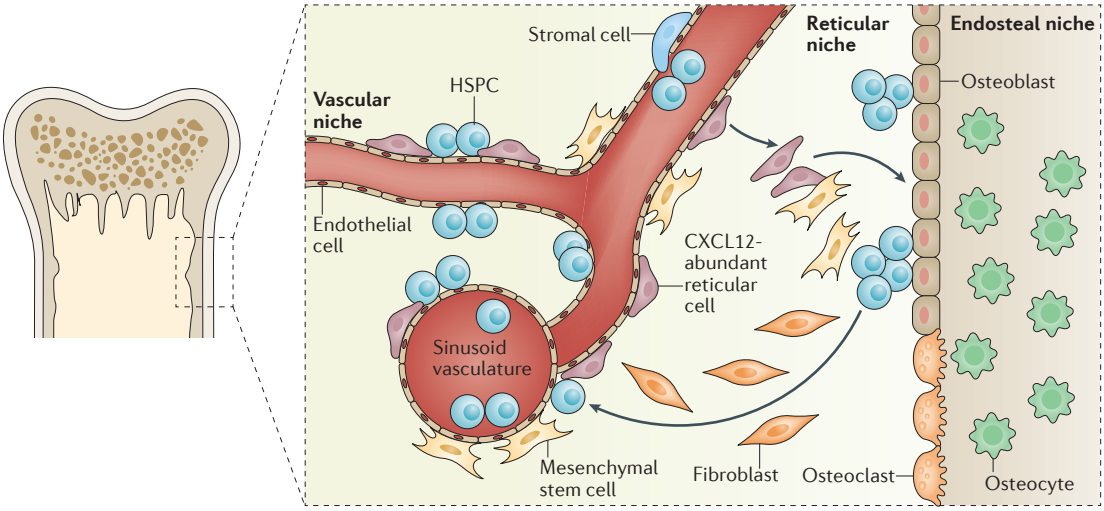

Figure 1 | **Stem cell niches in normal bone marrow.** The self-renewal and quiescence of the haematopoietic stem and progenitor cells (HSPCs) is maintained by the bone-marrow microenvironment, which is composed of multiple different niches. The vascular niche fosters the maintenance of HSPCs through self-renewal and their expansion to form the various haematopoietic cell lineages, the reticular niche regulates the production of stem cell factors, and the endosteal niche regulates the size of the HSPC pool by promoting the quiescence and long-term storage of HSPCs in the bone. Dysfunction within these microenvironmental niches can contribute to abnormal haematopoiesis and neoplasia. CXCL12, CXC-chemokine ligand 12.

the growth and dissemination of clonal neoplastic cells[40] (FIG. 2; TABLE 1). These microenvironmental cells are also essential for initiation of tumorigenesis and the selection of the dominant clones that lead to metastasis[41,42]. Indeed, changes in the tissue microenvironment can precede the initiation of genetic events associated with neoplasia by creating a 'pro-malignant' state characterized by disruption of factors regulating quiescence or increases in proliferative signalling[43,44]. This hypothesis has been validated in several mouse models, including those with interruption of TGFβ signalling in tissue fibroblasts[43] or deletion of the tumour-suppressor gene *Rb1* in stromal cells of the haematopoietic system[44], leading to epithelial malignancy and the expansion of myeloid progenitor cells, respectively. Additional examples of microenvironmental contributions to neoplasia include a role for mast cells in the development of *Nf1*-mutant neurofibromas and mesenchymal-cell-dependent alterations of epithelial tumour growth kinetics[45]. In one striking *in vivo* model of haematological malignancy, deletion of *Dicer1* (encoding an endoribonuclease with a central role in short-RNA-mediated post-transcriptional silencing of gene expression) in mouse osteoprogenitor cells reduced the integrity of haematopoiesis, leading to myelodysplasia, which subsequently evolved into AML despite the fact that *Dicer1* remained intact in the neoplastic haematopoietic cell clones[46]. In another compelling mouse model, constitutive activation of β-catenin specifically in osteoblasts resulted in forkhead box protein O1 (FOXO1)-dependent expression of the Notch ligand jagged 1, in turn leading to increased Notch 1 signalling in HSPCs, altered myeloid and lymphoid progenitor differentiation, and the development of MDS and AML with clonal somatic mutations, including loss of chromosome 5 (the mouse orthologue of human chromosome 7 that is frequently lost in clonal cells from patients with MDS or AML)[47,48].

The roles of bone-marrow stromal cells

Mesenchymal stem and progenitor cells. In the context of MM, multipotent MSCs or MSPCs present in the bone-marrow niche have been recognized for many years as critical regulators of the adhesion, migration, survival, and proliferation of myeloma cells through direct cell–cell interactions or via secretion of growth or anti-apoptotic factors, such as IL-6, IGF1, and CXCL12 (REFS 49–52) (FIG. 2; TABLE 1). Moreover, some results indicate that MM-MSPCs are inherently abnormal and remain dysfunctional after being removed from the influence of myeloma cells[53]. For example, many patients with MM have bone lesions or pathological fractures that never heal because of osteoblast malfunction and disrupted osteogenesis, even after successful eradication of the neoplastic cells, suggesting that MM-MSPCs have permanent defects[16].

In addition, MSPCs from patients with MM have been shown to secrete exosomes that can be taken up by MM cells[23]. In a mouse model, these MM-derived stromal-cell exosomes increased tumour growth and progression, compared with that seen in the absence of any purified exosomes, through the transfer of microRNAs (miRNAs) and specific proteins present in the exosomes[23]. By contrast, exosomes derived from non-malignant stromal cells from individuals without MM inhibited tumour growth by being nonpermissive for clonal proliferation[23]. Accordingly, exosomes released by MM-MSPCs had lower levels of the tumour-suppressor miRNAs miR-15a and miR-16-1 than those derived from

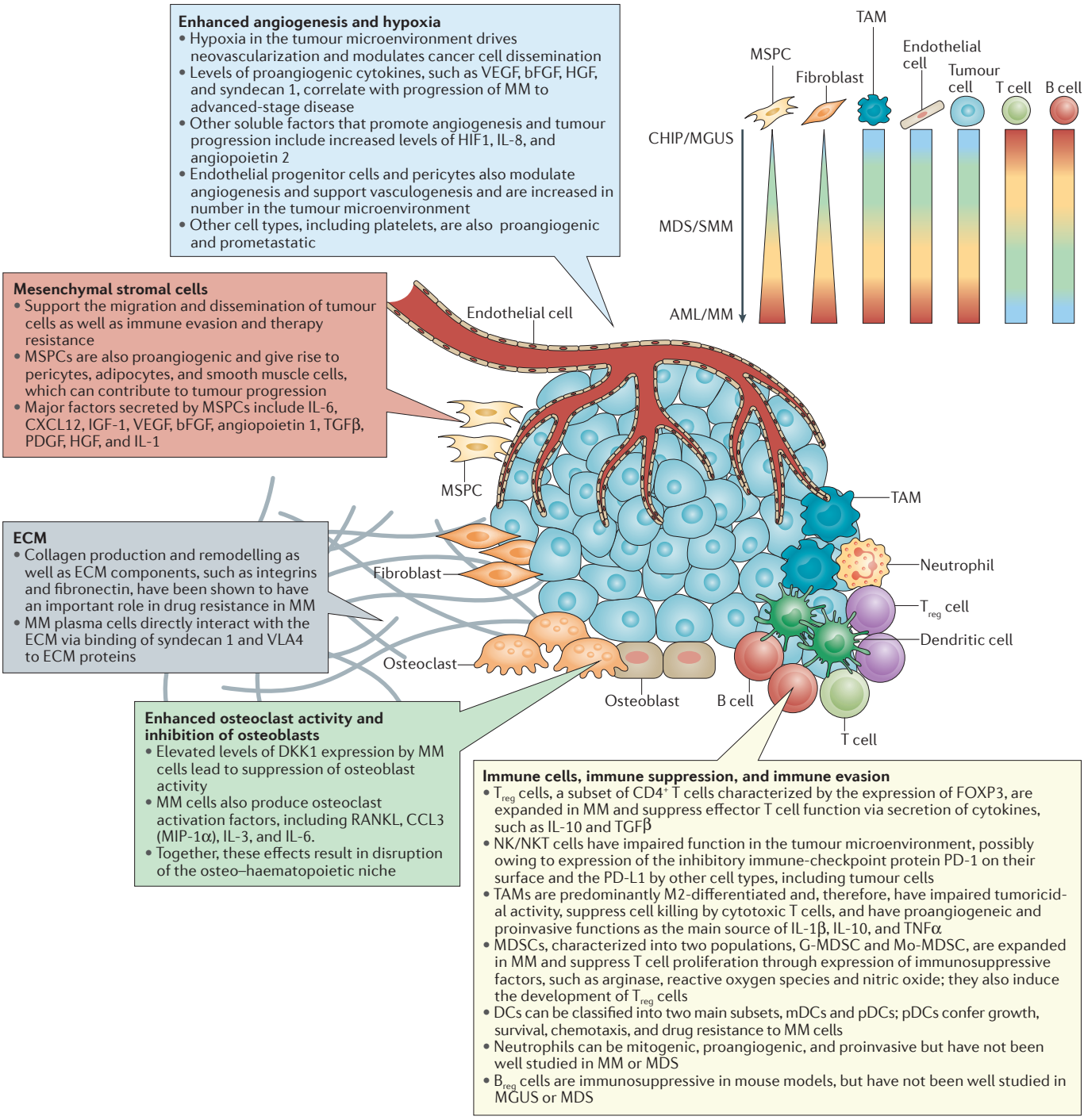

Figure 2 | **The components of the microenvironment in monoclonal gammopathy of undetermined significance and myelodysplastic syndrome.** The bone-marrow microenvironment acts as an ecosystem for disease progression from monoclonal gammopathy of undetermined significance (MGUS) or clonal haematopoiesis of indeterminate potential (CHIP) to smouldering multiple myeloma (SMM) and overt multiple myeloma (MM) or myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), respectively. The different components of the bone-marrow microenvironment are shown in this schema. Over the course of disease progression, mesenchymal stem and progenitor cells (MSPCs) and fibroblasts acquire pro-tumorigenic functions. Tumour-associated macrophages (TAMs) also support tumour growth, as well as the invasion of nonmalignant tissue and angiogenesis, leading to increased levels of neovascularization and enhanced tumour progression and dissemination. In parallel, as the tumour grows, immunosuppressive cells such as $CD4^+CD25^+$ regulatory T (T_{reg}) cells infiltrate the bone-marrow microenvironment and disrupt immune-surveillance mechanisms, leading to a decreased abundance of T cells and B cells, thus enabling tumour cells to evade recognition and elimination by the immune system. B_{reg}, regulatory B cell; CCL3, CC-chemokine ligand 3 (MIP1α); CXCL12, CXC-chemokine ligand 12; DC, dendritic cell; DKK1, Dickkopf-related protein 1; ECM, extracellular matrix; FOXP3, forkhead box protein P3; G-MDSC, granulocytic MDSC; MDSC, myeloid-derived suppressor cell; Mo-MDSC, monocytic MDSC; NK, natural killer; NKT, NK T cell; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; RANKL, receptor activator of nuclear factor-κB ligand.

Table 1 | **The roles of the microenvironment components in myelodysplastic syndrome and multiple myeloma**

Cell type	MM	MDS and/or leukaemia	Refs
Endothelial cells	• Increased vasculogenesis and neoangiogenesis • Increased numbers of endothelial progenitor cells • Chronic hypoxia induces angiogenesis • VEGF and HGF expression increases angiogenesis • IL-17, syndecan 1, and osteopontin expression promotes neoangiogenesis	VEGF and VEGFR are aberrantly expressed in MDS; VEGF and/or VEGFR expression has been associated with reduced survival, increased angiogenesis, and the presence of a specific aberrant morphological bone-marrow phenotype called ALIP	183–185
Osteoclasts	• Enhanced proliferation, differentiation, and activity of osteoclasts • Increased RANKL and decreased osteoprotegerin favour osteoclast activity • IL-6, IL-3, IL-17, and CCL3 enhance osteoclast activity	• Osteoclasts have a critical role in the initial steps of the osteo–haematopoietic niche formation • The osteoclast progenitors, monocytes, are responsible for the protection of the HSPC pool from exhaustion, both in steady-state conditions and during stress	19
Osteoblasts	• Decreased differentiation and activity of osteoblasts have been observed in MM • Wnt proteins activate and DKK1 inhibits osteoblast differentiation and activity in MM • HGF and TGFβ are secreted by MM cells and regulate osteoblast activity	• Altered expression of the matrix glycoproteins thrombospondin 2 and SPARC (osteonectin) as well as the integrin periostin (osteoblast-specific factor 2) in MDS and leukaemia • Constitutive activation of β-catenin enhances the development of MDS • Mutation of the endoribonuclease Dicer in mouse models enhances the development of MDS • APC haploinsufficient mice ($Apc^{del/+}$) develop MDS, which can be prevented with loss of one copy of *Ctnnb1* (encoding β-catenin) or treatment with the anthelmintic pyridium	46,186
MSPCs, fibroblasts, stromal cells, and/or adipocytes	• MSPCs enhance the adhesion, proliferation, and drug resistance of MM cells • Multiple pathways are implicated in these effects of MSPCs, including chemokine signalling, for example, via the CXCL12–CXCR4 axis; adhesion molecules, such as VCAM1 and ICAM1; cytokines, including IGF1, IL-6, and VEGF; extracellular matrix proteins, such as fibronectin; exosomes; and microRNAs	• MSPCs enhance the adhesion, proliferation, and drug resistance of MDS and leukaemia cells • Altered expression of various genes in MSPCs leads to the release of pro-inflammatory cytokines, including TNFα, IL-6, and TGFβ • CXCL12-abundant reticular cells localized to the perivascular area of bone marrow seem to support the survival and growth of MDS and leukaemia HSPCs and contribute to therapy resistance	187
Macrophages	• Differentiate into osteoclasts • Increased levels of IL-6 and IL-1β produced by macrophages lead to proliferation of MM cells	• Loss of macrophages results in the egression of HSPCs to the bloodstream. • Macrophages also indirectly support the expansion of HSPCs through modulation of the CXCL12–CXCR4 axis • Macrophages stimulate the proliferation of osteoblasts and bone mineralization and enhance the bone-anabolic effect of parathyroid hormone	19
MDSCs	• The abundance of MDSCs is increased in the bone marrow, contributing to immunosuppression • Dendritic cells and plasmacytoid dendritic cells have critical roles in MM progression	Primary bone-marrow expansion of MDSCs, driven by activation of the S100A9/CD33 pathway, perturbs haematopoiesis and contributes to the development of MDS	101, 188–190
T cells and B cells	• Increase in the numbers of T_{reg} cells, anergic exhausted NK-T cells and cytotoxic T cells, and T_H17 cells • Changes contribute to immunological escape of neoplastic cells	• Accompanying increase in T-cell clonality might contribute to cytopenias • Downregulation of B-cell receptor signalling has been observed in some cases	191,192
Extracellular matrix	• Remodelling of bone-marrow extracellular matrix is observed during disease progression • Mediated by chemokines and cytokines, such as IL-6, IGF1, CXCL12, and VEGF, and fibronectin as well as exosomes and microRNAs released by tumour cells	Remodelling of extracellular matrix occurs during disease progression, including fibroblast activation and development of bone fibrosis in some patients	64

ALIP, abnormal or atypical localization of immature precursors; APC, adenomatous polyposis coli; CCL3, CC-chemokine ligand 3; CXCL12, CXC-chemokine ligand 12; CXCR4, CXC-chemokine receptor 4; DKK1, DKK1, Dickkopf-related protein 1; HSPC, haematopoietic stem and progenitor cell; ICAM1, intercellular adhesion molecule 1; MDS, myelodysplastic syndrome; MDSC, myeloid-derived suppressor cell; MM, multiple myeloma; MSPC, mesenchymal stem and progenitor cell; NK-T natural killer T cell; RANKL, receptor activator of nuclear factor-κB; TNFα, tumour necrosis factor α; T_{reg}, regulatory T cells; VCAM1, vascular cell adhesion molecule 1; VEGFR, VEGF receptor.

a 'normal donor' (ND)-MSPCs, and exosomes isolated from MSPCs transfected with pre-miR-15a inhibited the growth of MM cells *in vitro*[23]. This permissive microenvironment, together with the presence of protein activators of MM cells, such as IL-6, CC-chemokine ligand 2 (CCL2), and fibronectin, on MM-MSPC-derived exosomes might explain the increased tumour growth and dissemination observed in the animal models[23]. Of note, Manier *et al.*[54] reported that the levels of circulating exosomal miRNAs, specifically let-7b and miR-18a, are negatively associated with prognosis in patients with MM.

Similarly, several observations relating to MSPCs in primary samples from patients with MDS, such as altered expression of adhesion proteins and/or intrinsic growth deficiency, indicate that these cells have important

roles in sustaining the MDS phenotype[55–58] (TABLE 1). Interestingly, MSPCs isolated from patients with MDS can harbour clonal chromosomal alterations, with reported frequencies ranging from 16–55%[59,60]; these alterations include trisomy 12 or t(14;15) translocations, which are distinct from those commonly observed in leukaemic HSPCs[61]. In mouse models of paediatric MDS and leukaemia, transferring nonmalignant HSPCs to a matrix of MDS-MSPCs resulted in haematopoietic dysplasia, but the converse — ND-MSPCs and malignant HSPCs — did not result in an obvious disease phenotype[62]. More generally, in xenograft models, engraftment of human clonal MDS cells with stem-cell characteristics in immunodeficient mice is augmented by co-injection of MSPCs from patients with MDS, and expression of the cell-surface glycoprotein MUC18 (also known as melanoma cell adhesion molecule (MCAM) or CD146) on stromal cells is especially important for robust cell engraftment[63,64]. Overproduction of the microenvironmental factors N-cadherin, IGF-binding protein 2 (IGFBP2), VEGFA, and leukaemia inhibitory factor (LIF) have all been associated with the enhancement of MDS cell expansion by MDS-MSPCs. In addition, healthy MSPCs adopt MDS-derived MSPC-like molecular features when they are exposed to malignant MDS cells, indicating instructive remodelling of the microenvironment by neoplastic cells[63,64].

Gene-expression profiling studies have revealed a variety of additional abnormalities in MSPCs from patients with MM or MDS compared with those from individuals without these diseases (TABLE 1). With regard to MM, the results of two studies[65,66] have demonstrated that numerous genes are differentially expressed by human MM-MSPCs and ND-MSPCs, including *IL6, DKK1*, and *HOXB*. In one of these studies, whole-genome array comparative genomic hybridization analyses identified no chromosomal abnormalities in MM-MSPCs or MM osteoblasts[65]. By contrast, using the same type of assay, the other group detected genomic imbalances in MM-MSPCs that were absent in ND-MSPCs[66], similar to the findings of studies examining chromosomal differences in MDS-MSPCs and ND-MPSCs[59,60,67]. Gene-expression profiling of MDS-derived MSPCs and ND-MSPCs has revealed that the former cells have reduced expression of a distinct set of genes encoding the endonucleases Dicer and ribonuclease 3 (also known as Drosha), various microRNAs (including miR-155, miR-181a, and miR-222), and the ribosome maturation protein SBDS (which is involved in the congenital marrow-failure disorder Shwachman–Bodian–Diamond syndrome (SDS))[19,68,69]. Subsequently, using a mouse model of SDS and mesenchymal cells from patients with various pre-leukaemia syndromes, Zambetti *et al.*[69] identified a mesenchymal-niche-induced inflammatory signalling axis that results in genotoxic stress in HSPCs as a targetable determinant of disease outcome in human MDS.

Osteoblasts and osteoclasts. The final differentiation stages of MSPCs include bone-forming osteoblasts and osteocytes, which develop under the influence of hormonal stimuli, including parathyroid hormones, glucocorticoid hormones, and oestrogens, as well as paracrine stimuli, such as TGFβ and related bone morphogenetic proteins (BMPs). The canonical Wnt signalling pathway also has a key role in mediating osteoblastogenesis and drives expression of the transcription factor Runt-related transcription factor 2 (RUNX2), which is the master regulator of osteoblast differentiation[70,71].

Patients with MM have a pathological imbalance with depletion of osteoblasts in favour of proliferation and activation of bone-resorbing osteoclasts, which, in a vicious circle, creates an environment that further enhances neoplastic progression (FIG. 2). Indeed, the presence of bone lytic lesions is one of the hallmarks of MM owing to the imbalance in bone turnover resulting from activation of osteoclasts with concurrent suppression of osteoblast function[72] (TABLE 1). Functionally, MM cells cause downregulation of Wnt, BMP2, and RUNX2 expression, induction of apoptosis, suppression of proliferation, and inhibition of osteogenic differentiation in osteoprogenitors[72,73]. This suppression occurs through increased production of Wnt pathway inhibitors, including Dickkopf-related protein 1 (DKK1), secretion of antiosteoblastic factors such as TGFβ and HGF, and constitutive activation of Notch signalling[74,75]. Conversely, MM cells can stimulate osteoclast activity by disrupting the balance between expression of the pro-osteoclastogenic protein receptor activator of nuclear factor-κB ligand (RANKL; also known as tumour necrosis factor ligand superfamily member 11 (TNFSF11)) and the anti-osteoclastogenic RANKL-decoy receptor osteoprotegerin (also known as tumour necrosis factor receptor superfamily member 11B (TNFRSF11B)), leading to higher levels of RANKL in the bone marrow and, thus, increased osteoclastogenesis[72]. Other factors such as CXCR-chemokine receptor 3 (CXCR3), IL-6, IL-7, and IL-3 have also been shown to enhance osteoclast proliferation and activation in the context of MM[76].

In comparison with plasma-cell disorders, less is known about dysregulation of bone-marrow osteoblastic activity in the setting of myeloid neoplasia (TABLE 1). Osteoblasts in MDS and AML seem, however, to have an altered behaviour and increased expression of the matrix glycoprotein thrombospondin 2, the calcium-binding glycoprotein SPARC (also known as osteonectin), and the integrin periostin (also known as osteoblast-specific factor 2)[77,78]. Moreover, in mouse models, constitutive expression of β-catenin in osteoblasts induced myeloid leukaemia and chromosomal instability, which could be prevented by inhibiting Notch signalling[47,48]. In addition, mice with conditional *Cre*-mediated knockout of *Dicer1* in osteoprogenitor cells, but not mature osteoblasts, have a dysplasia phenotype associated with a risk of progression to leukaemia, providing strong evidence that disruption of the bone-marrow niche could alter the behaviour of HSPCs in a fashion similar to that reported in MM[46]. Notably, however, *DICER1* mutations have not been described in humans, and the relevance of this model to human MDS remains unclear.

Other stromal cells, cytokines, and chemokines. Similar to the altered gene-expression profiles observed in osteoblasts from patients with MDS, stromal fibroblasts and macrophages in the bone marrow of patients with MDS also have altered expression of various genes, including several encoding pro-inflammatory cytokines, such as tumour necrosis factor-α (TNFα), IL-6, IFNγ, and TGFβ[79–81]. Increased levels of these cytokines can also be detected in bone-marrow extracts and serum from patients with MDS compared with samples from individuals without this disease[79,81,82]; these cytokines might contribute to MDS-related anaemia via paracrine mechanisms overlapping with anaemia associated with chronic inflammation[83].

Similar to their contribution to MDS, stromal cells in MM also secrete several soluble cytokines and chemokines that have been implicated in disease progression, including VEGF, IL-6, IL-1β, and TNFα. Notably, IL-6 secreted by stromal cells promotes plasma-cell proliferation, and IGF1 and CXCL12 have also been implicated in tumour progression and dissemination of MM cells through activation of the PI3K–AKT pathway and MAPK and nuclear factor-κB (NF-κB) pathways, respectively[84–87]. Integrin expression in the microenvironment mediates the interactions between clonal myeloid cells and stromal components and might also have a role in chemoresistance. For example, in one preclinical model, interaction between vascular cell adhesion protein 1 and very late antigen 4 activated NF-κB in tumour cells and promoted chemoresistance[88].

The immune microenvironment

Evasion and suppression of the host immune system is an important step in the progression of tumours[89,90]. In the nonmalignant bone-marrow microenvironment, natural killer (NK) cells and cytotoxic T lymphocytes are capable of driving potent anticancer responses. However, the presence of established tumour cells that have evolved to evade the immune system instead fosters an immunosuppressive microenvironment in which these anticancer responses are blunted (FIG. 2; TABLE 1). Bone-marrow stromal cells in the tumour microenvironment are also subverted to exert suppressive and regulatory effects on both T lymphocytes and B lymphocytes[91]. These stromal cells primarily promote the activation of regulatory T (T_{reg}) cells and inhibit B-cell proliferation in a T cell-dependent manner[91,92]. Notwithstanding, stromal cells have been shown to regulate both innate and adaptive immune responses in a primarily cytokine-dependent manner through the secretion of TGFβ, IFNγ, prostaglandin E_2, IL-10, and TNFα[93,94].

Indeed, disease evolution from MGUS to SMM to MM is associated with an immunosuppressive milieu that fosters the immune escape of neoplastic cells and tumour growth[89,90]. This state is characterized by loss of effective antigen presentation, immune effector cell dysfunction, deletion of myeloma-specific T cells, and the increasing presence of immunosuppressive cell types, such as T_{reg} cells and myeloid-derived suppressor cells (MDSCs)[33]. The composition of the immune microenvironment in MM has not been fully elucidated[33,75]; however, some studies have revealed that T helper 17 (T_H17) cells are abundant in the bone marrow and suppress immune surveillance in MM[95,96]. Moreover, increasing numbers of functional T_{reg} cells in the peripheral blood of patients with MM directly correlate with a worse prognosis[97]. MM-associated $CD8^+$ T cells express high levels of programmed cell death protein 1 (PD-1), an inhibitory T-cell co-receptor that functions as an immune checkpoint), and contribute to immune tolerance[98]. Similarly, NK cells, dendritic cells, osteoclasts, and tumour-associated macrophages (TAMs) have been implicated in the pathogenesis of MM, although not specifically in the progression of MGUS to MM[99–102].

Perhaps one of the most convincing pieces of evidence that the immune microenvironment has a critical role in driving the progression from MGUS to MM came from the aforementioned study in which patient-derived bone-marrow mononuclear cells were transplanted into a genetically humanized mouse model, indicating that MGUS cells can proliferate rapidly (similar to MM cells) in the absence of a microenvironment that enables effective immunosurveillance[34]. We have obtained similar results in mice lacking T_{reg} cells (owing to conditional knockout of the *Foxp3* gene that encodes a T_{reg} cell-specific master transcription factor), which have prolonged survival after injection of mouse VK*MY MM cells compared with that of mice without T_{reg}-cell depletion or in wild-type littermates[103]. These findings further confirm the critical roles of the immune system in promoting clonal expansion and progression in MM.

With regard to MDS, several investigations have been focused on the potential importance of the inflammasome and novel mechanisms of intramedullary HSPC death, such as disordered autophagy, pyroptosis, and necroptosis, in mediating bone-marrow failure[104–106]. However, the extent to which these phenomena are drivers of MDS biology versus a reactive consequence of clonal HSPC expansion remains unclear.

With the advent of single-cell sequencing technologies, tumour-infiltrating T cells have been shown to play an integral part in clonal expansion in solid tumours, such as melanoma[107]. Similar studies in the context of MGUS and MDS will help to better define the characteristics of the immune microenvironment during disease progression.

Hypoxia and angiogenesis

The bone-marrow niche includes areas of hypoxia, which can influence the behaviour of both microenvironmental components and neoplastic stem cells via the hypoxia-inducible factor 1 (HIF1)–von Hippel–Lindau disease tumour suppressor (VHL) signalling pathway. Hypoxia promotes HSPC quiescence and is accompanied by changes in oxidative metabolism that can result in oncogenic changes in epigenetic patterns, especially in the citric acid cycle, such as alterations affecting the isocitrate dehydrogenase enzymes (which are mutated in 5–10% of MDS cases and 15–25% of AMLs)[108,109]. In addition, the vascular architecture, including the 'leakiness' of blood vessels, is abnormal in

both primary AML samples and patient-derived AML xenografts, and inhibition of nitric oxide production reduces vascular permeability and improves treatment responses in the latter model[110,111].

Neoangiogenesis is a well-established hallmark of the bone-marrow microenvironment of MM, and the number of new blood vessels increases during disease progression from MGUS to MM[24]. In addition, endothelial progenitor cells, which are key mediators of angiogenesis, have been shown to be critical for disease evolution from MGUS to MM[24] (TABLE 1). The fact that the bone-marrow microenvironment is hypoxic relative to other tissues, resulting in expression of HIF1 and VEGF, contributes to increased neoangiogenesis in patients with MM[112] (FIG. 2). Hypoxia also drives epithelial-to-mesenchymal transition of MM cells, thereby promoting tumour dissemination[113]. This mechanism is principally dependent on decreased expression of E-cadherin, limiting the adhesion of the malignant plasma cells to the bone-marrow stroma and consequently increasing egress of MM cells into the circulation[113]. In addition, hypoxia leads to overexpression of C-X-C-motif chemokine receptor 4 (CXCR4) on plasma cells, promoting the dissemination and homing of circulating MM cells to novel bone-marrow sites[113].

The extracellular matrix

The extracellular matrix (ECM) is a major component of the tumour microenvironment, contributing to the regulation of cell survival, proliferation, differentiation, and migration (metastasis) (TABLE 1). In 2017, a proteomic study revealed that the composition of the ECM differs between nonmalignant, MGUS, and MM bone-marrow samples and that remodelling of the ECM to create a permissive environment is associated with tumour progression (FIG. 2); two ECM components, annexin A2 and galectin 1, were expressed at greater levels in patients with MM versus MGUS, and high expression levels of these proteins correlated with a worse prognosis[114]. The results of prior studies have also highlighted the role of syndecan 1 (also known as CD138), a type I transmembrane heparan sulfate proteoglycan that is expressed by MM cells and can be shed in the microenvironment, in promoting tumour growth, invasion, and dissemination[115]. Less is known about the role of the ECM in MDS or AML, although results of a network analysis have demonstrated underexpression of matrix metalloproteinase 9 (MMP9) in primary AML samples[116].

Therapeutic opportunities

Towards prevention and interception

The stepwise evolution of these haematological malignancies presents an opportunity to prevent disease progression and complications and to improve patient outcomes by intervening at an early stage. Indeed, treatment of plasma-cell disorders — which was once restricted to patients with symptomatic, active MM — is now being considered for those with SMM. This paradigm shift towards early intervention to prevent or delay progression to MM was established in a study by Mateos *et al.*[117], in which treatment with the putative antiangiogenic agent lenalidomide, combined with dexamethasone, prolonged progression-free survival and overall survival durations in patients with SMM. Similarly, in the 1990s, the observation that patients with low-risk MDS had increased intramedullary vascular density and markers of neoangiogenesis prompted clinical trials of thalidomide and other putative antiangiogenic agents in this disease, with modest haematological improvements observed in 20–30% of the patients treated[118,119]. This trend towards earlier treatment will probably also be extended to myeloid neoplasias once drugs with promising activity become available.

Immunomodulatory agents and angiogenesis

These therapeutic benefits of putative antiangiogenic and immunomodulatory drugs were initially attributed to alterations in the bone-marrow niche, and specifically the levels of VEGF, various immune-cell mediators, and other microenvironmental molecules (FIG. 3); however, these effects are now recognized to be epiphenomena given the observation in the context of MM and MDS that lenalidomide interacts with cereblon and its associated ubiquitin ligase complex, thereby mediating selective depletion of clonal cells via increased ubiquitylation and proteasomal degradation of haploinsufficient casein kinase 1α (encoded by a gene located on chromosome 5q (REFS 120,121), which is commonly deleted in this disease)[122–125]. Nevertheless, the rationale supporting the use of agents that target the bone-marrow microenvironment (TABLE 2) in an attempt to delay or prevent progression of precursor conditions to overt disease remains strong. For example, in the early stages of MM progression, tumour growth can be abrogated by enhancing the growth of osteoblasts: activation of osteoblasts by bone-homing polymeric nanoparticles loaded with bortezomib, before injection of MM cells, was associated with markedly decreased tumour burdens and prolonged survival in mouse models compared with the use of empty nanoparticles or the free drug[126]. Another example of the potential for angiogenesis-directed therapy is provided by a mouse model involving the targeting of endothelial progenitor cells, which promote progression from MGUS to MM[24], through the use of an antiangiogenic anti-VEGF receptor 2 antibody: early treatment delayed tumour progression in a mouse model of MM, whereas use of the same agent at later stages of disease was ineffective in improving disease outcomes. However, the use of antiangiogenic agents other than thalidomide and other immunomodulatory agents has not been shown to be successful in patients with MM[127].

Agents that regulate immune cells

In the past 5 years, immunotherapy with immune-checkpoint inhibitors and bioengineered chimeric antigen receptor (CAR) T cells has revolutionized anticancer therapy. By targeting the immune microenvironment, the next wave of therapeutic advances will likely involve targeting the complex ecosystem of malignant cells together with immune and other cell types located in the tumour microenvironment.

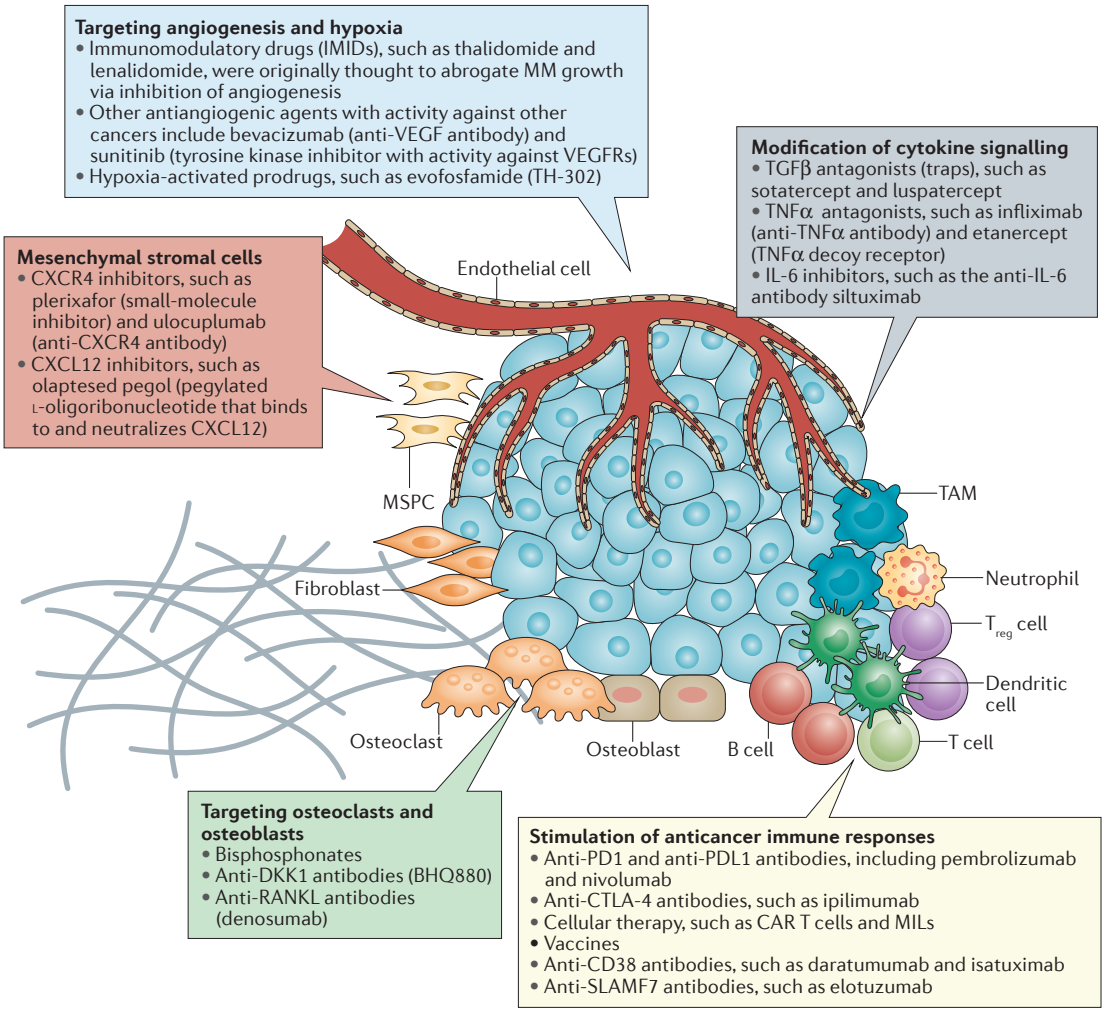

Figure 3 | **Therapeutic agents that target the aberrant tumour microenvironment in multiple myeloma and myelodysplastic syndromes or acute myeloid leukaemia.** The figure depicts some of the agents that are currently being used in therapy or are being tested in clinical trials for the treatment of patients with multiple myeloma (MM) or myelodysplastic syndrome (MDS) and/or acute myeloid leukaemia (AML), that target components of the bone-marrow microenvironment. CAR, chimeric antigen receptor; CTLA-4, cytotoxic T lymphocyte protein 4; CXCL12, CXC-chemokine ligand 12; CXCR4, CXC-chemokine receptor 4; DKK1, Dickkopf-related protein 1; IMIDs, immunomodulatory drugs; MILs, marrow-infiltrating lymphocytes; TAM, tumour-associated macrophages; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; RANKL, receptor activator of nuclear factor-κB ligand; VEGFR, VEGF receptor.

The altered bone-marrow niche is ideally suited to both sustaining proliferating MM cells and protecting and facilitating immune evasion of their dormant, drug-resistant counterparts. Therefore, the possibility of deepening responses to treatment, maintaining remissions, or even eradicating therapy-resistant stem cells by pharmacologically manipulating the interactions of tumours with their aberrant niche should be a major driving force in current myeloma and leukaemia research and beyond. In patients with MM, many studies have been conducted using the anti-SLAMF7 antibody elotuzumab or the anti-CD38 antibody daratumumab alone or in combination with bortezomib or lenalidomide, and both approaches have shown superior activity compared with the standard of care[128–130]. The anti-SLAMF7 antibody elotuzumab activates NK cells and macrophages, and the anti-CD38 antibody daratumumab activates the immune system through reduction in T_{reg} cell numbers and increases in the numbers of helper and cytotoxic T cells[25] (FIG. 3). In specimens collected from patients treated in clinical trials, daratumumab also induced marked increases in $CD8^+$:$CD4^+$ and $CD8^+$:T_{reg}-cell ratios and increased memory T-cell numbers while decreasing naive T cell populations[25]. Indeed, trials involving these antibodies provide the first proof of concept that activation of the immune system has therapeutic benefits in patients with MM. In addition, studies involving large numbers of patients with melanoma, lung cancer, or Hodgkin lymphoma, among other cancers, have indicated the striking clinical efficacy of immune-checkpoint blockade targeting PD-1 (REFS 131–133). A strong rationale exists to support the hypothesis that PD-1 immune-checkpoint blockade should also be effective in patients with MM: programmed cell death 1 ligand 1 is highly expressed by MM cells, and blockade of

Table 2 | **Strategies for targeting the microenvironment of multiple myeloma or acute myeloid leukaemia that have reached clinical trials**

Target	Agent	Representative clinical trials in MM or AML
Regulation of angiogenesis, including immunomodulatory agents	Thalidomide and lenalidomide were originally used as antiangiogenic agents in MM	• Phase II clinical trial of thalidomide in relapsed and/or refractory MM[193] • Phase III clinical trials of lenalidomide and dexamethasone compared with dexamethasone in MM[194,195] • Phase III clinical trial of lenalidomide and dexamethasone in high-risk smouldering MM[117] • Clinical trial of lenalidomide in del(5q) MDS[120,121]
Immune system regulation, including immune-checkpoint inhibitors and cellular therapy	• PD-1 and PD-L1 inhibitors, including pembrolizumab and nivolumab • CTLA-4 inhibitor, such as ipilimumab • Cellular therapy, such as CAR–T cells, MILs, and vaccines	• Daratumumab alone or in combination with lenalidomide or bortezomib in MM[128–130] • Elotuzumab in combination with lenalidomide in MM[130,196] • Nivolumab in haematological malignancies[131,197] • Pembrolizumab in combination with immunomodulatory drugs in MM[137,198] • Ipilimumab in haematological malignancies[199] • Cellular therapy, including CAR–T cell therapy, MILs, and vaccines[142,143,200–202]
Regulation of stroma–tumour interaction, including CXCR4 and CXCL12	• Plerixafor • Ulocuplumab • Olaptesed pegol	• Phase II clinical trial of plerixafor in combination with chemotherapy in AML[148] • Phase II trial of plerixafor and bortezomib in relapsed MM[203] • Phase II trial of ulocuplumab in AML (NCT01120457) • Phase II trial of ulocuplumab in MM (NCT01359657) • Phase I trial of olaptesed pegol in MM[147] • Phase II study of GMI-1271, an antagonist of E-selectin (NCT02306291)
Regulation of osteoclasts and osteoblasts	Bisphosphonates, DKK1 inhibitors (BHQ880), and RANKL inhibitors (denosumab)	• Multiple clinical trials of pamidronate and zoledronic acid in MM, including a phase III trial of zoledronic acid in MM[149–153] • Bisphosphonate trials in smouldering MM[150,157] • Anti-DKK1 antibody (BHQ880) clinical trials in MM[154,155] • Anti-RANKL antibody (denosumab) clinical trial in MM[156]
Cytokines	• TGFβ antagonists, such as sotatercept and luspatercept • Tumour necrosis factor-α inhibitors such as infliximab and etanercept • IL-6 antagonists such as siltuximab	• Sotatercept for MDS-associated anaemia[169] • Luspatercept for anaemia in patients with MDS[167] • Infliximab and etanercept for anaemia in low-risk MDS[158–161] • Siltuximab showed no activity in MDS but had significant activity in Castleman disease[162–165]
Hypoxia	Evofosfamide (TH-302), an investigational hypoxia-activated prodrug	• Phase II clinical trial of evofosfamide alone or in combination with bortezomib in MM[178]

AML, acute myeloid leukaemia; CAR, chimeric antigen receptor; CTLA-4, cytotoxic T lymphocyte protein 4; CXCL12, CXC-chemokine ligand 12; CXCR4, CXC-chemokine receptor 4; DKK1, Dickkopf-related protein 1; MDS, myelodysplastic syndrome; MIL, marrow-infiltrating lymphocytes; MM, multiple myeloma; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; RANKL, receptor activator of nuclear factor-κB.

PD-1 *in vitro* and in mouse models of MM improves the immune responses against MM cells[134–136] (FIG. 3). Indeed, a phase II trial of pembrolizumab, a monoclonal antibody that blocks PD-1 activity, used in combination with immunomodulators and dexamethasone revealed a high response rate (76%) in patients with MM[137–140]. However, controversial data exist regarding the efficacy and toxicity of these agents in combination with lenalidomide, specifically the combination of pembrolizumab and lenalidomide, in patients with MM, and have led the FDA to place these studies on hold[141]. This scenario underscores the need to better understand the immune environment of MM and test other immunotherapies in patients with this disease. In addition, studies of CAR–T-cell therapy targeting B cell maturation antigen (BCMA; also known as TNF receptor superfamily member 17 (TNFRSF17)) have revealed very high response rates in heavily pretreated patients with MM[142,143]. However, further studies in greater numbers of patients and with longer follow-up durations are required to truly understand the role of CAR–T-cell therapy in the treatment of MM.

Agents that target the stroma

Tumour-associated stromal cells secrete the chemokine CXCL12, leading to adhesion and drug resistance of neoplastic clones[23,27,30,144–146]. In MM models, therapeutic targeting of CXCL12 or its ligand CXCR4 at very early time points in malignant development can prevent or delay disease progression in mouse models[27,30]. Clinical trials using CXCR4 inhibitors in combination with bortezomib or lenalidomide have been conducted in patients with MM (TABLE 2). Additionally, therapeutic targeting of the CXCL12–CXCR4 axis through the use of olaptesed pegol (a CXCL12-neutralizing pegylated mirror-image L-oligoribonucleotide) or ulocuplumab (an anti-CXCR4 monoclonal antibody) is currently under clinical investigation in patients with MM (FIG. 3). Olaptesed pegol binds to and neutralizes CXCL12, a chemokine that signals through CXCR4 and CXCR7. The efficacy of combining CXCL12 inhibition with bortezomib and dexamethasone was investigated in 28 patients with relapsed and/or refractory MM who were either bortezomib-naive or considered not refractory to bortezomib. In this patient population, the rate of clinical benefit rate was 75%,

indicating the promising activity of this combination therapy in a relapsed and/or refractory disease setting[147].

CXCL12 is also of particular therapeutic interest in the context of myeloid neoplasias because CXCL12-abundant reticular cells localize to the perivascular area of bone marrow, where they support the survival and growth of MDS and AML HSPCs and contribute to therapy resistance[144–146]. Thus, disrupting the CXCL12–CXCR4 axis might be a therapeutic opportunity. In patients with MDS, CXCL12 expression is increased in those with low-grade disease compared with individuals without this disease but diminishes at later stages of the disease; the inverse is true for CXCR4 (REF. 145). In AML, the CXCR4 antagonist plerixafor is being explored as a sensitizing agent to conventional cytotoxic agents in order to disrupt the interaction between leukaemic stem cells and the supportive bone-marrow niche that contributes to chemoresistance[144–146]. In a phase I and II trial involving 52 patients with relapsed and/or refractory AML[148], this strategy was associated with an encouraging response rate (overall complete remission with or without complete blood count recovery rate of 46%); however, delayed haematopoietic recovery after myelosuppression has been problematic in some patients.

Targeting osteoclasts and osteoblasts

Many studies involving bisphosphonates (pamidronate or zoledronic acid)[149–153], DKK1 inhibitors (BHQ880)[154,155], and RANKL inhibitors (denosumab)[156] have been conducted in patients with MM, owing to the fact that these agents have the potential to disrupt the interactions of osteoclasts and osteoblasts with MM cells (FIG. 3). Indeed, results of a phase III trial showed that the addition of zoledronic acid to standard therapy improves survival outcomes in patients with newly diagnosed MM[149]. The available evidence does not suggest that bisphosphonates can prevent disease progression in patients with SMM, but the use of these agents can decrease the incidence of bone-related adverse events[150,157].

Agents that target cytokines

Other immunomodulatory mediators have been explored as therapeutic targets in patients with MDS. For example, results of preliminary clinical trials with the anti-TNFα antibodies infliximab and etanercept have demonstrated modest improvements in erythropoiesis in some patients with anaemia and low-risk MDS[158–161] (FIG. 3). By contrast, no clinical activity was detected in a trial involving the anti-IL-6 chimeric antibody siltuximab[158–161]. Siltuximab has also been tested in patients with MM and has substantial activity in patients with Castleman disease[162–165].

Among the immunosuppressive cytokines that contribute to the supportive tumour niche in MDS, TGFβ currently is arguably the most promising target for therapeutic intervention[21]. Two recombinant activin receptor–immunoglobulin G (IgG) Fc fragment fusion proteins, sotatercept and luspatercept, have been developed as antagonistic 'traps' for cytokines of the TGFβ superfamily; these agents bind to and sequester ligands of activin receptor type 2A and activin receptor type 2B, respectively, including TGFβ and growth and differentiation factor 11 (GDF11), thereby relieving suppression of erythropoiesis[166,167]. Indeed, these agents are also being explored clinically in noncancer indications, including non-neoplastic forms of anaemia (such as thalassemia major) and osteoporosis (owing to their effect on BMPs, which are also TGFβ superfamily cytokines)[168]. Sotatercept has demonstrated clinical activity in the treatment of MDS-associated anaemia[169], but for commercial reasons, is not being developed further in MDS. Luspatercept treatment has been shown to reduce the requirement for red blood cell transfusions in >40% of patients with MDS, including a subset who were heavily dependent on red blood cell transfusion[167]. Unexpectedly, the most striking activity of luspatercept was observed in patients with either ring sideroblasts or mutations in *SF3B1*, a genetic aberration that is strongly correlated with the presence of ring sideroblasts and causes a specific erythropoietic defect[167]. This observation prompted the development of an ongoing registration trial (NCT02631070), in which the benefit of luspatercept versus placebo is being evaluated in 210 patients who have anaemia associated with low-risk MDS and either ring sideroblasts or *SF3B1* mutations. In summary, mechanisms of stromal protection of clonal cells, such as upregulation of adhesion molecules, potentiation of cytopenias by TGFβ and other cytokines, and alterations in vascular dynamics and angiogenesis, might serve as therapeutic targets in both patients with MGUS and/or MM and in those with MDS and/or AML.

Drug resistance

In addition to mediating haematological neoplasia, the stromal compartment of the bone marrow might also be a critical regulator of drug resistance. In a profiling study investigating 23 stromal cell types and their roles in influencing the innate resistance of 45 cancer cell lines to a total of 35 anticancer drugs[170], stroma-mediated resistance was found to be common, particularly with targeted agents. For example, proteomic analyses revealed that resistance of cancer cells to BRAF inhibition is associated with secretion of HGF by stromal cells, resulting in activation of the HGF receptor MET and reactivation of the MAPK and PI3K–AKT signalling pathways[171]. The findings of this study indicate that the systematic dissection of the interactions between tumours and their microenvironment can uncover important mechanisms underlying drug resistance.

The role of the stroma in inducing drug resistance in patients with MM has been well documented. *In vitro*, adhesion of MM cells to MPSCs, endothelial cells, and proteins including fibronectin enhances MM cell growth and provides protection against drug-induced apoptosis[23,26,27,29,31,170,172–175]. These sequelae are dependent on cell–cell contact as well as NF-κB-dependent transcription and secretion of IL-6 — a cytokine with important activities that promotes the growth, survival, and drug resistance of MM cells. Other cytokines, such as IGF1, and chemokines, such as CXCL12, have also been implicated in the drug resistance of MM cells through activation of the PI3K–AKT, MAPK,

and NF-κB pathways[23,26,27,29,31,170,172–175]. Furthermore, exosomes secreted by MSPCs have been shown to mediate resistance to bortezomib in preclinical models of MM[173]. By use of a bioluminescence imaging assay, investigators screened multiple drugs for their activity against MM cells in the presence or absence of MSPCs and identified a stroma-induced signature in tumour cells that correlates with drug resistance and an adverse patient prognosis[170].

Hypoxia can also induce drug resistance in MM cells and might also result in resistance to radiotherapy[176]. Targeting of potentially therapy-resistant cancer cells through the use of the hypoxia-activated prodrug evofosfamide (TH-302), which is an alkylating agent only under hypoxic conditions, has been tested in clinical trials involving patients with MM[177]. The final results have not been published, but preliminary data demonstrate a 31% clinical benefit rate in heavily pretreated patients with MM[178]. Neoangiogenic mechanisms can also have a role in the development of resistance to antiangiogenic drugs and could serve as targets when designing new antivascular agents for the treatment of haematological malignancies[24].

Less is known about the contribution of the bone-marrow niche to drug resistance in MDS. In AML, however, the integrin-binding glycoprotein CD98 promotes survival of leukaemia stem cells through interactions with their microenvironment, and is potentially amenable to intervention; the growth of patient-derived AML xenografts can be inhibited using an anti-CD98 antibody[179]. Similarly, the regulator of apoptosis nucleolar protein 3 confers drug resistance to AML cells via NF-κB-dependent induction of IL-1β expression, which in turn stimulates secretion of CCL2, CCL4, and CXCL12 by co-cultured MSPCs — suggesting reciprocal tumour–stroma crosstalk that results in cytoprotection and is potentially targetable[180]. In addition, microenvironmental factors might also mediate resistance to FLT3 inhibitors, including midostaurin, a multikinase inhibitor that, in 2017, became the first new FDA-approved drug for AML in nearly 20 years[181,182].

Conclusions

Numerous observations indicate that an altered bone-marrow microenvironment provides a nurturing niche that sustains haematological neoplasia and might even contribute to the emergence and evolution of neoplastic clones. Targeting microenvironment-specific alterations might not only prevent disease progression from precursor states such as CHIP or MDS, and MGUS or SMM to AML and MM, respectively, but also enhance the effectiveness of available therapies for the overt malignancies once progression has occurred. Further studies are required to better characterize and understand the aberrant bone-marrow microenvironment in patients with these diseases in order to identify rational therapeutic targets and develop optimal strategies for interventions.

1. Schanz, J. *et al.* Coalesced multicentric analysis of 2,351 patients with myelodysplastic syndromes indicates an underestimation of poor-risk cytogenetics of myelodysplastic syndromes in the international prognostic scoring system. *J. Clin. Oncol.* **29**, 1963–1970 (2011).
2. Papaemmanuil, E. *et al.* Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood* **122**, 3616–3627 (2013).
3. Greenberg, P. L. *et al.* Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* **120**, 2454–2465 (2012).
4. Steensma, D. P. *et al.* Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood* **126**, 9–16 (2015).
5. Jaiswal, S. *et al.* Age-related clonal hematopoiesis associated with adverse outcomes. *N. Engl. J. Med.* **371**, 2488–2498 (2014).
6. Parker, J. E. *et al.* 'Low-risk' myelodysplastic syndrome is associated with excessive apoptosis and an increased ratio of pro- versus anti-apoptotic bcl-2-related proteins. *Br. J. Haematol.* **103**, 1075–1082 (1998).
7. Mittelman, M., Oster, H. S., Hoffman, M. & Neumann, D. The lower risk MDS patient at risk of rapid progression. *Leuk. Res.* **34**, 1551–1555 (2010).
8. Walter, M. J. *et al.* Clonal architecture of secondary acute myeloid leukemia. *N. Engl. J. Med.* **366**, 1090–1098 (2012).
9. Enrico, A. *et al.* Influence of acute myeloid leukemia progression on the prognosis of 831 patients with myelodysplastic syndromes from the Argentine database. *Clin. Lymphoma Myeloma Leuk.* 743–752. e5 (2017).
10. Østgård, L. S. *et al.* Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. *J. Clin. Oncol.* **33**, 3641–3649 (2015).
11. Lindsley, R. C. *et al.* Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood* **125**, 1367–1376 (2015).
12. Landgren, O. *et al.* Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood* **113**, 5412–5417 (2009).
13. Weiss, B. M., Abadie, J., Verma, P., Howard, R. S. & Kuehl, W. M. A monoclonal gammopathy precedes multiple myeloma in most patients. *Blood* **113**, 5418–5422 (2009).
14. Landgren, O. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: biological insights and early treatment strategies. *Hematol. Am. Soc. Hematol. Educ. Program* **2013**, 478–487 (2013).
15. Kyle, R. A. & Rajkumar, S. V. Multiple myeloma. *Blood* **111**, 2962–2972 (2008).
16. Rajkumar, S. V. Multiple myeloma: 2011 update on diagnosis, risk-stratification, and management. *Am. J. Hematol.* **86**, 57–65 (2011).
17. Lopez-Corral, L. *et al.* SNP-based mapping arrays reveal high genomic complexity in monoclonal gammopathies, from MGUS to myeloma status. *Leukemia* **26**, 2521–2529 (2012).
18. Cogle, C. R. *et al.* Bone marrow niche in the myelodysplastic syndromes. *Leuk. Res.* **39**, 1020–1027 (2015).
19. Bulycheva, E. *et al.* Myelodysplasia is in the niche: novel concepts and emerging therapies. *Leukemia* **29**, 259–268 (2015).
20. Calvi, L. M. & Link, D. C. The hematopoietic stem cell niche in homeostasis and disease. *Blood* **126**, 2443–2451 (2015).
21. Mies, A., Bulycheva, E., Rogulj, I. M., Hofbauer, L. C. & Platzbecker, U. Alterations within the osteo-hematopoietic niche in MDS and their therapeutic implications. *Curr. Pharm. Des.* **22**, 2323–2332 (2016).
22. Raza, A., Cruz, R., Latif, T., Mukherjee, S. & Galili, N. The biology of myelodysplastic syndromes: unity despite heterogeneity. *Hematol. Rep.* **2**, e4 (2010).
23. Roccaro, A. M. *et al.* BM mesenchymal stromal cell-derived exosomes facilitate multiple myeloma progression. *J. Clin. Invest.* **123**, 1542–1555 (2013).
24. Moschetta, M. *et al.* Role of endothelial progenitor cells in cancer progression. *Biochim. Biophys. Acta* **1846**, 26–39 (2014).
25. Muz, B., de la Puente, P., Azab, F., Ghobrial, I. M. & Azab, A. K. Hypoxia promotes dissemination and colonization in new bone marrow niches in Waldenstrom's macroglobulinemia. *Mol. Cancer Res.* **13**, 263–272 (2015).
26. Reagan, M. R. *et al.* Investigating osteogenic differentiation in multiple myeloma using a novel 3D bone marrow niche model. *Blood* **124**, 3250–3259 (2014).
27. Roccaro, A. M. *et al.* SDF-1 inhibition targets the bone marrow niche for cancer therapy. *Cell Rep.* **9**, 118–128 (2014).
28. Zingone, A. *et al.* Altered cytokine and chemokine profiles in multiple myeloma and precursor disease. *Cytokine* **69**, 294–297 (2014).
29. Kawano, Y. *et al.* Targeting the bone marrow microenvironment in multiple myeloma. *Immunol. Rev.* **263**, 160–172 (2015).
30. Roccaro, A. M. *et al.* CXCR4 regulates extra-medullary myeloma through epithelial-mesenchymal-transition-like transcriptional activation. *Cell Rep.* **12**, 622–635 (2015).
31. Moschetta, M. *et al.* Targeting vasculogenesis to prevent progression in multiple myeloma. *Leukemia* **30**, 1103–1115 (2016).
32. Sacco, A. *et al.* Cancer cell dissemination and homing to the bone marrow in a zebrafish model. *Cancer Res.* **76**, 463–471 (2016).
33. Kawano, Y., Roccaro, A. M., Azzi, J. & Ghobrial, I. M. Multiple myeloma and the immune microenvironment. *Curr. Cancer Drug Targets* **17**, 806–818 (2017).
34. Das, R. *et al.* Microenvironment-dependent growth of preneoplastic and malignant plasma cells in humanized mice. *Nat. Med.* **22**, 1351–1357 (2016).
35. Schepers, K., Campbell, T. B. & Passegue, E. Normal and leukemic stem cell niches: insights and therapeutic opportunities. *Cell Stem Cell* **16**, 254–267 (2015).
36. Sperling, A. S., Gibson, C. J. & Ebert, B. L. The genetics of myelodysplastic syndrome: from clonal haematopoiesis to secondary leukaemia. *Nat. Rev. Cancer* **17**, 5–19 (2017).
37. Park, D., Sykes, D. B. & Scadden, D. T. The hematopoietic stem cell niche. *Front. Biosci.* **17**, 30–39 (2012).
38. Papayannopoulou, T. & Scadden, D. T. Stem-cell ecology and stem cells in motion. *Blood* **111**, 3923–3930 (2008).
39. Yu, V. W. & Scadden, D. T. Hematopoietic stem cell and its bone marrow niche. *Curr. Top. Dev. Biol.* **118**, 21–44 (2016).
40. Kaplan, R. N. *et al.* VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature* **438**, 820–827 (2005).

41. Valastyan, S. & Weinberg, R. A. Tumor metastasis: molecular insights and evolving paradigms. *Cell* **147**, 275–292 (2011).
42. Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646–674 (2011).
43. Bhowmick, N. A. *et al.* TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. *Science* **303**, 848–851 (2004).
44. Walkley, C. R., Shea, J. M., Sims, N. A., Purton, L. E. & Orkin, S. H. Rb regulates interactions between hematopoietic stem cells and their bone marrow microenvironment. *Cell* **129**, 1081–1095 (2007).
45. Yang, F. C. *et al. Nf1*-dependent tumors require a microenvironment containing *Nf1*$^{+/-}$ and c-kit-dependent bone marrow. *Cell* **135**, 437–448 (2008).
46. Raaijmakers, M. H. *et al.* Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. *Nature* **464**, 852–857 (2010).
47. Kode, A. *et al.* Leukaemogenesis induced by an activating beta-catenin mutation in osteoblasts. *Nature* **506**, 240–244 (2014).
48. Kode, A. *et al.* FoxO1-dependent induction of acute myeloid leukemia by osteoblasts in mice. *Leukemia* **30**, 1–13 (2016).
49. Roodman, G. D. Role of the bone marrow microenvironment in multiple myeloma. *J. Bone Miner. Res.* **17**, 1921–1925 (2002).
50. Podar, K., Richardson, P. G., Hideshima, T., Chauhan, D. & Anderson, K. C. The malignant clone and the bone-marrow environment. *Best Pract. Res. Clin. Haematol.* **20**, 597–612 (2007).
51. Podar, K., Hideshima, T., Chauhan, D. & Anderson, K. C. Targeting signalling pathways for the treatment of multiple myeloma. *Expert Opin. Ther. Targets* **9**, 359–381 (2005).
52. Podar, K., Chauhan, D. & Anderson, K. C. Bone marrow microenvironment and the identification of new targets for myeloma therapy. *Leukemia* **23**, 10–24 (2009).
53. Reagan, M. R. & Ghobrial, I. M. Multiple myeloma mesenchymal stem cells: characterization, origin, and tumor-promoting effects. *Clin. Cancer Res.* **18**, 342–349 (2012).
54. Manier, S. *et al.* Prognostic role of circulating exosomal miRNAs in multiple myeloma. *Blood* **129**, 2429–2436 (2017).
55. Wang, J. & Xiao, Z. Mesenchymal stem cells in pathogenesis of myelodysplastic syndromes. *Stem Cell. Investig.* **1**, 16 (2014).
56. Aanei, C. M. *et al.* Focal adhesion protein abnormalities in myelodysplastic mesenchymal stromal cells. *Exp. Cell Res.* **317**, 2616–2629 (2011).
57. Aanei, C. M. *et al.* Intrinsic growth deficiencies of mesenchymal stromal cells in myelodysplastic syndromes. *Stem Cells Dev.* **21**, 1604–1615 (2012).
58. Geyh, S. *et al.* Insufficient stromal support in MDS results from molecular and functional deficits of mesenchymal stromal cells. *Leukemia* **27**, 1841–1851 (2013).
59. Blau, O. *et al.* Mesenchymal stromal cells of myelodysplastic syndrome and acute myeloid leukemia patients have distinct genetic abnormalities compared with leukemic blasts. *Blood* **118**, 5583–5592 (2011).
60. Blau, O. *et al.* Chromosomal aberrations in bone marrow mesenchymal stroma cells from patients with myelodysplastic syndrome and acute myeloblastic leukemia. *Exp. Hematol.* **35**, 221–229 (2007).
61. Oliveira, F. M. *et al.* Differential expression of *AURKA* and *AURKB* genes in bone marrow stromal mesenchymal cells of myelodysplastic syndrome: correlation with G-banding analysis and FISH. *Exp. Hematol.* **41**, 198–208 (2013).
62. Borojevic, R. *et al.* Bone marrow stroma in childhood myelodysplastic syndrome: composition, ability to sustain hematopoiesis *in vitro*, and altered gene expression. *Leuk. Res* **28**, 831–844 (2004).
63. Li, X. & Deeg, H. J. Murine xenogeneic models of myelodysplastic syndrome: an essential role for stroma cells. *Exp. Hematol.* **42**, 4–10 (2014).
64. Medyouf, H. *et al.* Myelodysplastic cells in patients reprogram mesenchymal stromal cells to establish a transplantable stem cell niche disease unit. *Cell Stem Cell* **14**, 824–837 (2014).
65. Todoerti, K. *et al.* Distinct transcriptional profiles characterize bone microenvironment mesenchymal cells rather than osteoblasts in relationship with multiple myeloma bone disease. *Exp. Hematol.* **38**, 141–153 (2010).
66. Garayoa, M. *et al.* Mesenchymal stem cells from multiple myeloma patients display distinct genomic profile as compared with those from normal donors. *Leukemia* **23**, 1515–1527 (2009).
67. Flores-Figueroa, E., Arana-Trejo, R. M., Gutiérrez-Espíndola, G., Pérez-Cabrera, A. & Mayani, H. Mesenchymal stem cells in myelodysplastic syndromes: phenotypic and cytogenetic characterization. *Leuk. Res.* **29**, 215–224 (2005).
68. Santamaria, C. *et al.* Impaired expression of DICER, DROSHA, SBDS and some microRNAs in mesenchymal stromal cells from myelodysplastic syndrome patients. *Haematologica* **97**, 1218–1224 (2012).
69. Zambetti, N. A. *et al.* Mesenchymal inflammation drives genotoxic stress in hematopoietic stem cells and predicts disease evolution in human pre-leukemia. *Cell Stem Cell* **19**, 613–627 (2016).
70. Olechnowicz, S. W. & Edwards, C. M. Contributions of the host microenvironment to cancer-induced bone disease. *Cancer Res.* **74**, 1625–1631 (2014).
71. Yavropoulou, M. P. & Yovos, J. G. The role of the Wnt signaling pathway in osteoblast commitment and differentiation. *Hormones* **6**, 279–294 (2007).
72. Roodman, G. D. Pathogenesis of myeloma bone disease. *Leukemia* **23**, 435–441 (2009).
73. Roodman, G. D. New potential targets for treating myeloma bone disease. *Clin. Cancer Res.* **12**, 6270s–6273s (2006).
74. Toscani, D., Bolzoni, M., Accardi, F., Aversa, F. & Giuliani, N. The osteoblastic niche in the context of multiple myeloma. *Ann. NY Acad. Sci.* **1335**, 45–62 (2015).
75. Bianchi, G. & Munshi, N. C. Pathogenesis beyond the cancer clone(s) in multiple myeloma. *Blood* **125**, 3049–3058 (2015).
76. Huston, A. & Roodman, G. D. Role of the microenvironment in multiple myeloma bone disease. *Future Oncol.* **2**, 371–378 (2006).
77. Tripodo, C. *et al.* Stromal SPARC contributes to the detrimental fibrotic changes associated with myeloproliferation whereas its deficiency favors myeloid cell expansion. *Blood* **120**, 3541–3554 (2012).
78. Balderman, S. R. *et al.* Targeting of the bone marrow microenvironment improves outcome in a murine model of myelodysplastic syndrome. *Blood* **127**, 616–625 (2016).
79. Kitagawa, M. *et al.* Overexpression of tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma by bone marrow cells from patients with myelodysplastic syndromes. *Leukemia* **11**, 2049–2054 (1997).
80. Wang, Z. *et al.* The different immunoregulatory functions on dendritic cells between mesenchymal stem cells derived from bone marrow of patients with low-risk or high-risk myelodysplastic syndromes. *PLoS ONE* **8**, e57470 (2013).
81. Allampallam, K. *et al.* Biological significance of proliferation, apoptosis, cytokines, and monocyte/macrophage cells in bone marrow biopsies of 145 patients with myelodysplastic syndrome. *Int. J. Hematol.* **75**, 289–297 (2002).
82. Feng, X. *et al.* Cytokine signature profiles in acquired aplastic anemia and myelodysplastic syndromes. *Haematologica* **96**, 602–606 (2011).
83. Weiss, G. & Goodnough, L. T. Anemia of chronic disease. *N. Engl. J. Med.* **352**, 1011–1023 (2005).
84. Qiang, Y. W., Kopantzev, E. & Rudikoff, S. Insulinlike growth factor-I signaling in multiple myeloma: downstream elements, functional correlates, and pathway cross-talk. *Blood* **99**, 4138–4146 (2002).
85. Alsayed, Y. *et al.* Mechanisms of regulation of CXCR4/SDF-1 (CXCL12)-dependent migration and homing in multiple myeloma. *Blood* **109**, 2708–2717 (2007).
86. Dankbar, B. *et al.* Vascular endothelial growth factor and interleukin-6 in paracrine tumor-stromal cell interactions in multiple myeloma. *Blood* **95**, 2630–2636 (2000).
87. Chauhan, D. *et al.* SHP2 mediates the protective effect of interleukin-6 against dexamethasone-induced apoptosis in multiple myeloma cells. *J. Biol. Chem.* **275**, 27845–27850 (2000).
88. Jacamo, R. *et al.* Reciprocal leukemia-stroma VCAM-1/VLA-4-dependent activation of NF-kappaB mediates chemoresistance. *Blood* **123**, 2691–2702 (2014).
89. Quail, D. F. & Joyce, J. A. Microenvironmental regulation of tumor progression and metastasis. *Nat. Med.* **19**, 1423–1437 (2013).
90. Swann, J. B. & Smyth, M. J. Immune surveillance of tumors. *J. Clin. Invest.* **117**, 1137–1146 (2007).
91. Coulson-Thomas, V. J., Coulson-Thomas, Y. M., Gesteira, T. F. & Kao, W. W. Extrinsic and intrinsic mechanisms by which mesenchymal stem cells suppress the immune system. *Ocul. Surf.* **14**, 121–134 (2016).
92. Uccelli, A. & de Rosbo, N. K. The immunomodulatory function of mesenchymal stem cells: mode of action and pathways. *Ann. NY Acad. Sci.* **1351**, 114–126 (2015).
93. Ghannam, S., Pene, J., Moquet-Torcy, G., Jorgensen, C. & Yssel, H. Mesenchymal stem cells inhibit human Th17 cell differentiation and function and induce a T regulatory cell phenotype. *J. Immunol.* **185**, 302–312 (2010).
94. Ghannam, S., Bouffi, C., Djouad, F., Jorgensen, C. & Noel, D. Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. *Stem Cell Res. Ther.* **1**, 2 (2010).
95. Bettelli, E. *et al.* Reciprocal developmental pathways for the generation of pathogenic effector T_H17 and regulatory T cells. *Nature* **441**, 235–238 (2006).
96. Noonan, K. *et al.* A novel role of IL-17-producing lymphocytes in mediating lytic bone disease in multiple myeloma. *Blood* **116**, 3554–3563 (2010).
97. Feyler, S. *et al.* $CD4^+CD25^+FoxP3^+$ regulatory T cells are increased whilst $CD3^+CD4^-CD8^-\alpha\beta TCR^+$ double negative T cells are decreased in the peripheral blood of patients with multiple myeloma which correlates with disease burden. *Br. J. Haematol.* **144**, 686–695 (2009).
98. Zelle-Rieser, C. *et al.* T cells in multiple myeloma display features of exhaustion and senescence at the tumor site. *J. Hematol. Oncol.* **9**, 116 (2016).
99. Giuliani, N. *et al.* Human myeloma cells stimulate the receptor activator of nuclear factor-kappa B ligand (RANKL) in T lymphocytes: a potential role in multiple myeloma bone disease. *Blood* **100**, 4615–4621 (2002).
100. Roussou, M. *et al.* Increased expression of macrophage inflammatory protein-1α on trephine biopsies correlates with extensive bone disease, increased angiogenesis and advanced stage in newly diagnosed patients with multiple myeloma. *Leukemia* **23**, 2177–2181 (2009).
101. Gorgun, G. T. *et al.* Tumor-promoting immune-suppressive myeloid-derived suppressor cells in the multiple myeloma microenvironment in humans. *Blood* **121**, 2975–2987 (2013).
102. Gabrilovich, D. I. & Nagaraj, S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat. Rev. Immunol.* **9**, 162–174 (2009).
103. Kawano, Y. *et al.* Characterization of the role of regulatory T cells (T_{regs}) in inducing progression of multiple myeloma. *Blood* **126**, 502 (2015).
104. Sallman, D. A., Cluzeau, T., Basiorka, A. A. & List, A. Unraveling the pathogenesis of MDS: the NLRP3 inflammasome and pyroptosis drive the MDS phenotype. *Front. Oncol.* **6**, 151 (2016).
105. Basiorka, A. A. *et al.* The NLRP3 inflammasome functions as a driver of the myelodysplastic syndrome phenotype. *Blood* **128**, 2960–2975 (2016).
106. Xin, J. *et al.* Necroptosis in spontaneously-mutated hematopoietic cells induces autoimmune bone marrow failure in mice. *Haematologica* **102**, 295–307 (2017).
107. Tirosh, I. *et al.* Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq. *Science* **352**, 189–196 (2016).
108. Testa, U., Labbaye, C., Castelli, G. & Pelosi, E. Oxidative stress and hypoxia in normal and leukemic stem cells. *Exp. Hematol.* **44**, 540–560 (2016).
109. Laukka, T. *et al.* Fumarate and succinate regulate expression of hypoxia-inducible genes via TET enzymes. *J. Biol. Chem.* **291**, 4256–4265 (2016).
110. Passaro, D. *et al.* Increased vascular permeability in the bone marrow microenvironment contributes to disease progression and drug response in acute myeloid leukemia. *Cancer Cell* **32**, 324–341 (2017).
111. Teofili, L. *et al.* Endothelial progenitor cell dysfunction in myelodysplastic syndromes: possible contribution of a defective vascular niche to myelodysplasia. *Neoplasia* **17**, 401–409 (2015).
112. Colla, S. *et al.* Low bone marrow oxygen tension and hypoxia-inducible factor-1α overexpression characterize patients with multiple myeloma: role on the transcriptional and proangiogenic profiles of $CD138^+$ cells. *Leukemia* **24**, 1967–1970 (2010).
113. Azab, A. K. *et al.* Hypoxia promotes dissemination of multiple myeloma through acquisition of epithelial to mesenchymal transition-like features. *Blood* **119**, 5782–5794 (2012).
114. Glavey, S. V. *et al.* Proteomic characterization of human multiple myeloma bone marrow extracellular matrix. *Leukemia* **31**, 2426–2434 (2017).

115. Yang, Y. *et al.* Soluble syndecan-1 promotes growth of myeloma tumors *in vivo*. *Blood* **100**, 610–617 (2002).
116. Foroushani, A. *et al.* Large-scale gene network analysis reveals the significance of extracellular matrix pathway and homeobox genes in acute myeloid leukemia: an introduction to the Pigengene package and its applications. *BMC Med. Genom.* **10**, 16 (2017).
117. Mateos, M. V. *et al.* Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N. Engl. J. Med.* **369**, 438–447 (2013).
118. Zorat, F. *et al.* The clinical and biological effects of thalidomide in patients with myelodysplastic syndromes. *Br. J. Haematol.* **115**, 881–894 (2001).
119. Aguayo, A., Giles, F. & Albitar, M. Vascularity, angiogenesis and angiogenic factors in leukemias and myelodysplastic syndromes. *Leuk. Lymphoma* **44**, 213–222 (2003).
120. Ebert, B. L. *et al.* An erythroid differentiation signature predicts response to lenalidomide in myelodysplastic syndrome. *PLoS Med.* **5**, e35 (2008).
121. Lu, L. *et al.* The anti-cancer drug lenalidomide inhibits angiogenesis and metastasis via multiple inhibitory effects on endothelial cell function in normoxic and hypoxic conditions. *Microvasc. Res.* **77**, 78–86 (2009).
122. Kronke, J. *et al.* Lenalidomide induces ubiquitination and degradation of CK1α in del(5q) MDS. *Nature* **523**, 183–188 (2015).
123. Kronke, J. *et al.* Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science* **343**, 301–305 (2014).
124. Oliva, E. N. *et al.* Lenalidomide in International Prognostic Scoring System Low and Intermediate-1 risk myelodysplastic syndromes with del(5q): an Italian phase II trial of health-related quality of life, safety and efficacy. *Leuk. Lymphoma* **54**, 2458–2465 (2013).
125. Wang, E. S. *et al.* A randomized, double-blind, placebo-controlled phase 2 study evaluating the efficacy and safety of romiplostim treatment of patients with low or intermediate-1 risk myelodysplastic syndrome receiving lenalidomide. *J. Hematol. Oncol.* **5**, 71 (2012).
126. Swami, A. *et al.* Engineered nanomedicine for myeloma and bone microenvironment targeting. *Proc. Natl Acad. Sci. USA* **111**, 10287–10292 (2014).
127. Rajkumar, S. V. & Kyle, R. A. Angiogenesis in multiple myeloma. *Semin. Oncol.* **28**, 560–564 (2001).
128. Palumbo, A. *et al.* Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N. Engl. J. Med.* **375**, 754–766 (2016).
129. Dimopoulos, M. A. *et al.* Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N. Engl. J. Med.* **375**, 1319–1331 (2016).
130. Lonial, S. *et al.* Elotuzumab therapy for relapsed or refractory multiple myeloma. *N. Engl. J. Med.* **373**, 621–631 (2015).
131. Ansell, S. M. *et al.* PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N. Engl. J. Med.* **372**, 311–319 (2015).
132. Topalian, S. L. *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* **366**, 2443–2454 (2012).
133. Akbay, E. A. *et al.* Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. *Cancer Discov.* **3**, 1355–1363 (2013).
134. Benson, D. M. Jr *et al.* The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody. *Blood* **116**, 2286–2294 (2010).
135. Rosenblatt, J. *et al.* PD-1 blockade by CT-011, anti-PD-1 antibody, enhances *ex vivo* T-cell responses to autologous dendritic cell/myeloma fusion vaccine. *J. Immunother.* **34**, 409–418 (2011).
136. Atanackovic, D., Luetkens, T. & Kroger, N. Coinhibitory molecule PD-1 as a potential target for the immunotherapy of multiple myeloma. *Leukemia* **28**, 993–1000 (2014).
137. Badros, A. *et al.* Pembrolizumab, pomalidomide, and low-dose dexamethasone for relapsed/refractory multiple myeloma. *Blood* **130**, 1189–1197 (2017).
138. Ayed, A. O., Chang, L. J. & Moreb, J. S. Immunotherapy for multiple myeloma: current status and future directions. *Crit. Rev. Oncol. Hematol.* **96**, 399–412 (2015).
139. Cheah, C. Y., Fowler, N. H. & Neelapu, S. S. Targeting the programmed death-1/programmed death-ligand 1 axis in lymphoma. *Curr. Opin. Oncol.* **27**, 384–391 (2015).
140. Jelinek, T. & Hajek, R. PD-1/PD-L1 inhibitors in multiple myeloma: the present and the future. *Oncoimmunology* **5**, e1254856 (2016).
141. [No authors listed] FDA alerts healthcare professionals and oncology clinical investigators about two clinical trials on hold evaluating KEYTRUDA® (pembrolizumab) in patients with multiple myeloma. *US Food and Drug Administration* https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm (2017).
142. Agazzi, A. Report on the 56th ASH Annual Meeting, San Francisco, 4–9 December 2014. *ecancermedicalscience* **9**, 514 (2015).
143. Atanackovic, D., Radhakrishnan, S. V., Bhardwaj, N. & Luetkens, T. Chimeric antigen receptor (CAR) therapy for multiple myeloma. *Br. J. Haematol.* **172**, 685–698 (2016).
144. Abe-Suzuki, S. *et al.* CXCL12 + stromal cells as bone marrow niche for CD34 + hematopoietic cells and their association with disease progression in myelodysplastic syndromes. *Lab. Invest.* **94**, 1212–1223 (2014).
145. Zhang, Y. *et al.* SDF-1/CXCR4 axis in myelodysplastic syndromes: correlation with angiogenesis and apoptosis. *Leuk. Res.* **36**, 281–286 (2012).
146. Sison, E. A., McIntyre, E., Magoon, D. & Brown, P. Dynamic chemotherapy-induced upregulation of CXCR4 expression: a mechanism of therapeutic resistance in pediatric AML. *Mol. Cancer Res.* **11**, 1004–1016 (2013).
147. Ludwig, H. *et al.* Olaptesed pegol, an anti-CXCL12/SDF-1 Spiegelmer, alone and with bortezomib dexamethasone in relapsed/refractory multiple myeloma: a phase IIa study. *Leukemia* **31**, 997–1000 (2017).
148. Uy, G. L. *et al.* A phase 1/2 study of chemosensitization with the CXCR4 antagonist plerixafor in relapsed or refractory acute myeloid leukemia. *Blood* **119**, 3917–3924 (2012).
149. Morgan, G. J. *et al.* Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. *Lancet Oncol.* **12**, 743–752 (2011).
150. D'Arena, G. *et al.* Pamidronate versus observation in asymptomatic myeloma: final results with long-term follow-up of a randomized study. *Leuk. Lymphoma* **52**, 771–775 (2011).
151. Dong, M. *et al.* Phase III clinical study of zoledronic acid in the treatment of pain induced by bone metastasis from solid tumor or multiple myeloma [Chinese]. *Zhonghua Zhong Liu Za Zhi* **30**, 215–220 (2008).
152. Rosen, L. S. *et al.* Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* **98**, 1735–1744 (2003).
153. Musto, P. *et al.* Pamidronate reduces skeletal events but does not improve progression-free survival in early-stage untreated myeloma: results of a randomized trial. *Leuk. Lymphoma* **44**, 1545–1548 (2003).
154. Iyer, S. P. *et al.* A phase IB multicentre dose-determination study of BHQ880 in combination with anti-myeloma therapy and zoledronic acid in patients with relapsed or refractory multiple myeloma and prior skeletal-related events. *Br. J. Haematol.* **167**, 366–375 (2014).
155. Qian, J. *et al.* Dickkopf-1 (DKK1) is a widely expressed and potent tumor-associated antigen in multiple myeloma. *Blood* **110**, 1587–1594 (2007).
156. Vij, R. *et al.* An open-label, phase 2 trial of denosumab in the treatment of relapsed or plateau-phase multiple myeloma. *Am. J. Hematol.* **84**, 650–656 (2009).
157. Ghobrial, I. M. & Landgren, O. How I treat smoldering multiple myeloma. *Blood* **124**, 3380–3388 (2014).
158. Stasi, R. & Amadori, S. Infliximab chimaeric anti-tumour necrosis factor alpha monoclonal antibody treatment for patients with myelodysplastic syndromes. *Br. J. Haematol.* **116**, 334–337 (2002).
159. Scott, B. L. *et al.* Anti-thymocyte globulin plus etanercept as therapy for myelodysplastic syndromes (MDS): a phase II study. *Br. J. Haematol.* **149**, 706–710 (2010).
160. Scott, B. L. *et al.* Prolonged responses in patients with MDS and CMML treated with azacitidine and etanercept. *Br. J. Haematol.* **148**, 944–947 (2010).
161. Garcia-Manero, G. *et al.* A phase 2, randomized, double-blind, multicenter study comparing siltuximab plus best supportive care (BSC) with placebo plus BSC in anemic patients with International Prognostic Scoring System low- or intermediate-1-risk myelodysplastic syndrome. *Am. J. Hematol.* **89**, E156–E162 (2014).
162. Magarotto, V., Salvini, M., Bonello, F., Bringhen, S. & Palumbo, A. Strategy for the treatment of multiple myeloma utilizing monoclonal antibodies: a new era begins. *Leuk. Lymphoma* **57**, 537–556 (2016).
163. Orlowski, R. Z. *et al.* A phase 2, randomized, double-blind, placebo-controlled study of siltuximab (anti-IL-6 mAb) and bortezomib versus bortezomib alone in patients with relapsed or refractory multiple myeloma. *Am. J. Hematol.* **90**, 42–49 (2015).
164. Shah, J. J. *et al.* Siltuximab (CNTO 328) with lenalidomide, bortezomib and dexamethasone in newly-diagnosed, previously untreated multiple myeloma: an open-label phase I trial. *Blood Cancer J.* **6**, e396 (2016).
165. van Rhee, F. *et al.* A phase 2, open-label, multicenter study of the long-term safety of siltuximab (an anti-interleukin-6 monoclonal antibody) in patients with multicentric Castleman disease. *Oncotarget* **6**, 30408–30419 (2015).
166. Carrancio, S. *et al.* An activin receptor IIA ligand trap promotes erythropoiesis resulting in a rapid induction of red blood cells and haemoglobin. *Br. J. Haematol.* **165**, 870–882 (2014).
167. Giagounidis, A. *et al.* Luspatercept treatment leads to long term increases in hemoglobin and reductions in transfusion burden in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS): preliminary results from the phase 2 PACE-MDS extension study. *Blood* **126**, 92 (2015).
168. Dussiot, M. *et al.* An activin receptor IIA ligand trap corrects ineffective erythropoiesis in beta-thalassemia. *Nat. Med.* **20**, 398–407 (2014).
169. Mies, A. & Platzbecker, U. Increasing the effectiveness of hematopoiesis in myelodysplastic syndromes: erythropoiesis-stimulating agents and transforming growth factor-beta superfamily inhibitors. *Semin. Hematol.* **54**, 141–146 (2017).
170. McMillin, D. W. *et al.* Tumor cell-specific bioluminescence platform to identify stroma-induced changes to anticancer drug activity. *Nat. Med.* **16**, 483–489 (2010).
171. Straussman, R. *et al.* Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature* **487**, 500–504 (2012).
172. Yaccoby, S. *et al.* Myeloma interacts with the bone marrow microenvironment to induce osteoclastogenesis and is dependent on osteoclast activity. *Br. J. Haematol.* **116**, 278–290 (2002).
173. Wang, J. *et al.* Bone marrow stromal cell-derived exosomes as communicators in drug resistance in multiple myeloma cells. *Blood* **124**, 555–566 (2014).
174. Tai, Y. T. *et al.* CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. *Leukemia* **28**, 155–165 (2014).
175. Roccaro, M. *et al.* Stroma-derived exosomes mediate oncogenesis in multiple myeloma *Blood* **118**, 625 (2011).
176. Maiso, P. *et al.* Metabolic signature identifies novel targets for drug resistance in multiple myeloma. *Cancer Res.* **75**, 2071–2082 (2015).
177. Hu, J. *et al.* Targeting the multiple myeloma hypoxic niche with TH-302, a hypoxia-activated prodrug. *Blood* **116**, 1524–1527 (2010).
178. Laubach, J. *et al.* Preliminary safety and efficacy of TH-302, an investigational hypoxia-activated prodrug, combined with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma (RR MM) [abstract]. *J. Clin. Oncol.* **32** (Suppl.), 8534 (2014).
179. Bajaj, J. *et al.* CD98-mediated adhesive signaling enables the establishment and propagation of acute myelogenous leukemia. *Cancer Cell* **30**, 792–805 (2016).
180. Carter, B. Z. *et al.* Anti-apoptotic ARC protein confers chemoresistance by controlling leukemia-microenvironment interactions through a NFκB/IL1β signaling network. *Oncotarget* **7**, 20054–20067 (2016).
181. Stone, R. M. *et al.* Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N. Engl. J. Med.* **377**, 454–464 (2017).
182. Ghiaur, G. & Levis, M. Mechanisms of Resistance to FLT3 Inhibitors and the Role of the Bone Marrow Microenvironment. *Hematol. Oncol. Clin. North Am.* **31**, 681–692 (2017).

183. Verstovsek, S. *et al.* Clinical relevance of vascular endothelial growth factor receptors 1 and 2 in acute myeloid leukaemia and myelodysplastic syndrome. *Br. J. Haematol.* **118**, 151–156 (2002).
184. Hu, Q. *et al.* Soluble vascular endothelial growth factor receptor 1, and not receptor 2, is an independent prognostic factor in acute myeloid leukemia and myelodysplastic syndromes. *Cancer* **100**, 1884–1891 (2004).
185. Verburgh, E. *et al.* Additional prognostic value of bone marrow histology in patients subclassified according to the International Prognostic Scoring System for myelodysplastic syndromes. *J. Clin. Oncol.* **21**, 273–282 (2003).
186. Stoddart, A. *et al.* Inhibition of WNT signaling in the bone marrow niche prevents the development of MDS in the $Apc^{del/+}$ MDS mouse model. *Blood* **129**, 2959–2970 (2017).
187. Shastri, A., Will, B., Steidl, U. & Verma, A. Stem and progenitor cell alterations in myelodysplastic syndromes. *Blood* **129**, 1586–1594 (2017).
188. Chen, X. *et al.* Induction of myelodysplasia by myeloid-derived suppressor cells. *J. Clin. Invest.* **123**, 4595–4611 (2013).
189. Chauhan, D. *et al.* Functional interaction of plasmacytoid dendritic cells with multiple myeloma cells: a therapeutic target. *Cancer Cell* **16**, 309–323 (2009).
190. Ray, A. *et al.* A novel agent SL-401 induces anti-myeloma activity by targeting plasmacytoid dendritic cells, osteoclastogenesis and cancer stem-like cells. *Leukemia* **31**, 2652–2660 (2017).
191. Vercauteren, S. M. *et al.* T cells of patients with myelodysplastic syndrome are frequently derived from the malignant clone. *Br. J. Haematol.* **156**, 409–412 (2012).
192. Epling-Burnette, P. K. *et al.* Prevalence and clinical association of clonal T-cell expansions in myelodysplastic syndrome. *Leukemia* **21**, 659–667 (2007).
193. Singhal, S. *et al.* Antitumor activity of thalidomide in refractory multiple myeloma. *N. Engl. J. Med.* **341**, 1565–1571 (1999).
194. Weber, D. *et al.* Lenalidomide plus high-dose dexamethasone provides improved overall survival compared to high-dose dexamethasone alone for relapsed or refractory multiple myeloma (MM): results of a North American phase III study (MM-009) [abstract]. *J. Clin. Oncol.* **24**, (Suppl.), 7521 (2006).
195. Dimopoulos, M. *et al.* Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N. Engl. J. Med.* **357**, 2123–2132 (2007).
196. Lonial, S. *et al.* Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. *J. Clin. Oncol.* **30**, 1953–1959 (2012).
197. Lesokhin, A. A. *et al.* Preliminary results of a phase I study of nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies. *Blood* **124**, 291 (2014).
198. Sidaway, P. Haematological cancer: Pembrolizumab is effective in multiple myeloma. *Nat. Rev. Clin. Oncol.* **14**, 393 (2017).
199. Davids, M. S. *et al.* Ipilimumab for patients with relapse after allogeneic transplantation. *N. Engl. J. Med.* **375**, 143–153 (2016).
200. Noonan, K. A. *et al.* Adoptive transfer of activated marrow-infiltrating lymphocytes induces measurable antitumor immunity in the bone marrow in multiple myeloma. *Sci. Transl Med.* **7**, 288ra78 (2015).
201. Pyzer, A. R., Avigan, D. E. & Rosenblatt, J. Clinical trials of dendritic cell-based cancer vaccines in hematologic malignancies. *Hum. Vaccin. Immunother.* **10**, 3125–3131 (2014).
202. Rosenblatt, J. *et al.* Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients. *Clin. Cancer Res.* **19**, 3640–3648 (2013).
203. Ghobrial, I. *et al.* Phase I trial of plerixafor and bortezomib as a chemosensitization strategy in relapsed or relapsed/refractory multiple myeloma. *Blood* **118**, 1874 (2011).

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