Metastasis

Metastasis

- Metastatic organotropism may be encoded by genetic traits and arise in primary tumours by various mechanisms
- Bone and bone marrow are frequently affected by metastasis from cancers in multiple organs, including breast, prostate, colon, lung, bladder, kidney and head and neck
- bone marrow-derived $VEGFR1^{+}$ cells can be mobilized by primary tumours and recruited to the lungs before the arrival of metastatic cancer cells

Bone metastasis

- three-quarters of patients with advanced metastatic disease and can contribute to further tumor dissemination, as tumor cells from bone metastases can seed secondary metastases
- The bone is essential in modulating metastasis in many cancers, even those that metastasize to distant sites
- BM can be altered by a distant tumor and consequently supplies potential metastatic sites with BM-derived cells that support the formation of a pre-metastatic niche (preMN), a phenomenon we refer to as ‘bone-mediated metastatic spread’

Bone microenvironment

Stromal Cells	Effect on metastasis
MSCs	• Mediates tumor homing and colonization • Regulation of dormancy • Enhancement of tumor growth • Secretion of tumor-supportive extracellular vesicles • Immune evasion • Supports the mobilization of HSCs in preMN formation and emergency myelopoiesis
Fibroblasts	• PreMN formation • Chemotaxis, adhesion and colonization • Bone pain • Dormancy escape • Immune evasion, • Angiogenesis • Correlate with bone metastasis
Endothelial cells	• Angiogenesis, vasculature remodeling, increase in vasculature leakiness • Regulation of dormancy • Therapeutic resistance
Adipocytes	• Tumor cell proliferation and survival • Metastatic seeding and migration • Therapeutic resistance • Enhanced apoptosis of tumor cells • Immune evasion

Bone microenvironment

Stromal Cells	Effect on metastasis
Osteoblasts	• Chemoattractant for cancer cells and involved in tumor cell adhesion • Osteolytic lesions, • Osteosclerotic lesions • Dormancy
Osteoclasts	• Formation of osteolytic lesions • Dormancy escape • Bone remodeling
Osteocytes	• Tumor cell proliferation, • Tumor cell migration • Bone remodeling • Pro- and anti-tumor effects • Induction of quiescence
Pericytes	• PreMN formation, pro-metastatic vascular niche formation[a] • Dormancy and resistance • Modulation of immune responses[a] • Angiogenesis[a], • Regulation of vasculature permeability
Neurons	• Tumor migration • Tumor proliferation • Bone pain • Regulation of preMN formation[a] • Immune modulation[a]

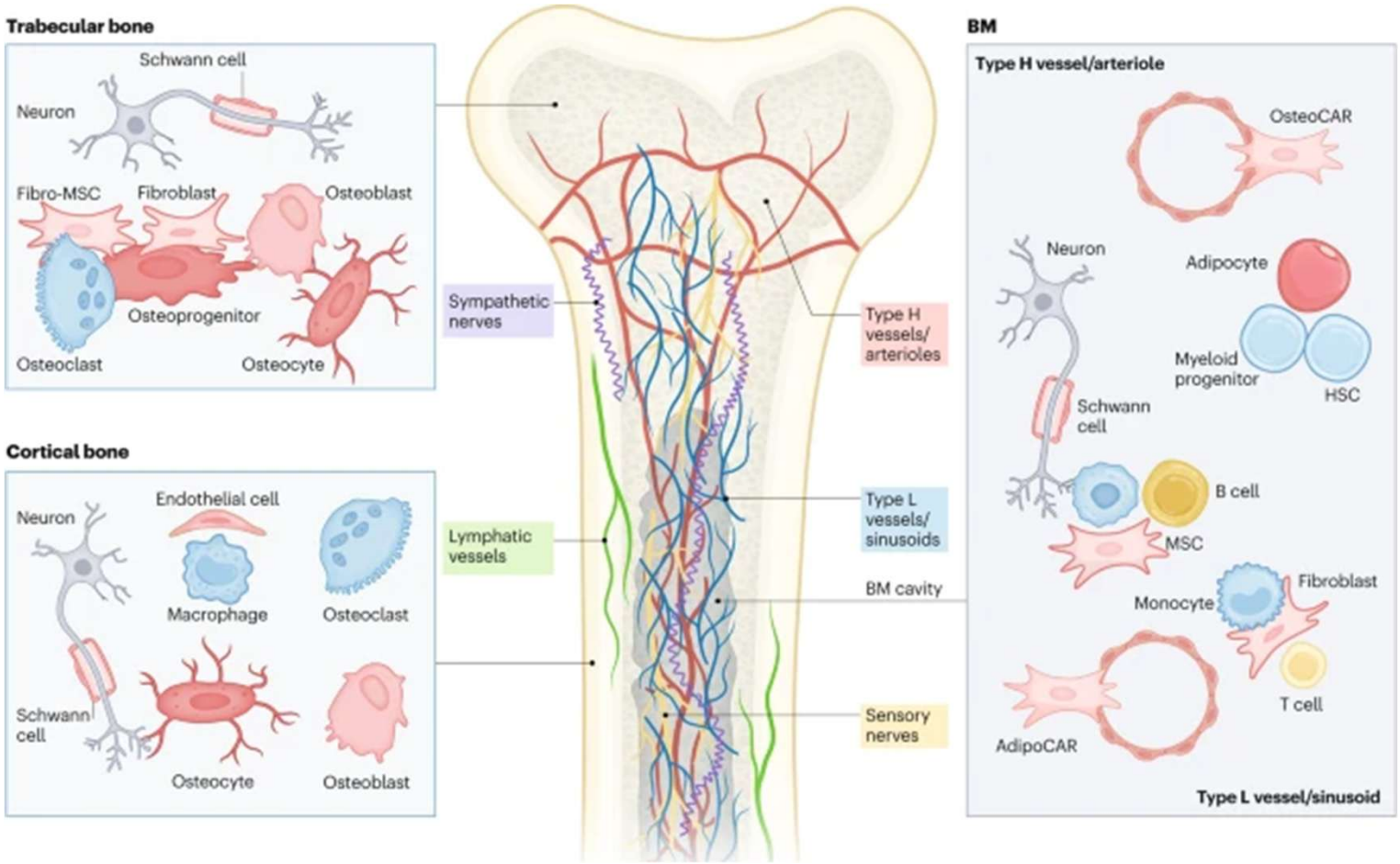
Bone microenvironment

Immune Cells	Effect on metastasis
HSCs	• Angiogenesis and vasculature remodeling • Competition with tumor cells • Immune modulation
Platelets	• Proliferation, • Migration and homing • Circulating tumor cell adhesion and survival • Extravasation • Angiogenesis • Formation of osteolytic lesions
B cells	• Immunosuppression or immune activation • Increase metastatic progression • Anti-tumor effects
T cells	• PreMN formation • Tumor cell killing • Formation of osteolytic lesions • Vascular remodeling[a]
NK cells	• Anti-tumor effects • Tumor cell killing • Bone remodeling • Upregulate EMT in tumor cells • Promote metastatic outgrowtha • Immunomodulation, • Angiogenesis

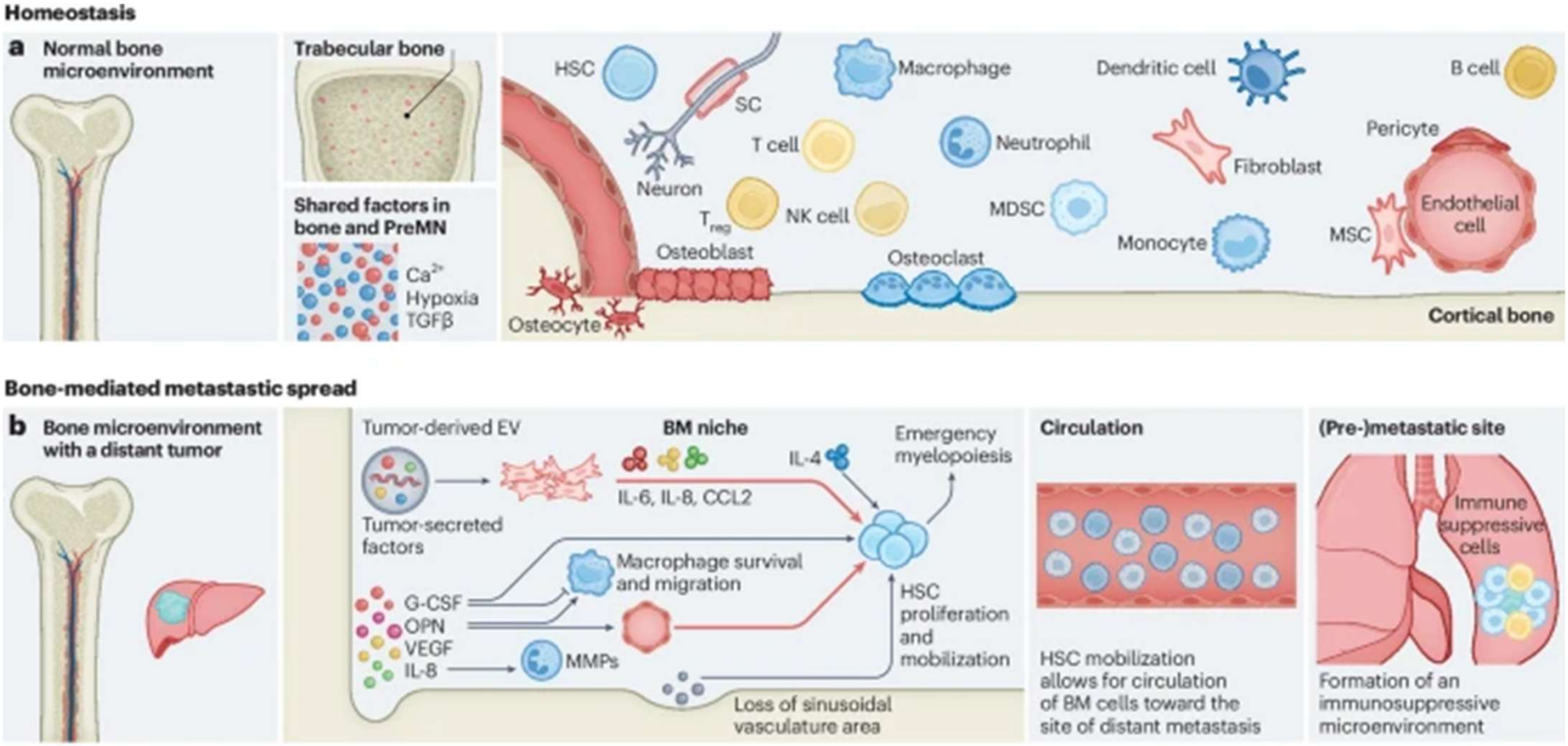
Bone microenvironment

Immune Cells	Effect on metastasis
Neutrophils	• Promoting and suppressing metastasis • Angiogenesis • Tumor cell dissemination, • Regulation of dormancy
MDSCs	• Priming of additional metastatic sites • PreMN formation • Promote angiogenesis, • Tumor cell proliferation • Osteolysis
DCs	• Tumor killing • Immune evasion, • Angiogenesis
Monocytes	• Immunosuppression • Tumor killing • Angiogenesis, • ECM remodeling
Macrophages	• Extravasation, • Immune activation or evasion • Tumor colonization • Promote metastatic outgrowth • Tumor-induced bone formation • Promote epithelial-to-mesenchymal transition[a] • Immunomodulation, • Angiogenesis

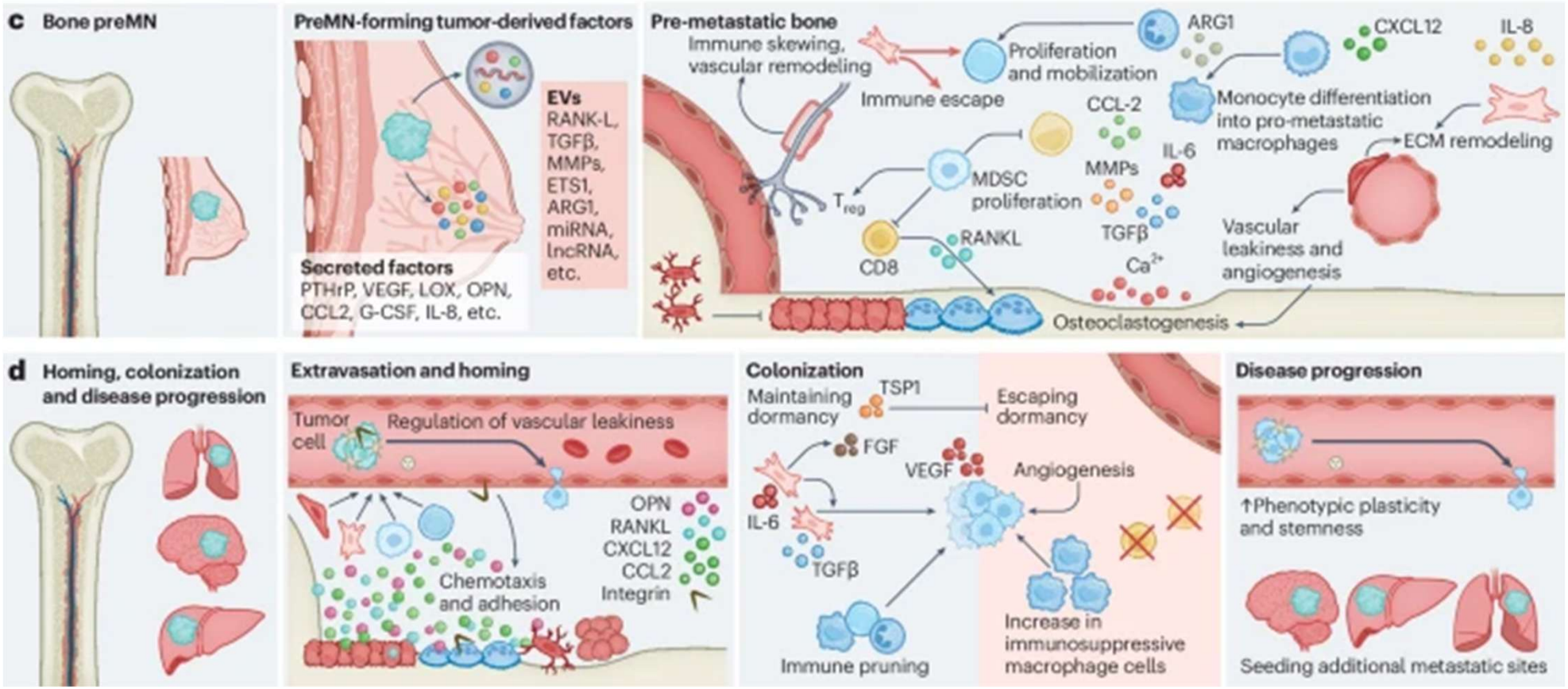
Bone microenvironment



Dysregulation of stromal and immune cell microenvironments throughout bone metastasis



Dysregulation of stromal and immune cell microenvironments throughout bone metastasis



Bone metastasis of breast cancer

- breast tumours skew haematopoiesis towards the myeloid lineage with cells of abnormal functionality
- breast tumours can induce systemic accumulation of immature myeloid cells that are immunosuppressive, known as myeloid-derived suppressor cells (MDSCs)
- organs frequently affected by breast cancer metastasis include bone, lung, brain and liver
- Different breast cancer subtypes exhibit largely different organ preferences: whereas luminal-like tumours (mostly oestrogen receptor positive (ER^+)) tend to metastasize first to bone, basal-like tumours (mostly ER^-, progesterone receptor negative (PR^-) and $HER2^-$, also known as triple negative breast cancer (TNBC)) aggressively disseminate initially to visceral organs, including the lungs

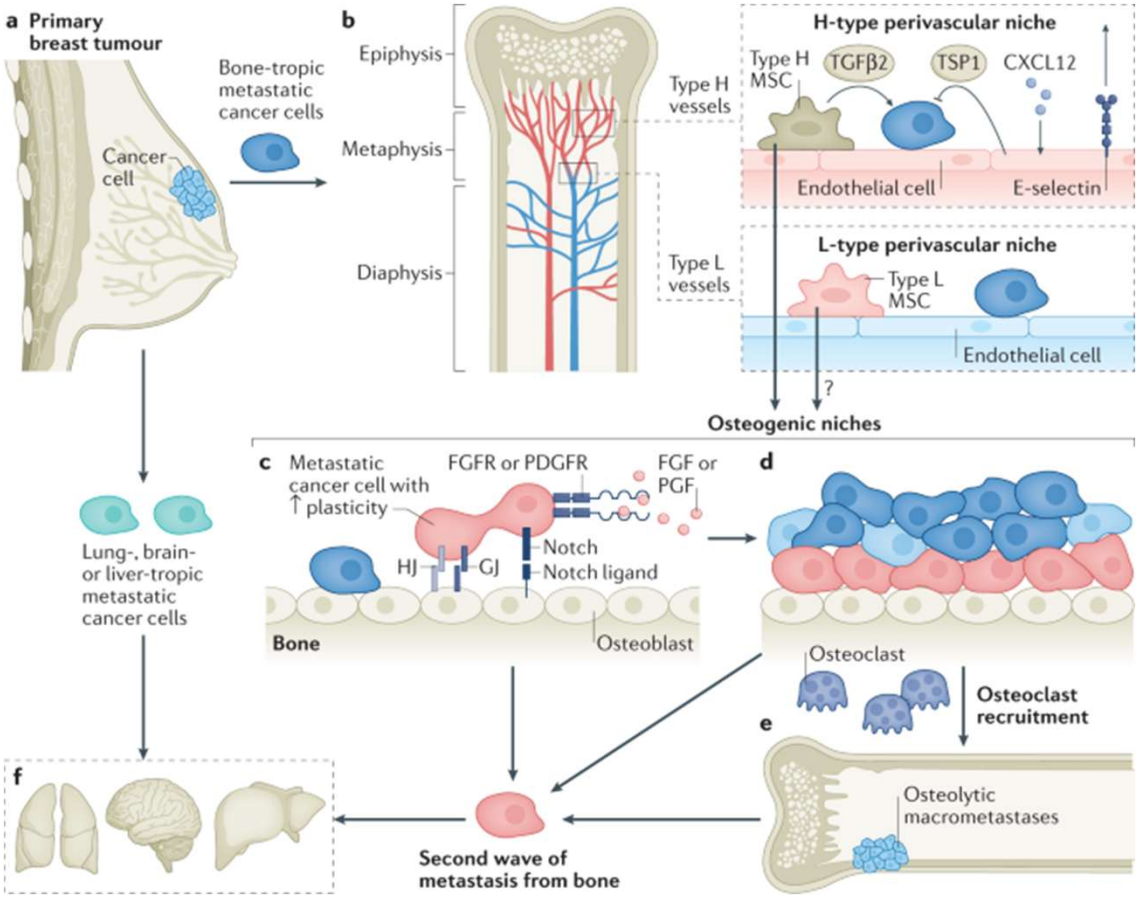
Bone metastasis of breast cancer

- Osteomimicry - mimicry of bone cytokine milieu in the primary tumour may pre-select metastatic seeds that might be ‘primed’ to survive and grow in the BME
- hypothesis - DTCs and HSCs both share and compete for the same niches
- E-selectin and CXCL12 induced the migration of DTCs towards the endosteal surface and the retention of DTCs at the perivascular niche
- perivascular niche renders cancer cells resistant to chemotherapies through integrin signalling

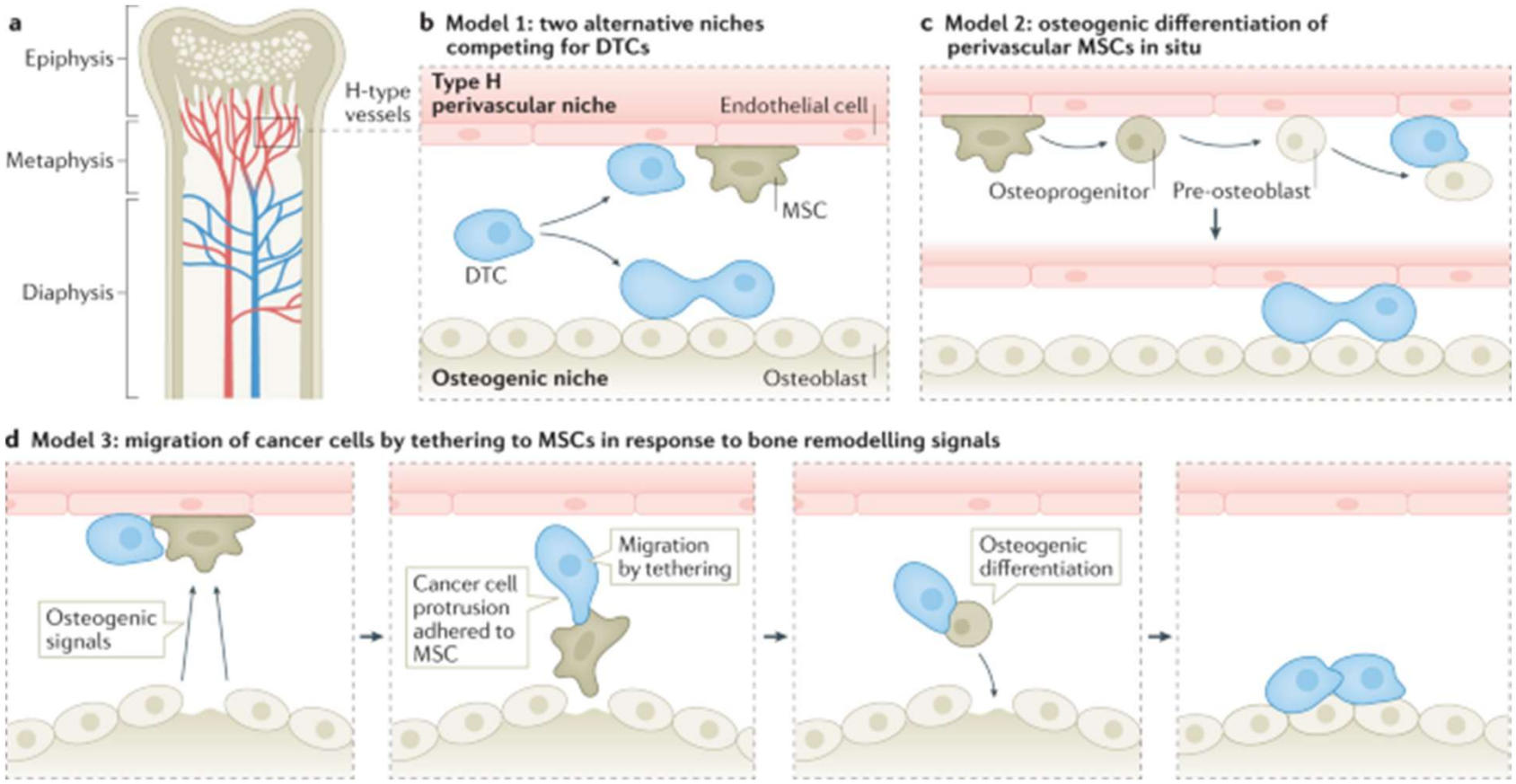
Bone metastasis of breast cancer

- endosteal niche and also hosts HSCs and other haematopoietic progenitor cells
- osteogenic niche may foster metastasis outgrowth, which represents one mechanism for activation of proliferation or the termination of dormancy
- cancer cells can produce PTHrP, which induces osteoblasts to secrete RANKL. The RANKL–RANK pathway is a master regulator of osteoclastogenesis. Resorption of bone matrix by osteoclasts leads to the release of TGFβ and IGFs, which reciprocally act on cancer cells to stimulate further progression

Bone metastasis of breast cancer



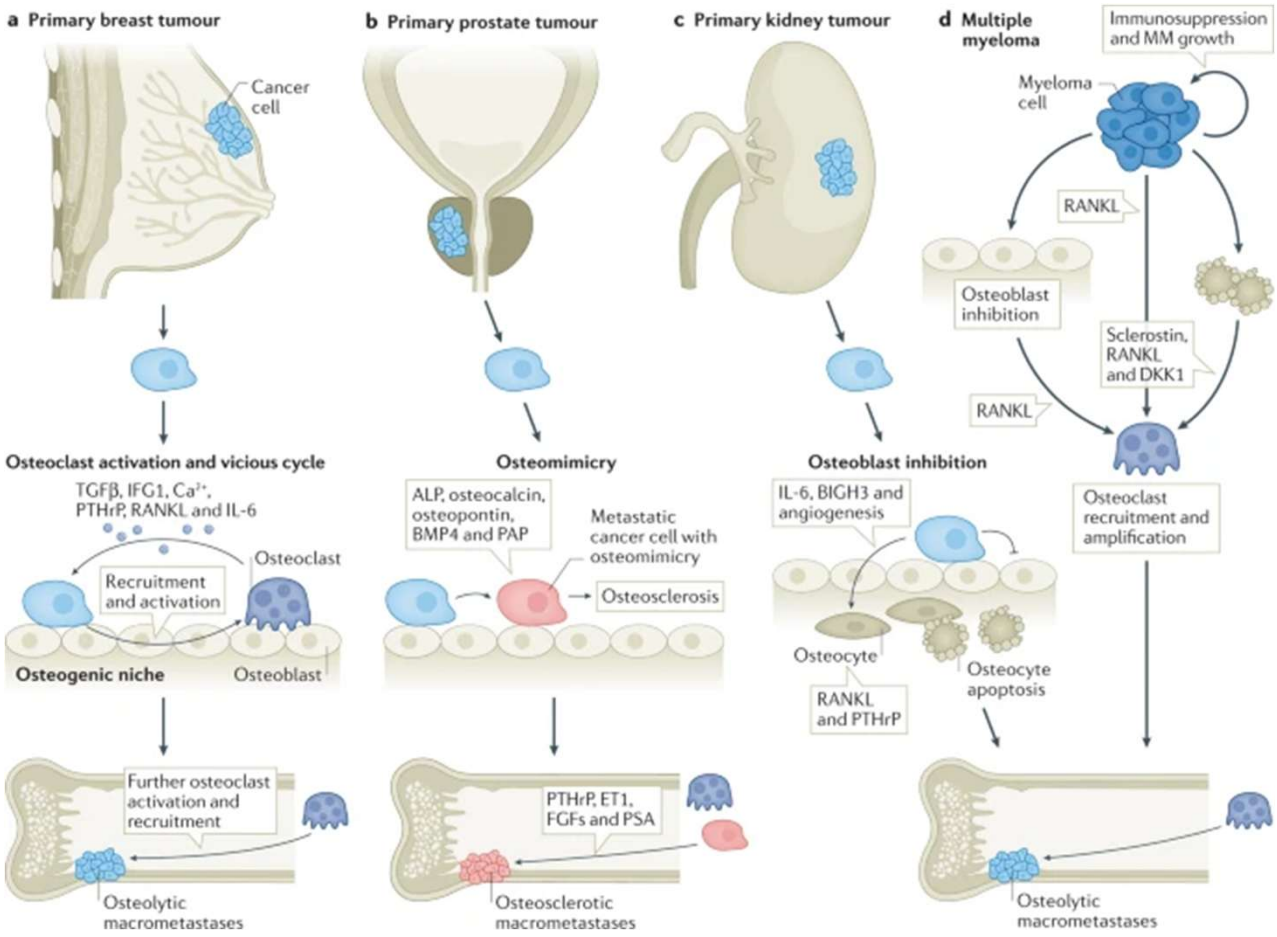
Bone metastasis of breast cancer



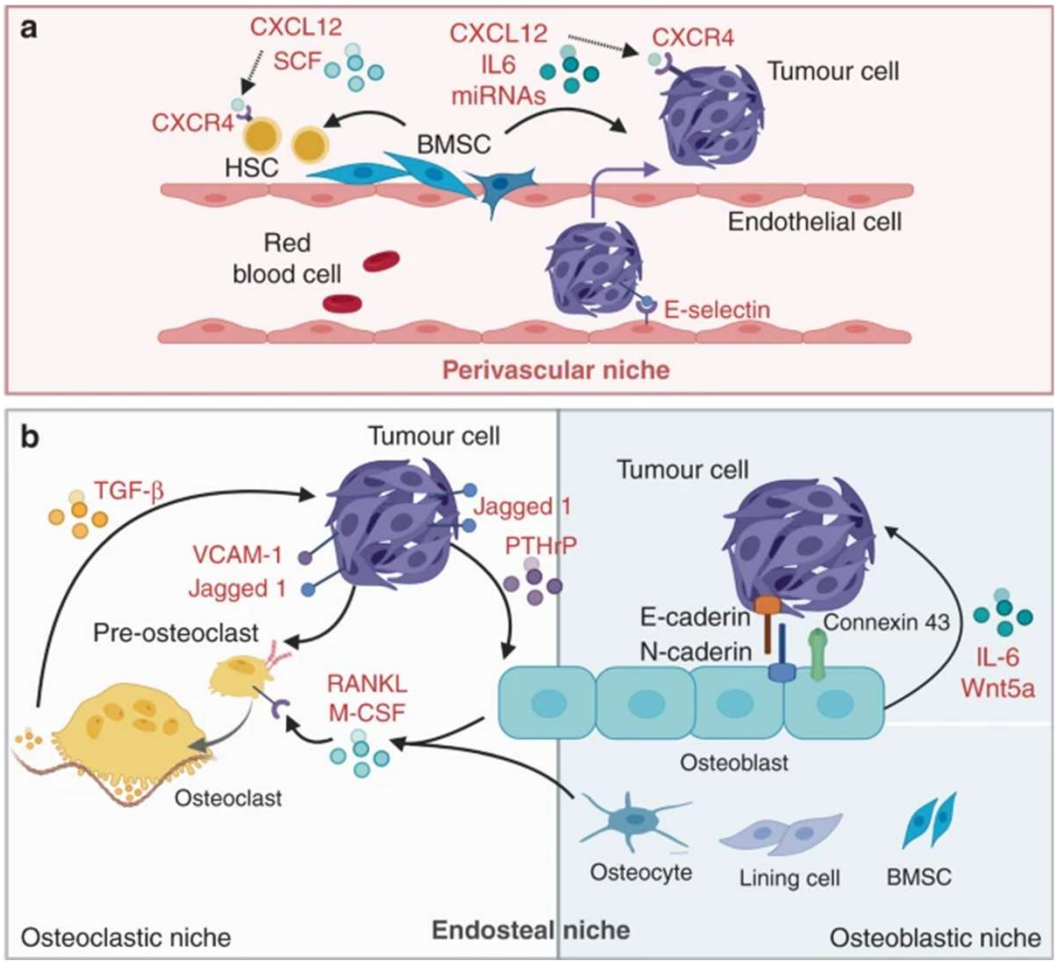
Bone metastasis of breast cancer

- perivascular and osteogenic niches seem to be associated with cellular quiescence and proliferation, respectively, in breast cancer models
- interaction with the BME may confer stemness on DTCs
- strong organotropism of first-site metastasis
- multi-organ distribution of metastases towards the terminal stage of diseases

Bone metastasis in other cancer



Vicious cycle



Bone metastasis -therapy