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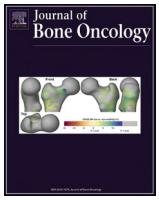

Phenotypic plasticity – Implications for tumours in bone

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A B S T R A C T

Metastasis is a major contributor to cancer patient mortality. Tumour cells often develop phenotypic plasticity to successfully metastasize to different target organs. Recent progress in the study of bone metastasis has provided novel insight into the biological processes that drive the spread and growth of cancer cells in the bone. In this review, we provide a summary of how the bone marrow microenvironment promotes phenotypic plasticity of metastatic tumour cells and alters therapeutic responses. We highlight pivotal transformations in cellular status driven by plasticity, including mesenchymal-epithelial transition, acquisition of stem-like traits, and awakening from dormancy. Additionally, we describe the phenomenon of host-organ mimicry and metabolic rewiring that collectively serve as key attributes of disseminated tumour cells, enabling their successful colonization and growth within the bone marrow microenvironment.

1. Introduction

Metastasis is a multistep process in which cancer cells escape from the primary site and intravasate into the bloodstream. After extravasation and colonization in distant organs, tumour cells survive, exit from dormancy, and start outgrowth in the new environment. Metastasis has long been recognized as a non-random process. In 1889, Stephen Paget observed a preferential pattern of metastatic colonization in autopsies of breast cancer patients and postulated the “seed and soil” hypothesis [1]. It is now widely recognized that different types of cancer are associated with different metastatic tropisms –known as organotropism. For instance, breast cancer and prostate cancer tend to primarily metastasize to the bones, with rates of 65–75 % and 68 %, respectively, while occurrences of brain metastasis are rare. Lung and kidney carcinomas exhibit bone metastasis in approximately 40 % of cases. In contrast, colon cancer tends to metastasize to the liver rather than the bone, with an incidence rate of 8 % for bone metastasis from liver cancers. Furthermore, differential tropism is also observed within various subtypes of breast cancer, where hormone receptor-positive cancers predominantly metastasize to the bone and lymph nodes, whereas basal-like breast cancers are more frequently associated with lung and brain metastases [2,3].

The “seed and soil” hypothesis suggested that the metastatic tumor cells can only survive and grow on congenial and fertile soil. Recent discoveries have shed light on the remarkable adaptability of disseminated tumour cells (DTCs) and the dynamic interplay with their surrounding niche, consistent with Paget’s visionary hypothesis. Phenotypic plasticity refers to reversible transitions between different cellular states, a concept coined in developmental biology that includes processes of differentiation, dedifferentiation, and transdifferentiation. Cancer cell plasticity arises from both cell-intrinsic and cell-extrinsic factors, leading to intratumour heterogeneity and fitness. Finally, plasticity becomes a major obstacle to efficacious anti-cancer therapies [3].

In this review we summarize the different types of cancer cell plasticity associated with metastatic colonization in the bone marrow microenvironment. Within the process of bone metastasis, plasticity manifests in diverse forms, encompassing a range of **cellular states** switching between epithelial and mesenchymal, stem-like and more differentiation states, as well as dormant and proliferative states (Fig. 1A). The expression levels of specific markers defining a cellular state are not fixed but rather shaped by the interplay of distinct genetic and epigenetic programs within the surrounding environment. This plasticity also allows tumour cells to **mimic features** found in normal host tissue, thereby enhancing their capacity to successfully colonize the bone (Fig. 1B). Additionally, metastatic cancer cells further exemplify their plasticity by adapting their **metabolic profiles** in response to the metabolic conditions of bone marrow [3] (Fig. 1C).

2. Plasticity in cellular state

2.1. Mesenchymal-epithelial transition and colonization in the bone

During embryonic development, cells exhibit a high degree of plasticity, allowing them to transition between epithelial and mesenchymal

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states. This dynamic process is central to various cellular behaviors. A shift towards the mesenchymal state, known as epithelial-mesenchymal transition (EMT), alters the adhesion molecules expressed by the cell, facilitating migration and invasion. EMT process is triggered by specific transcription factors, miRNAs, epigenetic changes, and post-translational regulators. Conversely, mesenchymal-epithelial transition (MET) is associated with a return to a more static, epithelial state [3].

Prior research has demonstrated that epithelial-mesenchymal transition was essential for cancer cells to acquire stem cell characteristics and to initiate metastasis. During epithelial-to-mesenchymal transition, cells bearing the hybrid phenotype have been shown to have the highest metastatic potential. While conversely, the process of mesenchymal-epithelial transition is essential for the subsequent stages of metastatic outgrowth [3]. Recent research by Esposito et al. has indicated that E-selectin in the bone vascular niche plays a pivotal role in promoting bone metastasis (Fig. 1A). Endothelial cell-expressing E-selectin binds directly to fucosylated Glg1 in cancer cells, inducing a non-canonical MET program and activating the Wnt signaling pathway in tumour cells [4]. Cancer cells exhibit elevated expression of epithelial marker EpCam and Keratin-14, whereas traditional EMT regulators like Snail1/2, Twist1/2 and Zeb1/2, remain unchanged. Wang et al. identified the role of heterotypic adherent junctions in driving tumour growth in bone. Cancer-derived E-cadherin and osteoblast derived N-cadherin can activate mTOR pathway in cancer cells to promote metastatic growth in bone [5]. This data is also consistent with the notion that tumour cells in metastatic outgrowths often resume a clear epithelial phenotype, both morphologically and molecularly (as marked by E-cadherin expression), like their primary counterparts.

2.2. Reprogramming of tumour cell to adopt stem-like traits in bone microenvironment

Stemness is characterized by the capacity for self-renewal and multipotency. During metastatic colonization, disseminated tumour cells (DTCs) may adopt stem-like traits. EMT programs are associated with stem-like traits; however, recent studies have unveiled E-selectin binding not only promotes MET in cancer but also activates Wnt signaling to promote cell stemness and bone metastasis formation through down-regulation of secreted Wnt signaling inhibitors [4]. This allows DTCs to revert to the epithelial state while maintaining high level of cancer stem cell activities, both are required for successful colonization. Using parabiosis and an evolving barcode system, Zhang et al. demonstrated that the bone microenvironment facilitates breast and prostate cancer cells to further develop multi-organ secondary metastases through enhanced EZH2 activity [6]. Estrogen receptor-positive (ER +) breast cancer exhibits a strong preference for metastasizing to the bone. Bado and collaborators discovered that the osteogenic niche transiently and reversibly reduces ER expression and activities specifically in bone micrometastases, resulting in endocrine resistance. Increased EZH2 expression leads to H3K27me3-mediated epigenetic silencing of estrogen receptor α (ERα), driving ER + BMMs toward a basal and stem-like state [7]. These findings highlight how epigenomic adaptation to the bone microenvironment promotes phenotypic plasticity of metastatic seeds and alters therapeutic responses.

2.3. Exit from dormancy and proliferate to form bone metastasis

Another remarkable aspect of cancer cell plasticity is the dormancy of DTCs and their reawakening years after reaching distant sites. At the cellular level, dormancy typically refers to temporary arrest in the growth and division of tumour cells, a state often referred as cellular dormancy. The transition from dormancy to the establishment of bone metastasis involves a shift from a quiescent state to active cell proliferation. This transition is characterized by the downregulation of genes associated with dormancy and the upregulation of genes that promote the cell cycle. Using a dormancy-reactivation model in breast cancer bone metastasis, Lu et al discovered that vascular cell adhesion molecule 1 (VCAM-1), which is produced by the tumour, plays a critical role in facilitating the transition from a state of dormant micrometastasis to active and overt metastasis by attracting and stimulating the differentiation of osteoclast precursors [8].Studies also suggested the involvement of canonical Wnt/β-catenin signaling in cancer cell dormancy.

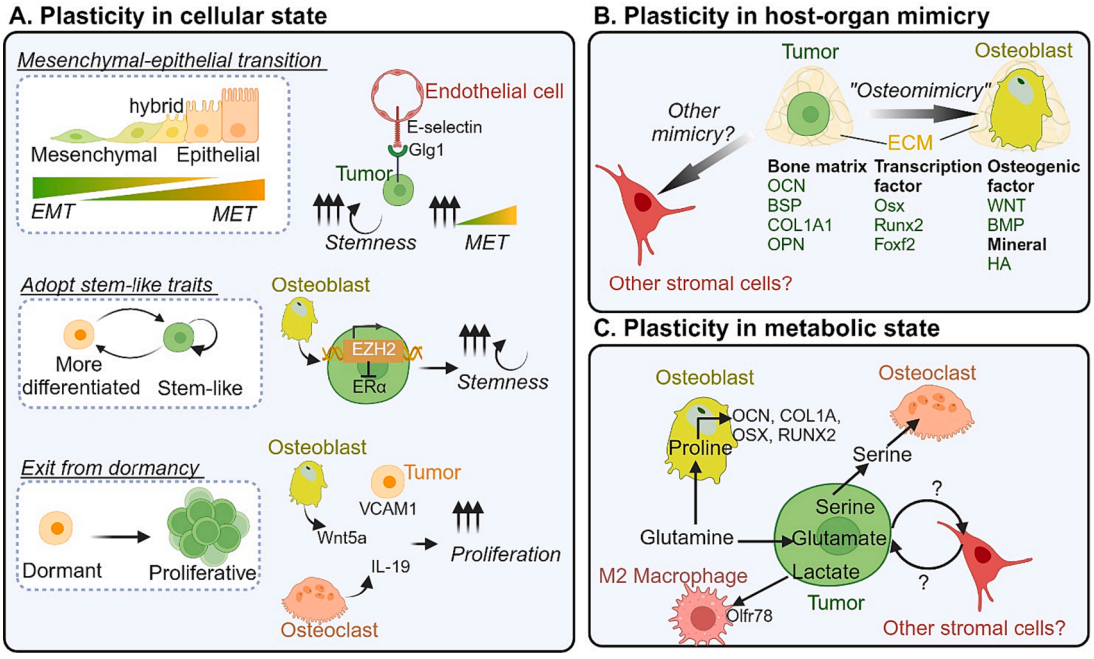

Fig. 1. Cancer cell plasticity in bone marrow microenvironment. Diagrammatic representation of different types of cancer cell plasticity associated with metastatic colonization in bone marrow microenvironment. Plasticity in (A) cellular state, (B) host-organ mimicry, and (C) metabolic state. Abbreviations: EMT: Epithelial-mesenchymal transition; MET: Mesenchymal-epithelial transition; OCN: Osteocalcin; BSP: Bone sialoprotein; COL1A1: Collagen type I alpha 1; OPN: Osteopontin; VCAM1: Vascular cell adhesion molecule1; OSX: Osterix; FOXF2: forkhead box F2; HA: hydroxyapatite.

Recently, Ren et al. reported that Wnt5a from the osteoblastic niche induces dormancy in prostate cancer cells in a reversible manner. This induction is mediated through Siah E3 Ubiquitin Protein Ligase 2 (SIAH2) and receptor tyrosine kinase-like orphan receptor 2 (ROR2) [9]. Osteoclast-secreted IL-19 stimulates IL-20RB–expressing tumour cells and activates downstream JAK1/STAT3 signaling. This stimulation leads to enhanced proliferation of lung cancer cells in bone [10].

When the tumor cells form micrometastatic lesions their growth can be restrained through a phenomenon known as tumor mass dormancy. This state is achieved by a balanced cell proliferation and cell death, largely due to inadequate blood supply and immune surveillance [11]. Overgrowth depletes oxygen and nutrients supplied by the preexisting blood vessels, leading to increased cell death. Pro-angiogenic factors produced by tumor and its microenvironment may wake up dormant tumor cells and facilitate their growth. In addition, an active host immune system could eliminate cancer cells or maintain their dormant status, causing immunogenic dormancy [11]. However, these dormant cancer cells could evolve to resist immune attacks. A recent study demonstrated that luminal breast cancer cells could secret SCUBE2, stimulating osteogenic niche formation. The osteogenic niche supported tumor survival by protecting the cancer cells from being eliminated by natural killer (NK) cells [12].

3. Plasticity in host-organ mimicry

In clinical practice, mammographic mammary microcalcifications are widely used for breast cancer screening [13]. Studies demonstrated that epithelial cells with mesenchymal characteristics become capable of producing breast microcalcifications and develop typical osteoblast features: expressing molecules typically involved during physiological mineralization (i.e. Collagen type 1 alpha 1 (COL1A1), and osteopontin (OPN)). Deposition of the minerals hydroxyapatite (HA) was also found in primary mammary tumours. In vitro experiment showed HA could enhance tumour cell migration, suggesting potential consequences of calcium deposition [13]. Forkhead box F2 (FOXF2) was found to drives breast cancer cells specifically metastasize to bone, functioning as a key transcription factor to induce epithelial-to-osteomimicry transition by transactivating BMP4/SMAD1 signaling and a set of genes expressed at early stages of bone differentiation, including RUNX2 [14] (Fig. 1B).

In addition to breast cancer cells displaying osteomimicry when forming bone metastases, there was also evidence of osteomimicry in other bone favorable cancer types, such as prostate cancer and lung cancer [2,15]. Two bone matrix proteins, bone sialoprotein (BSP) and osteocalcin (OCN), which typically produced by osteoblasts, were detected in both human prostate cancer and metastatic bone specimens. Notably, the extent of OCN/BSP promoter activation shows a positive correlation with the malignancy of prostate cancer cells [15] (Fig. 1B).

In summary, these findings strongly indicate a shared role for factors in the tumour microenvironment across osteotropic cancers. Tumor cells display osteomimetic properties at primary site, potentially resulting preferential metastasis to the bone, as the cells would be better suited to adapt to the bone microenvironment. Upon reaching the bone, cancer cells produce osteogenic factors to deposit a new, but not yet mineralized, growth factor-rich matrix and then quickly occupied the fertile "soil'. Uncovering these mechanisms and disrupting "mimicry-competition" cycle may lead to novel therapeutic opportunities.

4. Plasticity in metabolic state

During the metastatic cascade, DTCs encounter several environments characterized by distinct metabolites, nutrients, and oxygen availability. As a result, DTCs undergo metabolic rewiring, which involves changes in their ability to use different nutrients for the same metabolic requirement and to process a single metabolic substrate in various ways at specific steps of the metastatic cascade. The efficacy of targeting cancer cell metabolism is exemplified by the longstanding success of chemotherapy, which predominantly targets nucleotide metabolism [3].

Recent studies have provided evidence that underscores the metabolic plasticity of tumours when they metastasize to the bone. Kfoury et al. revealed a strong patient-specific expression differences in human prostate cancer cells from bone metastases. Analysis of intra-tumoural heterogeneity unveiled four key aspects of tumour cell variation shared by different patients. Notably, three aspects reflected variations in metabolic activity related to protein, nucleic acid, and ribosomal metabolism [16].

Additional studies conducted by Vadevoo demonstrated that Olfr78, found on bone marrow–derived macrophages (BMDMs), serves as a sensor for tumour-derived lactate. Olfr78 forms a heterodimer with Gpr132 to enhance its surface expression, thereby facilitating the lactate-induced M2 phenotype of tumour-associated macrophages (TAMs). Notably, the deficiency of Olfr78 led to the inhibition of tumour progression and metastasis while favoring an anti-tumour immune response in vivo [17].

Amino acids play a pivotal role in the identity and function of cells. During the differentiation process, osteoblasts significantly increase the expression of glutamine transporters SLC1A5/ASCT2 and SLC7A7 to facilitate glutamine uptake (Fig. 1C). Glutamine catabolism has been demonstrated to regulate both proliferation and lineage determination of skeletal stem cells, specifically, commit to osteogenesis rather than adipogenesis [18]. Glutamine plays a pivotal role as a precursor to proline, an essential component for the translation of proline-rich bone matrix proteins (such as OCN and COL1A1), as well as other osteoblast-associated proteins (like OSX and RUNX2) [19]. Notably, tumour cells have been identified as primary consumers of glutamine in tumour microenvironments, resulting in a constrained availability of interstitial glutamine. Consequently, it is reasonable to hypothesize that amino acids may become a limiting factor during metastatic outgrowth, potentially impacting the normal functioning of osteoblasts. While evidence suggests a potential cooperation for serine metabolism between osteoclasts and cancer cells. Bone-tropic variant of the MDA-MB-231 human breast cancer cell line significantly upregulated the expression of key genes involved in serine synthesis pathways. Then the excess serine exported into the tumour interstitium can stimulate osteoclast differentiation and bone resorption in vitro [20]. Despite the energetic demands of bone resorption, evidence supports the notion that osteoclasts exhibit greater metabolic adaptability to cope with nutrient limitations within the bone metastatic microenvironment.

In addition to concentrating on the metabolic plasticity linked to amino acids and their impact on osteoblasts and osteoclasts during metastasis, shifts in other metabolic processes, such as glucose and fatty acids, along with variations in metabolic dependencies with other cell types, offer fresh avenues for the treatment of cancers. Small molecule inhibitors or dietary modifications can be harnessed to disrupt these altered metabolic states, presenting promising strategies for therapeutic intervention.

5. Concluding remarks

This review highlights the multifaceted nature of cell plasticity in the context of bone metastasis. Although changes in cell state remains the most widely described example of phenotypic plasticity, recent studies suggest the existence of several other instances of phenotypic alterations that play a role in bone metastasis. The bone niche possesses distinct characteristics that emit signals attracting cancer cells. Do biochemical factors such as specific cytokines and growth factors within the bone, alongside physical attributes like an acidic pH and elevated extracellular calcium levels, confer advantages for tumour plasticity? Can the abundant adipocytes presented in both mammary gland and the aged bone marrow environment be leveraged to transdifferentiate breast cancer cells into adipocyte-like cells, thereby reducing invasion and metastasis? Given that DTCs mirror host-organ properties and become reliant on specific metabolic processes, targeting this phenomenon,

pharmacologically or via diet modification, may offer significant benefits to patients.

The development of single cell technologies and spatial transcriptomic has significantly enhanced our capacity to capture tumour heterogeneity. However, a major limitation still exists in accessing metastatic samples from both patients and spontaneous animal models. Comparing matched primary and metastatic samples from the same individuals with multi-omics will advance our understanding of metastatic disease in an organ-specific context. Plasticity allows tumour cells to transit dynamically between different states, which display distinct responses to drugs, presenting significant therapeutic challenges by promoting drug tolerance and resistance [3].

To effectively target plastic metastatic cells and enhance the efficacy of existing treatments, a set of key questions must be addressed in future research:

- Are there other forms of host-organ mimicry and metabolic plasticity yet to be discovered and characterized?
- How does the immune system influence other aspects of cancer cell plasticity?
- To what extent does the metabolic environment of the host organ reprogram the metabolism of DTCs, potentially leading to organ-specific metabolic dependencies?
- Could the heterogeneity of cancer cell plasticity in metastatic sites underlie drug resistance?
- How do mechanical forces shape the plasticity of cancer cell in bone? Is there any crosstalk between cancer cells and osteocytes, the major mechanosensory cells?

CRediT authorship contribution statement

Yujiao Han: Writing – original draft. **Yibin Kang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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