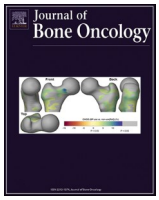
J BONE ONCOL 47 (2024) 100621

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo



Bone niches in the regulation of tumour cell dormancy

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ARTICLE INFO

Keywords:
Bone metastasis
Tumour cell dormancy
Bone niches
Bone stromal cells
Osteoblasts
Osteoclasts

ABSTRACT

Secondary metastases, accounting for 90 % of cancer-related deaths, pose a formidable challenge in cancer treatment, with bone being a prevalent site. Importantly, tumours may relapse, often in the skeleton even after successful eradication of the primary tumour, indicating that tumour cells may lay dormant within bone for extended periods of time. This review summarises recent findings in the mechanisms underlying tumour cell dormancy and the role of bone cells in this process. Hematopoietic stem cell (HSC) niches in bone provide a model for understanding regulatory microenvironments. Dormant tumour cells have been shown to exploit similar niches, with evidence suggesting interactions with osteoblast-lineage cells and other stromal cells via CXCL12-CXCR4, integrins, and TAM receptor signalling, especially through GAS6-AXL, led to dormancy, with exit of dormancy potentially regulated by osteoclastic bone resorption and neuronal signalling. A comprehensive understanding of dormant tumour cell niches and their regulatory mechanisms is essential for developing targeted therapies, a critical step towards eradicating metastatic tumours and stopping disease relapse.

1. Introduction

Secondary metastases pose a significant clinical challenge for the treatment of cancers, accounting for approximately 90 % of cancer-associated mortalities [1]. The skeleton is one of the most prevalent sites for these metastases, with secondary skeletal tumours developing in 6.9 % of solid tumour patients within 5 years [2]. This rises to approximately 25 % for patients with prostate cancer and 12 % for patients with lung cancer [2]. Metastatic tumours within bone induce changes to skeletal remodelling and lead to pain for patients, often resulting in fractures and even paralysis. Treating these metastases remains a key clinical challenge. Importantly, secondary tumours in the skeleton may develop even after successful eradication of the primary tumour, and may not present clinically for upwards of 20 years afterwards [3], indicating that cancers may lay dormant within bone for extended periods of time. Preventing metastatic outgrowths from occurring is therefore challenging, and there remains a need to develop therapeutic strategies to specifically target dormant tumours. Due to the high prevalence of metastases in bone, this tissue represents an important site within which to study tumour dormancy.

2. Tumour cell dormancy

The concept of tumour dormancy incorporates two related but distinct phenomena – tumour mass dormancy and tumour cell dormancy. The former refers to a state in which the simultaneous growth and death of the cancer cells is in equilibrium and hence the tumour remains at a constant size below standard clinical detection levels [4]. Tumour cell death may occur as a result of immune clearance (immunogenic dormancy), the lack of necessary nutrients and growth factors due to a restricted blood supply (angiogenic dormancy), or both. Importantly, tumour cells in this state remain active and continue to proliferate. By contrast, cellular dormancy refers to the process whereby individual tumour cells undergo G_0-G_1 cell cycle arrest and enter a state of non-proliferative quiescence [5]. These cells (termed dormant tumour cells) are able to survive for long periods of time in this state. Clinical evidence suggests that the presence of persistent, long-term disseminated tumour cells in the bone significantly increases the risk of disease relapse and death in patients [6]. Importantly, though they share many similar characteristics, dormant tumour cells are distinct from cancer stem cells (which have also been implicated in cancer metastasis) [5]. Unlike stem cells, dormant tumour cells do not sit atop a differentiation hierarchy, and whilst some studies have observed expression of stemness markers such as CD44 and NR2F1 in these cells [7,8], others

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https://doi.org/10.1016/j.jbo.2024.100621
Received 17 December 2023; Received in revised form 19 May 2024; Accepted 2 July 2024
Available online 6 July 2024

have shown this is not always the case [9].

Whilst mass dormancy and cellular dormancy are distinct from one another, the two may occur simultaneously, as shown by the co-existence of a small population of proliferative cells with dormant cells [10]. Therapeutic intervention may also play a role in both phenomena. For example, androgen-deprivation therapy (ADT) is often used to treat prostate cancer, but more than half of patients experience disease relapse within 2 years [11]. Interestingly, Dong et al recently showed that PDX murine models of ADT-induced dormancy can be divided into two categories: one exhibiting characteristics of tumour mass dormancy and the other exhibiting characteristics of cellular dormancy [11]. The exact relationship between these two phenomena remains poorly understood however it has been suggested that some of the pathways involved in both display some overlap, though further work is needed to determine exactly how each process is regulated and what precise roles the microenvironment plays in this regard [12].

To date, the overwhelming majority of cancer-related studies have focused on actively growing tumours and/or tumour mass dormancy, with cellular dormancy in tumour cells remaining a somewhat neglected aspect of cancer biology. Consequently, whilst the past few decades have seen the development of numerous anti-angiogenic and immunomodulatory cancer therapies, there are currently no treatments specifically targeting cellular dormancy, despite this representing a vital step towards the complete eradication of a cancer. A key factor that has limited our understanding of dormant tumour cells is that these cells represent very rare populations and typically exist as single cells, making their detection a significant technical challenge. Researchers have often used specific protein markers to attempt to isolate disseminated tumour cells from distant sites (e.g. cytokeratin/EpCAM for epithelial cancers, gp100 for melanoma); these methods have provided some significant insights, however they do not specifically select for dormant cells, and may also only identify sub-populations of disseminated cells [13]. In murine models of disease, the non-proliferative nature of dormant tumour cells may be used to more specifically isolate them: tumour cells can be pre-labelled with a fluorescent membrane dye such as 1,1-Dioctadecyl-3,3,3,3-tetramethylindodicarbocyanine (DiD), injected into mice and allowed to grow and proliferate over several weeks [10]. Dormant cells (which do not undergo cell division) can then be distinguished by retention of this fluorescent dye (DiD^+) from dividing cells (DiD^-) and isolated by conventional cell-sorting methods such as fluorescence-activated cell sorting (FACS).

These approaches have further facilitated some advances in our understanding of dormant tumour cell biology, and recently Phan and Croucher [5] proposed 6 defining hallmarks of tumour cell dormancy: cell-cycle arrest, drug resistance, immune cloaking, re-activation, reversibility and niche-dependency (Fig. 1). Collectively, these attributes enable dormant tumour cells to engage with the local microenvironment of a secondary tissue, survive for extended periods without being destroyed by the immune system and eventually grow into a metastatic tumour. Of particular importance, it has become increasingly clear that dormancy (both entry into and exit from) is strongly regulated by cell-extrinsic factors. Lawson et al. [14] used a tandem membrane dye approach to highlight the ability of tumour cells to readily switch between dormant and proliferating states. eGFP-tagged myeloma cells were labelled with the membrane dye DiD, injected into mice and then both dormant ($eGFP^+$ DiD^+) and dividing ($eGFP^+$ DiD^-) tumour cells were isolated from the bone marrow 21 days post-inoculation. The DiD^- cells were then re-labelled with a second membrane dye 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine (DiL), and then a new cohort of mice were inoculated with either $eGFP^+$ DiD^+ dormant cells or $eGFP^+$ DiL^+ re-labelled dividing cells. The identification of $eGFP^+$ DiD^- cells 21 days later indicated that previously dormant cells were able to reactivate and proliferate in the bone microenvironment, whilst the presence of $eGFP^+$ DiL^+ cells at this same time point showed that the reverse also occurs, with previously dividing tumour cells entering a state of dormancy. Dormancy therefore represents a transient state rather than a terminal differentiation and is regulated by local, cell-extrinsic factors within the microenvironment. This is reminiscent of haematopoietic stem cells (HSCs) reversibly switching from dormancy to self-renewal under conditions of hematopoietic stress and vice versa when homeostasis is re-established [15].

Interestingly, HER2 expression has been detected in early disseminated breast cancer cells and shown to play a role in driving metastasis [16]. High HER2 expression on the cell membrane is also associated with quiescence in prostate cancer cells and likely induced by the bone microenvironment [17]. Anti-HER2 therapies such as trastuzumab

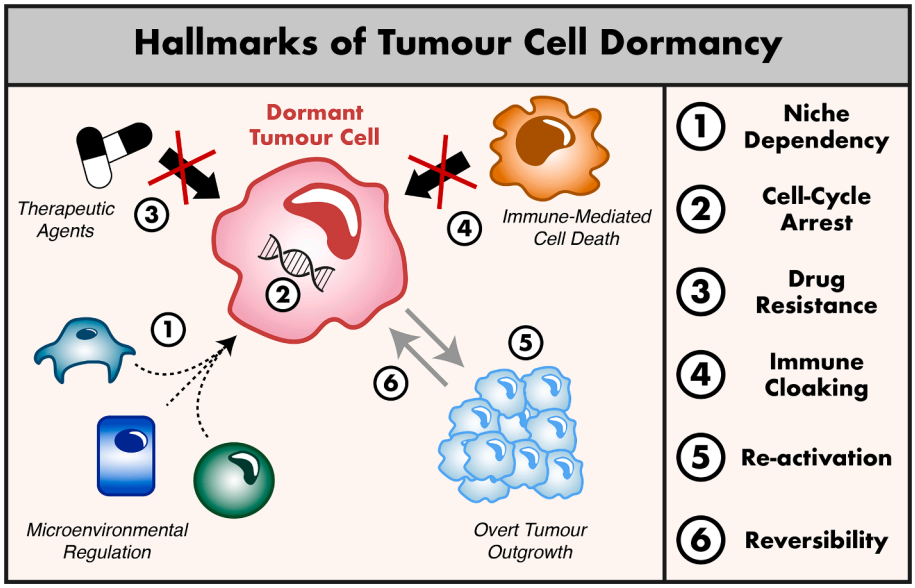

Fig. 1. Recently, Phan and Croucher [5] described 6 defining features of dormant tumour cells. 1) The transition of tumour cells into the dormant state is dependent upon cell-extrinsic factors within the niche. 2) Upon engagement with the niche, these cells enter a state of G0-G1 cell-cycle arrest. 3) In the dormant state, tumour cells are resistant to therapeutic agents. 4) Dormant tumour cells are able to avoid immune-mediated destruction for extended periods. 5) Eventually, these cells are able to reactivate and grow into a metastatic tumour. 6) Even post-reactivation, tumour cells are able to revert back into a dormant state, indicating that this transition is reversible.

appear to prevent micrometastases in breast cancer patients and delayed prostate cancer metastatic growth in mice. Whether these treatments simply delay metastatic outgrowth or eradicate dormant cells remains to be determined [18]. A recent transcriptomic study using the 5TGM1 multiple myeloma mouse model by Khoo et al. [9] identified a distinct transcriptional gene signature expressed by dormant cells compared to their reactivated counterparts. This gene signature was highly enriched for myeloid-related genes, with downstream analysis indicating that this was largely under the control of the *Irf7* and *Spic* transcription factors, suggesting a role for interferon (IFN) signalling. Further *in vitro* experiments found that the induction of this signature required the presence of osteoblast-lineage cells. Similar enrichments for IFN-response genes have also been observed for metastatic prostate cancer cells in bone [19], whilst additional studies on breast cancer [20] and lymphoma [21] have further indicated a role for this pathway in regulating dormancy. Microenvironmental cues therefore play a central role in regulating dormancy in these cells. Understanding the cellular niches that dormant tumour cells occupy within bone and how these niches regulate dormancy is critical to developing therapeutic strategies to target these cells.

3. Defining cellular niches

The term "niche" was first coined by Schofield [22] in the mid-twentieth century in the context of haematopoietic stem cells (HSCs) and has since been applied more broadly to a range of distinct cell types from a variety of tissues. Niches are specialised, local microenvironments that maintain a specific cell population and provide a conducive environment to support the functional responses of that cell. They may encompass a wide range of factors such as direct cell–cell contacts with neighbouring stromal cell populations, cytokines/chemokines and other secreted signalling molecules, vascular networks, the extracellular matrix, neuronal stimulation, the biophysical/biomechanical properties of the tissue and the microbiome. Importantly, niches are dynamically regulated – they are not passive structural bases, but rather play an active role in regulating the behaviour of a cell. Many of the factors involved are spatially and temporally regulated, allowing the niche to constantly adapt and respond to the needs of the wider tissue/organism.

Today, HSC niches in the skeleton remain among the best characterised. As their name suggests, HSCs sit atop a differentiation hierarchy that gives rise to all cells of the blood. These cells undergo asymmetric cell-division so as to simultaneously maintain their own population (self-renewal) whilst also giving rise to various progeny (differentiation), and thus their activity and maintenance is tightly regulated to ensure that they do not undergo excessive differentiation. Such regulation is achieved in the niches these cells occupy, which provide protective and supportive environments that facilitate their long-term survival and maintain their stemness. Imaging studies have revealed that HSCs preferentially localise around blood vessels and at the endosteal bone surface [23], giving rise to the terms "perivascular niche" and "endosteal niche" – terms which in fact define multiple similar but slightly distinct niches (for example, perivascular niches may include both perisinusoidal and periarteriolar niches), which are believed to separately house HSCs and their immediate progeny. A variety of factors have been identified within these niches (Fig. 2). Central among these are perivascular mesenchymal stromal cells (MSCs), which are abundant sources of the key chemotactic molecules *CXCL12* and *SCF* that facilitate HSC homing to niches [24]. Like HSCs, MSCs are similarly long-lived cells and thus are able to provide stable, long-term niches for these cells. Additional stromal cells, such as endothelial cells, osteoprogenitors and mature osteoblasts, have also been suggested to contribute to HSC niche maintenance [25], as have various immune cell populations (including macrophages and megakaryocytes [26]) and neuronal signals [27]. Recently, the advent of single-cell technologies has had led to significant advances in this area; such techniques have facilitated the agnostic and unbiased interrogation of the cellular landscapes of the bone microenvironment, and enabled detailed characterisation of the cell types and states present within this tissue (we point the reader to the following reviews on this topic [28,29]). Overall, HSC niches therefore represent highly complex regulatory networks

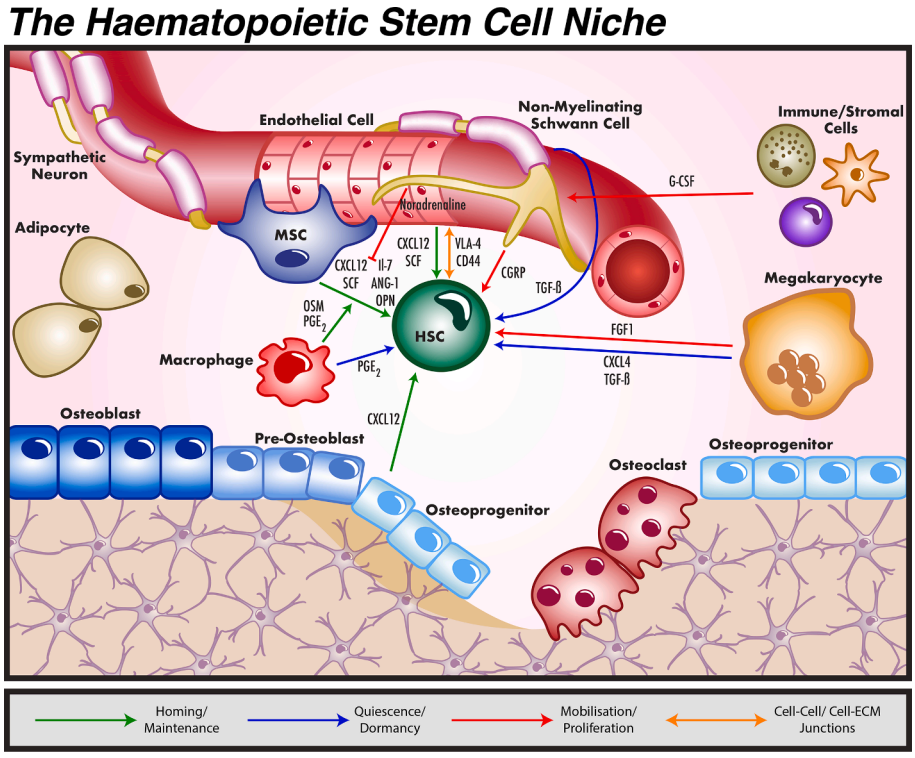

Fig. 2. Schematic of the haematopoietic stem cell (HSC) niche in bone. The long-term quiescence of HSCs in the bone microenvironment is maintained by specific cellular niches, which involve signalling contributions from tissue-resident stromal cells, immune cells, the vasculature, the extracellular matrix and neuronal cells.

involving a wide variety of local and systemic factors. Signals from each of these sources are integrated to provide a supportive microenvironment for HSCs that is conducive of quiescence and maintains their stemness.

4. Niche control of tumour dormancy

In the cancer setting, comparatively little is known about the mechanisms by which dormant tumour cells engage with niches. A series of early observations have indicated that these cells may possibly hijack HSC/progenitor cell niches (Fig. 3). Firstly, HSC mobilization via *G-CSF* stimulation simultaneously increased egress of cancer cells into the circulation in a patient with multiple myeloma [30]. Secondly, colonising prostate cancer cells were found to home to bone via the *CXCL12* signalling pathway, and inhibition of *CXCR4* (the receptor for *CXCL12*) releases myeloma cells from the bone [31,32]. Thirdly, prostate cancer cells were found to compete with HSCs for binding to annexin A2 (*ANXA2*) on endothelial and osteoblast-lineage cells via the annexin A2 receptor (*ANXA2R*) [33,34]. Finally, intravital imaging studies found that dormant myeloma cells preferentially reside in close proximity to the endosteal bone surface, though whether this is in the same niches as HSCs remains unclear [14]. The occupation of HSC niches by dormant tumour cells may be unsurprising: like HSCs, dormant tumour cells are long-lived, quiescent cells and hence require stable niches involving similarly long-lived cells that facilitate their survival over long periods of time. Furthermore, HSC niches are immune-privileged [35], and so their occupation by tumour cells may not only support dormancy but also confer immune resistance.

The first step in niche occupation by disseminated tumour cells involves homing to and initial engagement with the niche. As mentioned above, the *CXCL12-CXCR4* signalling pathway has been identified as a key chemoattractant required for homing. Beyond this pathway, integrins have been found to be critical in mediating direct engagement with niches. For example, the α5β3 integrin (which is upregulated in breast and prostate cancers) mediates interactions with bone matrix proteins such as vitronectin and fibronectin [36]. Knock-in of this gene in mammary carcinoma cells was sufficient to induce metastasis to the skeleton [37]. Similarly, antibodies inhibiting the binding of integrin α5β3 or integrin β1 to *VCAM1* and *vWF* at perivascular niches led to a reduction in tumour cell burden in bone and prevented metastasis at this site [38]. These observations may suggest that integrins may play a role in tumour cell engagement with endosteal and perivascular niches via their interactions with osteoblastic cells and bone ECM proteins. Indeed, disseminated tumour cells have been shown to survive in micro-anatomical niches rich in osteoblastic cells [39]. This aligns with the observation that the bone microenvironment's capacity to sustain disseminated tumour cells diminishes as the count of osteoblastic cells decreases during skeletal maturation.

Once these cells have homed to and engaged with the niche, the dormant state is induced, with TAM receptor (a receptor family which

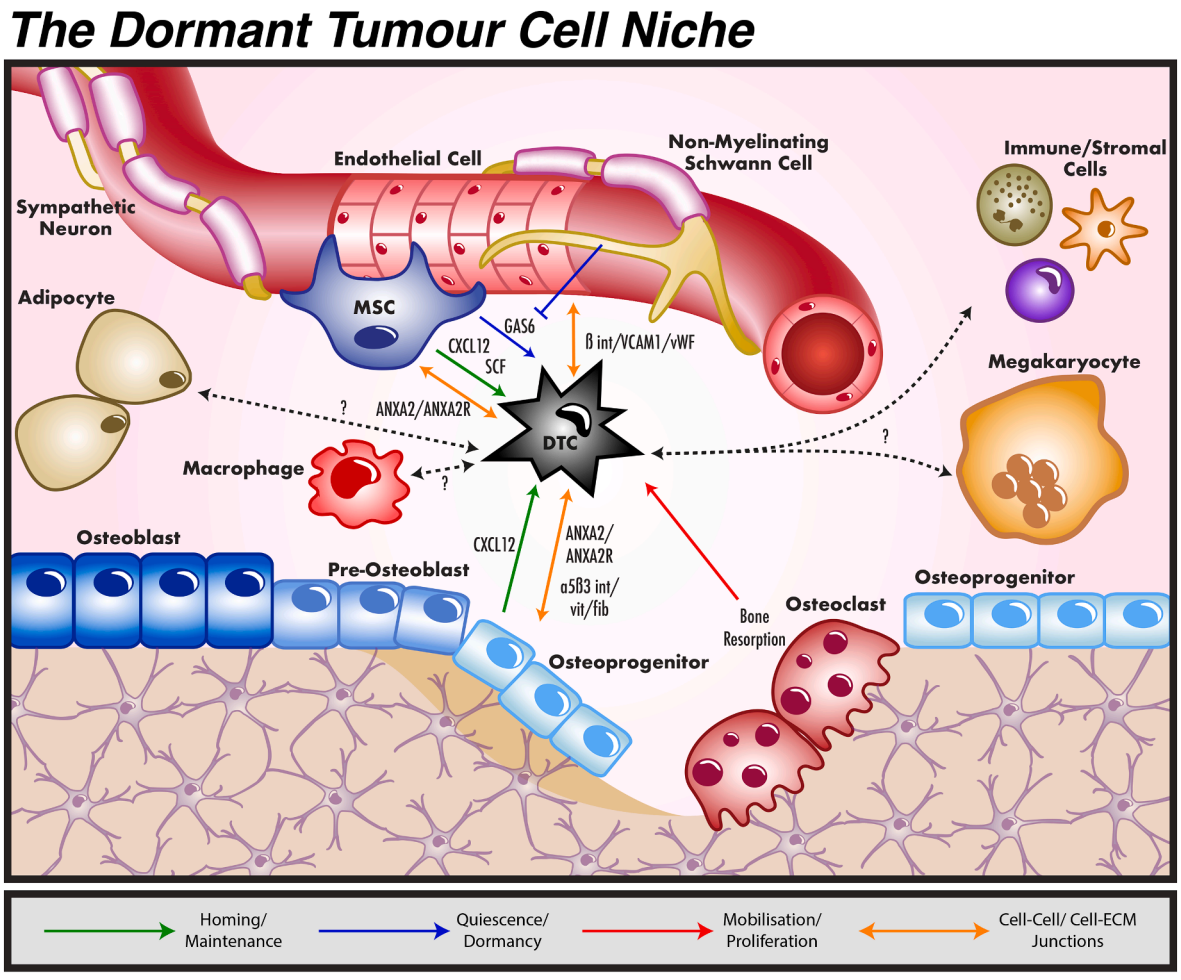

Fig. 3. Schematic of the dormant tumour cell niche in bone. Like HSCs, dormant tumour cells are maintained in a state of long-term quiescence within bone by specific cellular niches. Comparative studies have identified a variety of shared signalling pathways that regulate both HSC and dormant tumour cell quiescence, suggesting the niches occupied by these cells may involve similar cell types. Dormant tumour cell niches remain poorly characterised however, and it therefore remains unclear whether these cells occupy the same or distinct but similar niches as HSCs.

includes *AXL*, *TYRO3* and *MERTK*) signalling identified as a central pathway in this context. Binding of *ANXA2* on osteoblast-lineage cells to its receptor on prostate cancer cells was shown to induce expression of *AXL* in the tumour cells [40]. Osteoblast-lineage cells express growth arrest-specific 6 (*GAS6*), the ligand for these TAM receptors, which reduces prostate cancer cell proliferation and induces dormancy via binding to *AXL* [40]. In myeloma cells, pharmacological inhibition of AXL released cells from dormancy [9], whilst lymphoblastic leukaemia cells were shown to enter a dormant state upon binding of *GAS6* to *MERTK* [41]. *GAS6-AXL* signalling also slows cell-cycling in HSCs [42], suggesting this may be another example of dormant tumour cells utilising similar mechanisms for controlling quiescence in HSCs. It was later shown that *GAS6-AXL* signalling in prostate cancer cells upregulated the expression of *TGF-β2* and its receptors, which in turn drives dormancy via the upregulation of cyclin-dependent kinase inhibitors [43]. These findings were in concordance with previous studies that had found that stromal-derived *TGF-β2* in the bone marrow induced dormancy in disseminated head and neck squamous cell carcinoma via a low ERK/p38 signalling ratio [44]. *TGF-β2* signalling from $NG2^{+}$ MSCs has been shown recently to both promote HSC quiescence and also induce dormancy in disseminated breast cancer cells, further suggesting that cancer cell dormancy may be regulated by overlapping pathways with HSC niches [45]. Importantly, ER^{+} breast cancer patients with elevated *TGF-β2* and *BMP7* expression displayed reduced frequency of disease recurrence, suggesting these observations have clinical relevance [45].

Exit from dormancy is another critical step in the development of overt metastases. Osteoclastic bone resorption has been shown to increase metastatic tumour growth in the skeleton [46]. Treatments that cause an increase in bone turnover such as ovariectomy or vitamin D deficiency exacerbate this effect [47,48], whilst inhibitors of osteoclastic resorption such as bisphosphonates or *RANKL* inhibitors reduce skeletal metastases [49–51]. Accordingly, increased bone resorption also reduces the number of dormant cells in bone [14]. Whether this proliferation is triggered simply by the disruption of niches or by specific microenvironmental factors directly signalling to the dormant cells remains unclear. Neuronal signalling may also regulate release from dormancy; noradrenaline secreted by sympathetic nerves has been found to stimulate prostate cancer proliferation, both directly via β2-adrenergic receptors *in vitro* and also indirectly by reducing osteoblast-derived *GAS6* production *in vivo* [52]. Similarly, aging has been hypothesised to trigger release from dormancy due to changes in the cytokine balance over time [53], as well as a decrease in key niche cell types like osteoblasts [39], which leads to an environment more conducive of proliferative cells. Thus, microenvironmental changes are able to trigger dormant tumour cell exit from dormancy via release from niches. Exit from dormancy only occurs for a limited fraction of tumour cells, which may suggest that this process is random. A broad, agnostic approach to identify key cell types and signalling genes within dormant tumour cell niches is needed to elucidate how these niches mediates entry into and exit from dormancy and provide a more detailed mechanistic understanding of these processes.

5. Concluding remarks

Overall, early work studying dormant tumour cells residing in the skeleton has highlighted a fundamental role for microenvironmental regulation of dormancy. A number of cell types and signalling pathways have been identified in this regard, with cells of the osteoblast lineage centrally involved. Bone microenvironmental regulation of dormant tumour cells shares considerable overlap with that of HSCs, leading to the hypothesis that dormant tumour cells may hijack pre-existing HSC niches [34]. However, current understanding of the cell types involved and the key signalling pathways regulating tumour cell dormancy remains limited, with the potential roles of non-osteoblast lineage cells largely unknown. It may therefore be that dormant tumour cells occupy overlapping but distinct niches from HSCs – a more detailed characterisation of the dormant tumour cell niche is required to elucidate this. A better understanding of how dormancy is regulated may pave the way to developing novel therapies to target these cells in the clinic – a vital step towards fully eradicating metastatic tumours.

6. Outstanding questions

- Beyond those of the osteoblast-lineage, what other cells are involved in dormant tumour cell niches?
- What are the key signalling molecules and pathways within these niches that regulate the dormancy process?
- Similar to HSCs, are there multiple overlapping but distinct niches that dormant tumour cells may occupy?
- Are there shared and distinct cell types/signalling pathways involved for dormant tumour cells of different primary origins?
- Are there shared cell types/pathways involved in dormant tumour cell niches in other metastatic sites? What are the bone-specific components that may influence the distinct organotrophic patterns of different primary tumour types?

CRediT authorship contribution statement

James T. Smith: Writing – review & editing, Writing – original draft, Visualization. **Ryan C. Chai:** Writing – review & editing, Supervision, Conceptualization.

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.

Acknowledgements

This work was supported by the National Health and Medical Research Council of Australia.

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