Targeting tumour-osteoclast interactions: a trigger-explosion system to combat bone metastasis

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Cancer remains one of the leading causes of death worldwide, and tumour metastasis is responsible for more than 90% of cancer deaths.[1, 2] Bone is recognised as the most common site for metastasis of numerous malignancies, especially breast and prostate cancer.[3, 4] As a highly dynamic compartment, the bone microenvironment not only facilitates primary metastasis but also enhances secondary metastasis to organs, such as the brain, liver, and lung, liver, and brain.[5-7] Therefore, effectively preventing critical bone metastasis is pivotal for impeding systemic tumour spread. Unlike metastasis in other organs, the initiation of bone metastasis uniquely involves softening of the bone matrix, a process attributed to its specialised hard base interface.[8] In this context, osteoclasts, the only cells capable of acid secretion and osteolysis, play a crucial role in shaping the initial microenvironment for tumour bone metastasis.[9] While previous studies have explored the role of exosomes and cytokines in the formation of tumour-induced osteoclasts, the exact mechanisms and spatiotemporal characteristics of this process remain inconclusive.[10, 11] A recent study published in *Nature Nanotechnology* titled "Targeting initial tumour–osteoclast spatiotemporal interaction to prevent bone metastasis" by Gu et al.[12] explores the spatiotemporal coupling between osteoclasts and tumour cells during the early stages of metastasis, and proposes an in situ strategy to decouple and kill tumour cells to prevent early bone metastasis.

This research uncovers the spatiotemporal interaction between tumour cells and osteoclasts facilitated by migrasome-mediated transfer of cytoplasmic content from tumour cells to receptor activator of nuclear factor κ-β ligands (RANKL)-stimulated osteoclast precursors. They identify this tumour-associated osteoclast as 'tumasteoclast' (TAOC), and characterise by its induction mechanism (contact required), induction mediator (migrasomes), and transcription pathway (alternative transcription factor pathway) (**Figure 1A**). Firstly, the formation of TAOC requires direct physical contact with tumour cells. The research indicates that soluble factors alone, such as exosomes and cytokines, which can be transferred through the medium in a Transwell culture system, are insufficient to induce TAOC. The comparative success of induction comes from the co-cultures, where tumour cells and osteoclast precursors are grown together allowing for direct interaction. Secondly, migrasomes mediate the coupling between tumour cells and TAOC. Migrasomes are newly identified organelles involved in intracellular communication.[13] These micrometre-scale vesicles, typically filled with signalling molecules and cytoplasmic components, are released by tumour cells and subsequently taken up by osteoclast precursors. The delivery of migrasomes facilitates the transmission of signals that induce the differentiation of osteoclast precursors into TAOCs. This interaction opens up new avenues for therapeutic interventions, where targeting the formation, release, or uptake of migrasomes could potentially prevent or mitigate bone metastasis in cancer patients. Finally, TAOC possess an alternative transcription factor pathway. Influenced by mRNA transferred from tumour cells via migrasomes, TAOCs display transcriptional characteristics of both classic osteoclast and tumour cells, as evidenced by RNA sequencing results. In addition, single-cell omics data also confirm TAOC represent a unique subtype of osteoclasts in human bone metastasis. Overall, the contact-dependent induction via migrasomes and the subsequent activation of an alternative transcription factor pathway underscore the specialised nature of TAOCs in facilitating bone metastasis.

Understanding the spatiotemporal characteristics of tumour-TAOC coupling deepens our insight into the initiation and progression of bone metastases, highlighting potential targets for therapeutic intervention to disrupt these critical interactions and pathways. The researchers then introduce a decoupling–killing strategy that not only inhibits migrasome formation but also kills tumour cells at early stages of bone metastasis (**Figure 1B**). This approach involves the design and preparation of nanoliposomes, which encapsulate sodium bicarbonate and sodium hydrogen phosphate, and are modified by tetracycline (HC&HP@TNL). These bone-targeting nanoparticles function as a trigger-explosion system, activated by the acidic environment created by TAOC. Upon activation, they release high levels of hydrogen phosphate ions that react with local calcium ions, resulting in the formation of calcium-phosphorus (CaP) crystals. The formation of CaP crystals depletes local calcium levels, thereby exerting a significant inhibitory effect on the formation of migrasomes and the induction of TAOCs. Moreover, the distribution of CaP crystals across the cell membranes and cytoplasm of tumour cells causes overload of calcium and cell death induced by oxidative stress. Consequently, HC&HP@TNL effectively inhibit bone metastases and enhance prognosis as evidenced in mice.

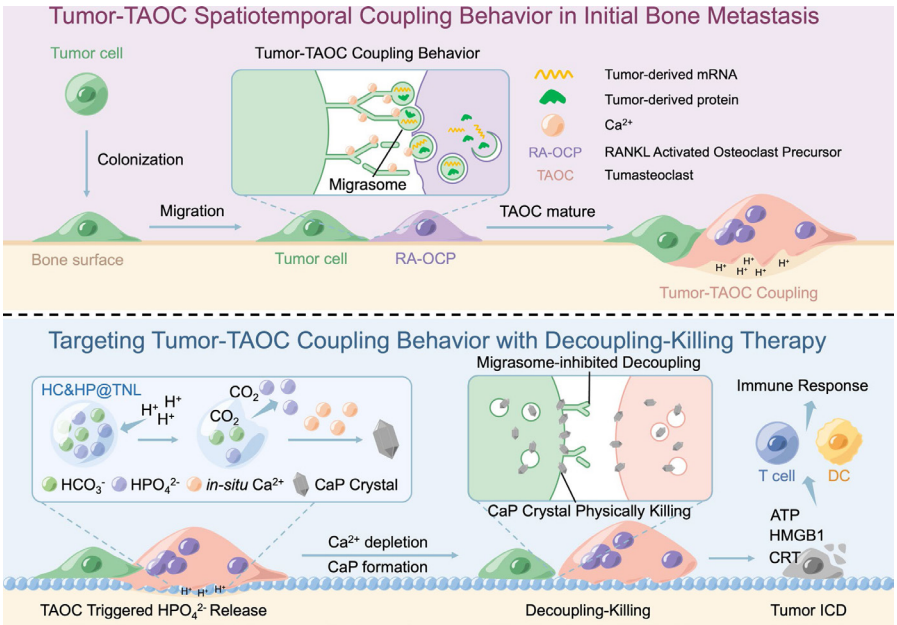

Figure 1. Schematic illustration depicts the interaction between tumour cells and TOACs mediated by migrasomes, and the strategy to disrupt and kill these cells. (A) Tumour cells directly contact with RANKL-stimulated osteoclast precursors (RA-OCP), inducing their transformation into "tumasteoclast" (TAOC) via migrasome-mediated cytoplasmic transfer, thus creating a tumour-TAOC spatiotemporal coupling. (B) Upon activation by the acidic environment created by TAOC, tetracycline-modified nanoliposomes containing sodium bicarbonate and sodium hydrogen phosphate (Na_2HPO_4) (HC&HP@TNL) release high levels of Na_2HPO_4, which reacts with local Ca^{2+} to form CaP crystals. These crystals deplete local calcium, inhibiting further formation of migrasome and compromising cell membrane integrity to induce immunogenic cell death (ICD) and provoke an immune response. Reprinted with permission from Gu et al.[12] Copyright 2024, Gu et al., under exclusive licence to Springer Nature Limited.

In summary, the study by Gu et al.[12] advances our understanding of the bone metastatic cascade, and introduces a proactive therapeutic strategy for early prevention of bone metastases. By targeting the microenvironment essential for metastasis before it fully establishes, this approach offers the potential to significantly alter the course of cancer progression. It underscores a broader application of nanotechnology and precision medicine in oncology, aiming not just at treatment but at prevention. Despite the promising results demonstrated in this study, several questions remain for future research. One major concern is the specificity and delivery of the nanoliposomes, which must be fine-tuned to consistently target only the tumour-associated osteoclasts without impacting other bone marrow cells. The delivery system could be further refined to enhance its specificity and efficiency, possibly by integrating it with other therapeutic modalities such as immunotherapy or radiotherapy to create a more comprehensive treatment approach. Additionally, the long-term effects and potential toxicity associated with chronic exposure to nanoliposome require thorough investigation. The adaptability of this strategy to other types of cancer and metastases also warrants exploration. Moreover, the real-world effectiveness of this strategy in a clinical setting, given the heterogeneity of tumour biology across patients, is yet to be determined.

Author contributions
Both authors approved the final version of the manuscript.
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Conflicts of interest statement
The authors declare no conflicts of interest.

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