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tiRNA Join Hematopoietic Niches

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Within bone marrow niches, complex networks of intercellular communications between bone marrow mesenchymal stromal cells (BM-MSCs) and hematopoietic stem cells (HSCs) regulate HSCs fate and maintenance. Soluble factors, cytokines and organelles, such as mitochondria, are part of these networks.[1]

A recent study from Kfoury et al[2] extends our understanding of these intercellular communications, reporting a previously unrecognized mechanism whereby niche cells control immunity.

The researchers first demonstrated that hematopoietic cells and BM mesenchymal stromal cells exchange cellular material not only in vitro, as previously described, but also in vivo. The authors transplanted wild-type bone marrow cells into distinct reporter mice expressing green fluorescent protein (GFP) under the control of promoters active in distinct BM-MSCs subtypes. Remarkably, GFP positive donor-derived hematopoietic cells were observed in recipients which expressed GFP in mature osteoblasts but not in animals which expressed GFP in osteoprogenitors or primitive mesenchymal stromal cells. Transmission electron microscopy confirmed these functional experiments, further indicating that GFP trafficking from mature osteoblasts occurs via extracellular vesicles (EVs), membrane-limited vesicles originating from the plasma membranes or endosomes. As evidenced by RNAseq, osteoblast-derived EVs were enriched in tiRNA, a subtype of small noncoding RNAs generated from tRNA upon endonuclease-mediated cleavage.

Interestingly, among different hematopoietic cell populations, granulocyte macrophage progenitors (GMPs) were the ones mostly up-taking GFP. This process significantly increased following exposure to genotoxic stresses, systemic inflammation or chemotherapeutic drugs. EVs most abundant ti-RNAs, 5′-ti-Pro-CGG-1, increased protein synthesis in recipients GMPs and promoted their cellular proliferation and differentiation. In vitro, moreover, 5′-ti-Pro-CGG-1 increased bacterial phagocytosis by granulocytic and monocytic cells. To confirm these findings in vivo, the researchers next used a transgenic murine model whereby the constitutive activation of parathyroid hormone receptor signaling in osteoblasts increases their numbers (Col1-caPPR mice). In these mice, an increased EVs transfer to GMPs correlated with an increased myeloid-based immunity during stress conditions: an increased myeloid response occurred upon a lethal dose of *Candida albicans,* thus increasing the animals survival. Similarly, parathyroid hormone injections in wild-type mice increased osteoblasts numbers, their EVs transfer to GMPs, and ultimately enhanced the animals myeloid recovery postirradiation.

Albeit the lack of murine models to manipulate in vivo EV-mediated tiRNA release allowed the researchers only correlative rather than causative evidences, these data are intriguing as they suggest the existence of a novel mechanism by which niche cells can modulate myeloid responses to stress (Figure 1). This opens up numerous interesting questions. First, understanding of the signal(s) regulating EVs-mediated tiRNA release within BM niches will be important to boost myeloid recovery upon infections or hematopoietic stem cells transplantations. Second, it remains to be established whether EVs-mediated tiRNA release is an exclusive features of osteoblasts or whether it extends to other niche components which were not analyzed in this study. Also hematopoietic stem/progenitor cells, moreover, produce tiRNA,[3] raising the question whether tiRNA transfer is a bidirectional process within bone marrow niches. The nature of EVs cargo remains also to be fully elucidated: since EVs carry not only nucleic acids but also proteins and lipids, it will be interesting to determine whether and which other EVs cargo components contribute to shape the intercellular communication between osteoblasts and myeloid progenitors. Last, since osteoblasts directly and indirectly sustain the development of myeloid malignancies,[4] it will worth investigating whether osteoblasts-derived tiRNA play any role(s) in this context.

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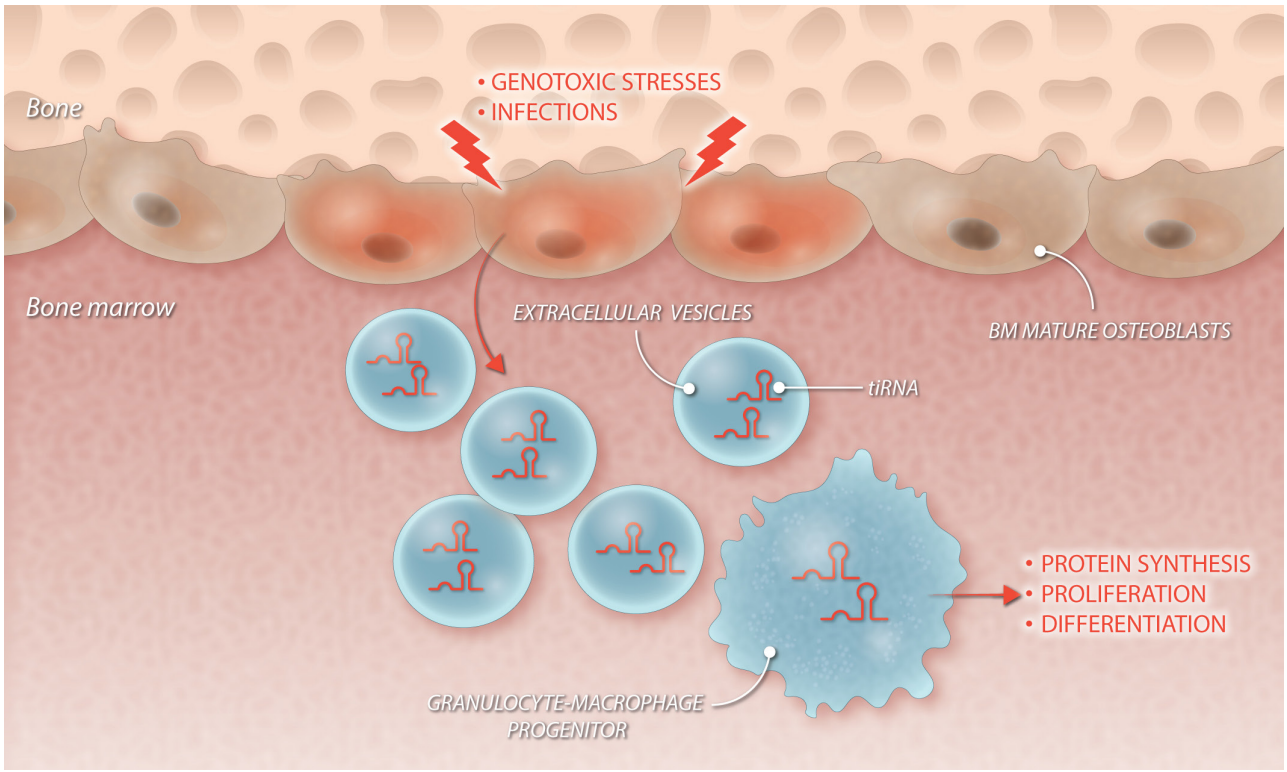

Figure 1. During stress conditions, osteoblasts-derived tiRNA are delivered to GMP progenitor cells via extracellular vesicles. This in turns increases GMPs proliferation and differentiation, ultimately enhancing myeloid-based immunity. BM = bone marrow; GMPs = granulocyte macrophage progenitors.

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