PUBLIC INSTITUTION NICOLAE TESTEMITANU STATE UNIVERSITY OF MEDICINE AND PHARMACY OF THE REPUBLIC OF MOLDOVA

THE BIOCHEMICAL ROLE OF microRNAs IN THE PATHOGENESIS AND REGULATION OF BONE METASTASIS

Authors: **Veronica SARDARI** [1,2] , Olga TAGADIUC [1,2] Daniel CRISTEA [1] , Nadejda RAILEAN[2] , Dionisie CEBOTARI[1,2]

Introduction. Bone metastasis is driven by a pathological feedback loop between tumor cells and the bone microenvironment. MicroRNAs (miRNAs), small non-coding ribonucleic acid (RNA) molecules, act as critical post-transcriptional regulators in this progression. This study explores how specific miRNAs biochemically modulate osteotropic signaling, emphasizing their diagnostic and therapeutic potential within clinical Biochemistry.

Materials and Methods. A systematic biochemical review was conducted utilizing data from molecular studies on miRNA-mediated regulation in bone colonization, particularly focusing on highly osteotropic malignancies such as breast and prostate cancers. We analyzed the interaction between specific miRNAs and target genes involved in the Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) pathway, Transforming Growth Factor-beta (TGF-β) signaling, and the Wingless-related integration site/β-catenin (Wnt/β-catenin) pathway.

Results. The analysis reveals that miRNAs act as molecular switches in the bone niche. Specifically, upregulated microRNA-21 and microRNA-141 promote RANKL-induced osteoclastogenesis, which is the process of forming mature osteoclasts, by targeting Osteoprotegerin (OPG). Conversely, other miRNAs suppress bone-derived growth factors, namely TGF-β and Insulin-like Growth Factors (IGFs). Their biochemical hallmark is the simultaneous targeting of multiple pathways—the RANKL/OPG axis, TGF-β signaling, and the Wnt/β-catenin cascade—amplifying the metabolic rewiring of bone cells. Exosomal miRNA secretion also serves as a primary communication channel between primary tumors and distant skeletal sites. By targeting components like low-density lipoprotein receptor-related protein (LRP5/6) co-receptors or biochemical antagonists like Dickkopf-1 (DKK-1), miRNAs disrupt the osteoblastic support system. This imbalance decreases Osteoprotegerin (OPG) production, directly fueling RANKL-mediated osteolysis and metastatic expansion.

Conclusions. MicroRNAs are fundamental biochemical regulators of the metastatic pathological positive feedback loop. Disrupting miRNA-target interactions could lead to novel biochemical therapies aimed at preserving bone integrity in oncological patients.

Keywords: Metastatic osteolysis, exosomal microRNAs, receptor activator of nuclear factor kappa-B ligand, Wingless-related integration site.

[1] He, W. & Wang, Z. & Li, Z. (2025). MicroRNAs in bone metastases: mechanisms and research progression. Frontiers in Oncology. 15. 1552902. 10.3389/fonc.2025.1552902. https://doi.org/10.3389/fonc.2025.1552902

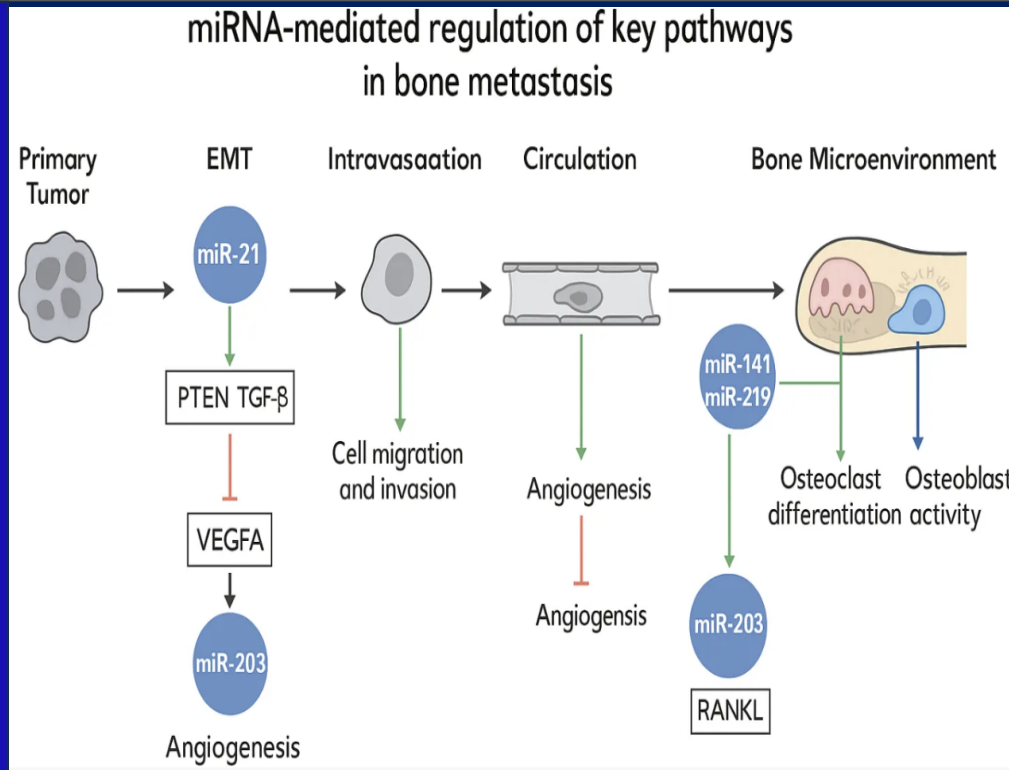

Fig.1. m*iRNA-mediated regulation along the metastatic cascade: exosomal transfer to the bone niche, RANKL/OPG imbalance and Wnt modulation sustain the osteolytic vicious cycle.*[1].

Address: *Nicolae Testemițanu* SUMPh, *27*, Nicolae Testemițanu str., MD-2004, Chisinau, Republic of Moldova; Phone: (+373)62015550; e-mail: cebotaridionisie@gmail.com
[1]Department of Biochemistry and Clinical Biochemistry, *Nicolae Testemitanu* State University of Medicine and Pharmacy, [2]*Laboratory of Systematics and Molecular Phylogeny, Institute of Zoology, Moldova State University* Chisinau, Republic of Moldova