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CIN85 PROMOTES OSTEOSARCOMA CELL MIGRATION VIA ROSDEPENDENT SIGNALING PATHWAYS

Background. Adaptor protein CIN85 (encoded by SH3KBP1) has been implicated in enhanced cell motility, metastatic progression, and poor clinical outcomes in several cancer types, including osteosarcoma [1–3]. This study investigated the contribution of reactive oxygen species (ROS) to CIN85-driven osteosarcoma cell migration. **Methods.** HOS and SAOS-2 osteosarcoma cells expressing CIN85 (upCIN85) or empty vector (Mock) were analyzed. Migration was assessed by scratch assay and intracellular ROS levels by flow cytometry. Bulk RNA sequencing was performed to identify CIN85-dependent transcriptional changes. The contribution of NADPH oxidase-derived ROS was evaluated using apocynin. **Results.** CIN85 overexpression significantly increased osteosarcoma cell migration, accelerating wound closure by up to 2-fold compared with Mock cells. Transcriptomic analysis revealed altered expression of genes involved in cell motility and extracellular matrix remodeling, including MMP2, VEGFA, INSR, COL1A2, and CDH3. CIN85-overexpressing cells also displayed elevated intracellular ROS levels, reaching up to 1.8-fold higher than in Mock cells. Consistently, MSigDB analysis identified enrichment of the Hypoxia, Epithelial-Mesenchymal Transition, Reactive Oxygen Species, IL-6/JAK/STAT3, Peroxisome, and IL-2/STAT5 signaling pathways. Inhibition of NADPH oxidase-dependent ROS production with 100 μ M apocynin reduced intracellular ROS levels by approximately 20% and decreased wound closure efficiency by 15.0–25.7%, partially reversing the CIN85-induced hypermigratory phenotype in a cell line-dependent manner. **Conclusions.** Together, these findings indicate that ROS contribute to CIN85-driven osteosarcoma cell migration, supporting ROS-modulating strategies as a potential therapeutic approach for CIN85-high cancers. **Funding.** This project has received funding through the MSCA4Ukraine project, which is funded by the European Union. This work was supported by a Ukrainian Short-Term Fellowship funded by FEBS, the Federation of European Biochemical Societies. This work was supported by the NRFU grant (project N2025.07/0367).

Keywords. Osteosarcoma, CIN85, migration, reactive oxygen species.

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