



UKE Paper of the Month Dezember 2022

Regulation of bone homeostasis by MERTK and TYRO3

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ABSTRACT:

The fine equilibrium of bone homeostasis is maintained by bone-forming osteoblasts and bone-resorbing osteoclasts. Here, we show that TAM receptors MERTK and TYRO3 exert reciprocal effects in osteoblast biology: Osteoblast-targeted deletion of MERTK promotes increased bone mass in healthy mice and mice with cancer-induced bone loss, whereas knockout of TYRO3 in osteoblasts shows the opposite phenotype. Functionally, the interaction of MERTK with its ligand PROS1 negatively regulates osteoblast differentiation via inducing the VAV2-RHOA-ROCK axis leading to increased cell contractility and motility while TYRO3 antagonizes this effect. Consequently, pharmacologic MERTK blockade by the small molecule inhibitor R992 increases osteoblast numbers and bone formation in mice. Furthermore, R992 counteracts cancer-induced bone loss, reduces bone metastasis and prolongs survival in preclinical models of multiple myeloma, breast- and lung cancer. In summary, MERTK and TYRO3 represent potent regulators of bone homeostasis with cell-type specific functions and MERTK blockade represents an osteoanabolic therapy with implications in cancer and beyond.

STATEMENT:

The paper reveals a regulatory system controlling osteoblast activity under physiological and pathological conditions induced by bone-seeking tumors. It provides rationale for novel bone anabolic treatment strategy.

BACKGROUND:

This work was performed in the group of Prof. Sonja Loges at the II. Medical Clinic and Polyclinic (Department of Oncology, Hematology and Bone Marrow Transplantation with Section Pneumology) and Institute of Tumor Biology, who hold a professorship at UKE since 2016. Since 2020 she is head of the DKFZ-Hector Cancer Institute at the University Medical Center Mannheim. The project was part of the MD thesis of first author Janik Engelmann. His Clinician Scientist position at the UKE was generously supported by the priority program μ bone from the DFG and he received the E.W. Kuhlmann scholarship from the University Cancer Center Hamburg. The collaborative project within the μ bone consortium with former UKE scientist Prof. Hanna Taipaleenmäki and collaboration partners from Yale and Jerusalem connected expertise in cancer research and the bone field.