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Calcitonin controls bone formation by inhibiting the release of sphingosine 1-phosphate from osteoclasts

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ABSTRACT: The hormone calcitonin (CT) is primarily known for its pharmacologic action as an inhibitor of bone resorption, yet CT-deficient mice display increased bone formation. These findings raised the question about the underlying cellular and molecular mechanism of CT action. Here we show that either ubiquitous or osteoclast-specific inactivation of the murine CT receptor (CTR) causes increased bone formation. CT negatively regulates the osteoclast expression of *Spns2* gene, which encodes a transporter for the signaling lipid sphingosine 1-phosphate (S1P). CTR-deficient mice show increased S1P levels, and their skeletal phenotype is normalized by deletion of the S1P receptor $S1P_3$. Finally, pharmacologic treatment with the non-selective S1P receptor agonist FTY720 causes increased bone formation in wildtype, but not in $S1P_3$-deficient mice. This study redefines the role of CT in skeletal biology, confirms that S1P acts as an osteoanabolic molecule *in vivo*, and provides evidence for a pharmacologically exploitable crosstalk between osteoclasts and osteoblasts.

STATEMENT: *Our manuscript fully clarifies the previously ambiguous role of the textbook hormone calcitonin (CT) in bone remodelling. We demonstrate that the primary physiological function of CT is to limit the activity of bone-forming osteoblasts, and we identified the underlying cellular and molecular mechanism. More specifically, we show that CT regulates bone formation indirectly, by reducing the release of the osteoanabolic molecule sphingosine 1-phosphate from bone-resorbing osteoclasts. We thereby uncovered a key mechanism coupling bone formation to bone resorption, and we have additionally identified the serpentine receptor $S1P_3$ as a putative drug target for osteoanabolic treatment of bone loss disorders, such as osteoporosis. Given the fact that the current treatment options for this highly prevalent disorder are still limited, our findings have a high clinical impact, in addition to their contribution towards a molecular understanding of bone remodelling.*

BACKGROUND: This work was performed at the Department of Osteology and Biomechanics (IOBM) under the supervision of Prof. Michael Amling and Prof. Thorsten Schinke. It was supported by DFG grants (AM103/15-1 and SCHI504/5-2) and primarily performed by Dr. Johannes Keller within the MD/PhD program of the UKE. We collaborated with several other UKE researchers from the Departments of Clinical Chemistry (genome-wide expression analysis), Nuclear Medicine (patient recruitment), and the Center of Molecular Neurobiology (targeted mutation in embryonic stem cells). Taken together, this manuscript is a perfect example for the success of an intact scientific infrastructure at the UKE.