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The epidermal growth factor (EGF)-like ligands and their cognate receptor EGFR constitute a well-studied signaling pathway that plays vital roles in many developmental and pathological processes. However, their function in the skeletal system has been poorly defined. We found that EGFR is expressed in osteoblastic lineage cells but not in osteoclasts. EGF-like ligands are potent growth factors and chemotactic factors for osteoprogenitors but strongly block their osteoblast differentiation. Our data show that EGFR activation not only decreases the expression of bone marker genes (alkaline phosphatase, osteocalcin, and BSP) but also strongly suppresses the expression of osteoblast-specific transcriptional factors, Runx2 and Osterix. The molecular mechanisms of how EGFR signaling regulates these genes were investigated. Moreover, we demonstrated that EGF-like ligands indirectly stimulate osteoclast formation by decreasing the expression of OPG, a decoy receptor for RANKL, and increasing the expression of MCP1, a chemokine that stimulates osteoclast fusion and activity, in osteoblasts. To understand the physiological role of EGFR, we constructed several transgenic and pharmacological mouse models with different levels of EGFR activity and used pQCT, micro-CT and histomorphometry to analyze their trabecular and cortical bone phenotypes. Interestingly, we found that deficiency in EGFR activity resulted in less trabecular bone with major decreases in osteoblast number and activity and opposite phenotypes were observed with mice expressing an EGFR constitutively active allele. Taken together, we propose that EGFR functions in maintaining osteoprogenitor pool and preventing them from differentiating into mature osteoblasts and therefore it primarily plays an anabolic role in bone remodeling.