Pmepa1 expressed in osteoclasts is specifically induced by bone components and regulates bone resorption

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（様式６－２）

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論　文　名	Pmepa1 expressed in osteoclasts is specifically induced by bone components and regulates bone resorption （Pmepa1 は Bone コンポーネントによって破骨細胞で発現が誘導され、骨吸収を制御する）
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論　文　審　査　の　結　果　の　要　旨

Osteoclasts are bone-resorbing multinucleated cells that are differentiated form hematopoietic stem cells. During bone resorption, osteoclasts are polarized to form ruffled borders, which are essential for bone degradation by the secretion of protons and acid proteases. In this study, prostate transmembrane protein androgen induced-1 (Pmepa1) was found to modulate bone resorption by regulating lysosomal secretion of osteoclasts. Pmepa1 was induced by RANKL and highly expressed in preosteoclasts *in vitro*, but also expressed in osteoclasts present in bone tissue of adjuvant arthritis rats and in osteoclasts formed on dentine. Expression of Pmepa1 was increased by treatment of calcium ionophore A23187, transforming growth factor-β and osteopontin, which were correlated with bone resorption activity. Knockdown of Pmepa1 decreased bone resorption activity by regulating the secretion of cathepsin K and protons to the extracelluar space. In addition, the localization of cathepsin K was impaired in Pmepa1-deficient osteoclasts. Pmepa1 protein was localized to lysosomes and early endosomes and also colocalized with LC3 and Nedd4 in osteoclasts. Pmepa1 knockdown decreased the expression of E3 ubiquitin ligase Nedd4 and increased Pten protein, which was related to cell proliferation and apoptosis.

These results suggest that Pmepa1 expressed in active osteoclasts regulates bone resorption by regulating the secretion of protons and cathepsin K to the extracelluar space. Therefore, the thesis is worthy of being defended for the Doctor of Philosophy.