

東北大学大学院歯学研究科 インターフェイス口腔健康科学 第14回学術フォーラム

Forum for Interface Oral Health Science

破骨細胞の分化に関わる新規分子について NHE-oc: a novel sodium/proton exchanger required for osteoclast-differentiation

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歯学部A1セミナー室(歯学部基礎棟1階)

抄録: We identified a gene, *nhe-oc*, that codes for a novel sodium/proton exchanger (NHE) expressed in osteoclasts. NHE-oc has strong homology with other putative NHEs, which have been identified as orthologues by reciprocal BLAST analysis. *nhe-oc* contains 13 exons that span 34.7 Kb on chromosome 3, giving rise to a 2.0 Kb transcript that codes for a 547 aa protein. Despite of the fact that NHE-oc has no significant sequence similarity to other NHEs, the hydropathic profiles of all NHE family members are very comparable. Northern Blot and RT-PCR analysis showed *nhe-oc* mRNA expression mainly in bone. *In situ* analysis of 17.5 dpc femur sections showed *nhe-oc* mRNA expression in cells adjacent to the growth plate, consistent with osteoclast expression. Confocal microscopy and cell fractionation analysis revealed that NHE-oc localize to the mitochondria. NHE-oc mediated a Na⁺-dependent increase in mitochondrial pH, indicating Na⁺/H⁺ exchange. NHE-oc also mediated passive mitochondrial swelling, induced by the addition of Na⁺ acetate. Both activities were sensitive to NHE inhibitors. Finally, mouse RAW 264.7 cells and rat Bone Marrow Monocytes were transfected with a cocktail of NHE-oc specific small inhibiting (si) RNAs and stimulated with RANKL. Si RNA treatment reduced osteoclast differentiation and resorption on osteologic disks by ~60%. We conclude that NHE-oc is a novel osteoclast-specific mitochondrial Sodium Proton Exchanger. NHE-oc mediates Na⁺-dependent changes in mitochondrial pH and matrix swelling in isolated mitochondria. Furthermore, NHE-oc activity is required for normal osteoclast differentiation and function. As a bone specific novel protein, NHE-oc has the potential to become a powerful anti-resorptive therapeutic target that may help prevent pathological bone loss.

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