S41-4 Involvement of zinc transporter Slc39a13/Zip13 in hereditary connective tissue disease

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Zinc (Zn) is an essential trace element and is crucial for the function of numbers of Zn-binding molecules, and its homeostasis is controlled by Zn transporters family members: SLC39/ZIP and SLC30/ZnT. In hard and connective tissues, Zn is relatively abundant but its biological roles in those tissues remain unknown. Here we report that mice deficient in Zn transporter Zip13 show changes in bone, teeth, and connective tissues, reminiscent of the clinical spectrum of human Ehlers-Danlos syndrome (EDS), and of Zn deficient diseases. The *Zip13* knockout (*Zip13*-KO) mice show defects in the maturation of osteoblasts, chondrocytes, odontoblasts, and fibroblasts. Zip13 protein is localized at Golgi in the corresponding cells, and impairment in BMP and TGF-β signaling were observed in *Zip13*-KO cells. In addition, we detected homozygosity for a ZIP13 loss of function mutation in sibs affected by a unique variant of EDS that recapitulates the phenotype in *Zip13*-KO mice. Hence, our results reveal a crucial role of ZIP13 in connective tissue development in mouse and human at least in part due to its involvement in the BMP/TGF-β signaling pathways, and the *Zip13*-KO mouse represents a novel animal model linking zinc metabolism, BMP/TGF-β signaling, and connective tissue dysfunction (Fukada T. et al., PLoS ONE, 2008).