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The Functional Crosstalk between MT1-MMP and Adams

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Matrix Metalloproteinases (MMPs) are essential for proper physiological tissue remodeling and homeostasis. They have a broad spectrum of substrates, ranging from extracellular matrix proteins to cytokines and membrane bound proteins [1]. One of the MMPs that draw worldwide research interests is membrane-type-1 metalloproteinase (MT1-MMP; also known as matrix metalloproteinase 14, MMP14). The physiological significance of MT1-MMP can be revealed by the severe phenotypes identified in MT1-MMP deficient mice that exhibit dwarfism, retarded skeletal growth, impaired branching morphogenesis in lung and submandibular gland, defective vascularization in endochondral ossification and cornea, and compromised adipogenesis in white adipose tissues [2-5]. Most previous studies on MT1-MMP have suggested that these developmental defects are attributable to impaired remodeling of type-I collagen [3]. However, a distinct mechanism by which MT1-MMP regulates intramembranous ossification is recently reported. The functional role of MT1-MMP in calvarial development is no longer to be restricted to extracellular remodeling, but also is applicable to the modulation of cellular signaling events essential for Calvarial Osteoblast (CO) development. We recently demonstrated a cell-autonomous and positive regulatory role of MT1-MMP in calvarial development via the modulation of Fibroblast Growth Factor (FGF) signaling pathway [6].

FGF signaling plays a fundamental role in craniofacial development. It regulates a variety of cellular events, particular in CO proliferation, differentiation and cell fate determination during calvarial bone formation [7]. Inactivation of FGF signaling resulted from genetic knockout of FGFRs or FGF ligands leads to dwarfism with defective ossification that can also be observed in Mmp14-/- mice [8-10]. The high degree of similarity in craniofacial defects between Mmp14-/- mice and mice with defective FGF signaling highlights the possible functional crosstalk between MT1-MMP and FGF signaling cascade. Indeed, examination of Mmp14-/- mice revealed that defective FGFR2-mediated signaling in CO development is the predominant mechanism leading to defects in intramembranous ossification of Mmp14-/- mice during embryonic development, implying that MT1-MMP is a potent positive modulator of FGF signaling.

MT1-MMP does not act alone on FGF signaling but rather functionally work with another metalloproteinase family, ADAMs. MT1-MMP proteolytically inactivates ADAM9 to protect FGFR2 from ectodomain shedding of ADAM9, which is important for the maintenance of optimal FGF signaling during calvarial development. The importance of ADAM9 in MT1-MMP/FGFR2 signaling cascade is further strengthened by the efficient rescue of calvarial defects of Mmp14-/- mice via depletion of ADAM9. The discovery of involvement of ADAM9 in MT1-MMP regulatory loop for FGF signaling not only provides a new molecular insight into the mechanism by which FGF signaling is regulated during intramembranous ossification, but also establishes a new research interest in which the newly identified crosstalk between MMP and ADAM families will be of great importance.

ADAM9 is not the solo ADAM family member regulated by MT1-MMP. We recently reported that ADAM15 is also proteolytically cleaved by MT1-MMP [11]. However, how the regulation of ADAM15 by MT1-MMP contributes to physiological development or pathologies remains largely unknown. It is clear that ADAM15 has a broad spectrum of substrates involved in many important physiological and pathological events, such as neovascularization, bone development, inflammation, cancer progression and metastasis [12-14]. It will be evitable to ask whether the interplay between ADAM15 and MT1-MMP plays a role in any physiological processes in which MT1-MMP is indispensable.

The newly-identified mechanism by which MT1-MMP regulates CO development suggests new therapeutic possibilities. Manipulation of MT1-MMP/ADAM9/FGFR2 signaling pathway will provide new approaches for the treatment of skeletal disorders and many cancers associated with deregulated FGF signaling.

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