第１３１回 病態生化学セミナー

日時：平成３１年４月８日（月曜日）午後６時００分～
場所：医学部講義棟１階 国際交流ラウンジ
演題：ヒト Site-1 protease の機能喪失バリアントは小胞体とライソゾームの機能異常を基盤とする骨格形成異常を招く
Compound defects in the endoplasmic reticulum and lysosome cause skeletal dysplasia in a patient with site-1 protease mutations
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脊椎および四肢の形成異常と細胞内ライソゾーム酵素の血液中への過剰放出を認める８歳女児における原因遺伝子の同定と、病態発生基盤を明らかにすることを目指した。Exome sequencing を利用して、患者ゲノムにおいて父、母の両アレルに変異を持つ遺伝子として *Membrane bound transcription factor peptidase, site 1* (*MBTPS1,* Site-1 protease)を同定した。Site-1 protease (S1P) は小胞体ストレス応答に必要な膜結合型転写因子 (ATF6, OASIS, BBF2H7 など) や脂質合成に必要な膜結合型転写因子(SREBP1/2)を切断により膜から遊離させ、それらの核内移行を促すセリンプロテアーゼである。最近になり、ライソゾームへのライソゾーム酵素の運搬に必要な Mannose-6-phosphorylation (M6P) 修飾を担う GlcNAc-1-phosphotransferase は、S1P により切断され活性化することが報告された。今回、我々が同定した S1P の変異は mRNA splicing 異常により機能喪失型であること、ライソゾームおよび小胞体の機能障害が骨格形成異常の分子基盤となることを患者由来誘導性多能性幹細胞、S1P ノックアウト細胞、S1P ノックアウトマウスを用いて明らかにした。

Site-1 protease (S1P), encoded by *MBTPS1* (membrane bound transcription factor peptidase, site 1), is a serine protease in the Golgi apparatus. S1P regulates lipogenesis, endoplasmic reticulum (ER) function, and lysosome biogenesis in mice and in cultured cells. However, how S1P differentially regulates these diverse functions in humans has been unclear. In addition, no human disease with S1P deficiency has been identified.

Here, we report a pediatric patient with an amorphic and a severely hypomorphic mutation in *MBTPS1*. The unique combination of these mutations results in a frequency of functional *MBTPS1* transcripts of approximately 1%, a finding that is associated with skeletal dysplasia and elevated blood lysosomal enzymes. We found that the residually expressed S1P is sufficient for lipid homeostasis but not for ER and lysosomal functions, especially in chondrocytes. The defective S1P function specifically impairs activation of the ER stress transducer BBF2H7, leading to ER retention of collagen in chondrocytes. S1P deficiency also causes abnormal secretion of lysosomal enzymes due to partial impairment of mannose-6-phosphate–dependent delivery to lysosomes. Collectively, these abnormalities lead to apoptosis of chondrocytes and lysosomal enzyme–mediated degradation of the bone matrix. Correction of an *MBTPS1* variant or reduction of ER stress mitigated collagen-trafficking defects.

These results define a new congenital human skeletal disorder and, more importantly, reveal that S1P is particularly required for skeletal development in humans. Our findings may also lead to new therapies for other genetic skeletal diseases, as ER dysfunction is common in these disorders.

Ref: Kondo Y, et al., Site-1 protease deficiency causes human skeletal dysplasia due to defective inter-organelle protein trafficking. JCI Insight 3: 121596, 2018
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