令和３年２月 10 日

大学院生各位
To All Graduate Students

2020 年度
基盤医学特論　開講通知
Information on Special Lecture Tokuron 2020

題目：「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」

Title:「Compound defects in the endoplasmic reticulum and lysosome cause skeletal dysplasia in a patient with site-1 protease mutations」

講師：近藤裕史 先生　　オクラホマ医学研究財団

Lecturer: Dr. Yuji Kondo Research assistant member

Oklahoma Medical Research Foundation

日時：令和３年２月 16 日（火曜日）　10 時 00 分～11 時 30 分

Time and Date：From　10：00～11：30 , Tuesday, Feb. 16, 2021

会場：　ZOOM　（Room: ZOOM）

要　旨（abstract）

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.

言語：日本語

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事前の申込は不要です。　No Registration required.

※Zoom にて開催します。This lecture is held through Zoom. 講義の URL は前週金曜日に学務課よりメールで送信される通知を確認してください。The URL for class will be announced by the e-mail“【med-all】RKR&TPRO Lectures Scheduled Coming Week” sent on Friday of the previous week.

※講義中の録画・録音は禁止します。Recording this lecture is not allowed.

※講義中はカメラをオンにして下さい。Please turn on a camera during class time.

※出席確認方法は授業中にお知らせします。Attendance is checked through this lecture.

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