第 468 回つくば分子生命科学セミナー

TSUKUBA MOLECULAR LIFE SCIENCE SEMINAR

演題：Elucidating the role of p300 catalysed butyrylation in adipogenesis using a small molecule modulator

演者：Tapas K Kundu 先生 (Jawaharlal Nehru Centre for Advanced Scientific Research)

日時：2022 年 10 月 24 日（月）　17:00-18:30

会場：健康医科学イノベーション棟 8 階講堂

要旨：The master epigenetic enzyme EP300 (p300) besides having lysine acetyltransferase activity can also catalyse other acylation modifications (propionylation, butyrylation, crotonylation etc.), the physiological implications of which are yet to be established fully. Here, by performing immunoblotting and chromatin immunoprecipitation assays, we report that histone butyrylation increases both globally as well as locally in the promoters of pro-adipogenic genes upon adipogenesis. Moreover, the enzyme ACSS2 which is responsible for generating acyl CoA for being used as a cofactor in acylation reactions is upregulated in adipogenesis and its genetic ablation leads to reduction of butyrylation. To delineate the role of p300 catalysed butyrylation from acetylation in adipogenesis, we have identified a semi-synthetic derivative (LTK-14A) of garcinol which specifically inhibited histone butyrylation without affecting the canonical acetyltransferase activity of p300. Treatment of 3T3L1 cells with LTK-14A significantly abolished adipogenesis with downregulation of pro-adipogenic genes along with the inhibition of H4K5 butyrylation. Administering the specific inhibitor to high fat diet fed C57BL6/J mice as well as genetically obese db/db mice led to an attenuation/decrease in their weight gain respectively. The reduced obesity could be at least partially attributed to the targeted inhibition of H4K5 butyrylation, as observed by immunofluorescence staining of the inhibitor treated mice liver sections and immunoblotting with histones extracted from epididymal fat pads. This report therefore not only for the first time causally links histone butyrylation with adipogenesis but also presents a novel small molecule modulator that could be developed for anti-obesity therapeutics. Pre-clinical studies are currently being performed to test the possibility of LTK-14A being developed as a candidate drug against obesity.

参考文献

Bhattacharya *et al.* (2022) *J. Med. Chem.*, 65, 12273-12291

＊ 医学セミナーと共催です。

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