The Hippo kinase LATS2 impairs pancreatic β-cell survival in diabetes through the mTORC1-autophagy axis

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1. 簡述論文的概要以及重大發現

糖尿病是由於人體胰臟的 β-cell 無法產生胰島素，導致沒辦法調節血糖，所以造成糖尿病。β-cell 的功能缺失或下降是第一型和第二型糖尿病的主要原因，所以了解 β-cell 凋亡的機制去改善、治療糖尿病是一個重要的研究領域。在過去的研究中發現 Hippo pathway 是調節 β-cell 發育、存活和增殖的主要路徑，LATS2 是 Hippo pathway 下游中其中一個蛋白，在糖尿病條件下被活化並誘導 β-cell 凋亡和功能受損，所以在本篇研究中作者研究了 LATS2 在 β-cell 中治病作用的分子機制，透過將 LATS2 overexpression 或是 Knock down 是否會造成 β-cell 凋亡和胰島素分泌受損，進而了解 LATS2 在 B-cell 中的角色。

2. 對論文內容的提問

Fig.7 a-d 確認了 LATS2 與 mTORC1 正相關，在前面幾個實驗中與已知的研究可以知道 LATS2 和 mTORC1 都會造成細胞凋亡，於是作者在 Fig.7e-g 用了 mTORC1 的抑制劑將 mTORC1 的 pathway 關閉，確認了 LATS2 和 mTORC1 和上下游關係，但是作者缺乏將 LATS2 關閉這個實驗，是否能做此實驗來更進一步確定 LATS2 和 mTORC1 和上下游關係。

3. 論文的缺點與評論

作者在本篇 paper 中，用了不同的 cell line，也在小鼠實驗中用了不同基因品系以及肥胖型跟非肥胖型的小鼠進行驗證，大大了增加這篇 paper 的可信度。

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The Hippo kinase LATS2 impairs pancreatic β-cell survival in diabetes through the mTORC1-autophagy axis

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Diabetes results from a decline in functional pancreatic β-cells, but the molecular mechanisms underlying the pathological β-cell failure are poorly understood. Here we report that large-tumor suppressor 2 (LATS2), a core component of the Hippo signaling pathway, is activated under diabetic conditions and induces β-cell apoptosis and impaired function. LATS2 deficiency in β-cells and primary isolated human islets as well as β-cell specific LATS2 ablation in mice improves β-cell viability, insulin secretion and β-cell mass and ameliorates diabetes development. LATS2 activates mechanistic target of rapamycin complex 1 (mTORC1), a physiological suppressor of autophagy, in β-cells and genetic and pharmacological inhibition of mTORC1 counteracts the pro-apoptotic action of activated LATS2. We further show a direct interplay between Hippo and autophagy, in which LATS2 is an autophagy substrate. On the other hand, LATS2 regulates β-cell apoptosis triggered by impaired autophagy suggesting an existence of a stress-sensitive multicomponent cellular loop coordinating β-cell compensation and survival. Our data reveal an important role for LATS2 in pancreatic β-cell turnover and suggest LATS2 as a potential therapeutic target to improve pancreatic β-cell survival and function in diabetes.

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