Citrullination of glucokinase is linked to autoimmune diabetes

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一、簡訴論文概要及重大發現

第一型糖尿病(T1D)的主要原因是自體免疫細胞 T cell 去破壞胰島 β 細胞造成胰島發炎，使胰島素無法正常分泌，造成高血糖引發糖尿病。發炎(Inflammation)會放大自身蛋白(post-translational modifications，PTM)，而 PTM 其中包括瓜氨酸化(Citrullination)。瓜氨酸已在多種組織中被發現，並被廣泛研究為類風濕性關節炎(RA)的生物標誌物(bio maker)，在糖解作用中葡萄糖激酶催化葡萄糖磷酸化，葡萄糖激酶(glucokinase)的活性調節了人體內葡萄糖穩定，而葡萄糖激酶基因突變，會導致胰腺 β 細胞和肝細胞中的葡萄糖激酶活性降低，關於葡萄糖激酶功能障礙在 T1D 中的作用還未清楚。此篇研究證明發炎所導致葡萄糖激酶的瓜胺酸化只會在胰腺中。而促炎細胞因子導致胰島素分泌受損，可以透過加入 PAD2/PAD4 抑製劑阻斷瓜胺酸化，恢復胰島素的分泌。瓜氨酸化也改變了胰腺葡萄糖激酶的酵素動力學；因此將葡萄糖激酶定義為 1 型糖尿病生物標誌物，為炎症如何驅動 PTM 以產生新自身抗原和影響 β 細胞代謝提供了新的見解。

二、對論文內容的提問

在 Fig 2 的動物實驗中為何使用 B10.BR 小鼠作為 control 組並不是使用 WT 的 B6 做為 control，在此部分未詳細說明。

三、論文的缺點與評論

此篇文獻證明發炎反應所導致瓜胺酸化的 glucokinase 功能障礙，會導致胰島素的分泌受損，並且也證實透過阻斷瓜胺酸化或是抑制促炎細胞因子可以治療。而瓜胺酸化的 glucokinase 如何影響糖解作用的下游 pathway 導致胰島素分泌受損也值得往後探討。

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Inflammation, including reactive oxygen species and inflammatory cytokines in tissues amplify various post-translational modifications of self-proteins. A number of post-translational modifications have been identified as autoimmune biomarkers in the initiation and progression of Type 1 diabetes. Here we show the citrullination of pancreatic glucokinase as a result of inflammation, triggering autoimmunity and affecting glucokinase biological functions. Glucokinase is expressed in hepatocytes to regulate glycogen synthesis, and in pancreatic beta cells as a glucose sensor to initiate glycolysis and insulin signaling. We identify autoantibodies and autoreactive $CD4^+$ T cells to glucokinase epitopes in the circulation of Type 1 diabetes patients and NOD mice. Finally, citrullination alters glucokinase biologic activity and suppresses glucose-stimulated insulin secretion. Our study define glucokinase as a Type 1 diabetes biomarker, providing new insights of how inflammation drives post-translational modifications to create both neoautoantigens and affect beta cell metabolism.

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