염증조절 유전자 발견 및 당뇨병과의 상관관계 규명

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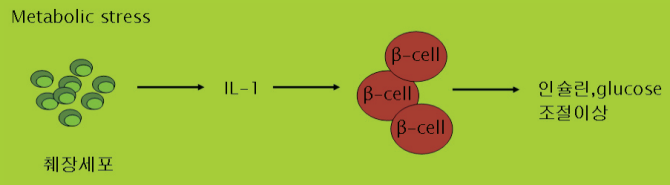
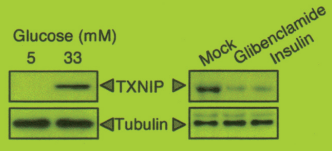
연구개요‥염증반응과 당뇨병은 밀접한 관계를 가지고 있는 것으로 알려지고 있는데, 본 연구에서는 염증과 당뇨병를 동시에 조절할 수 있는 두 개의 유전자를 찾았고 이들의 역할을 규명함.
‥이 두 개의 유전자가 세포내에서 결합을 통해 염증과 인슐린을 생성하는 베타세포의 기능 조절을 규명함.

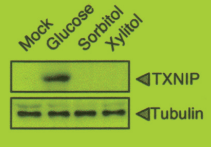
개발내용‥연구팀은 염증조절 결합체를 이루는 새로운 유전자 TXNIP(VDUP1)를 밝혔는데, VDUP1은 NLRP3과 결합하며 두 단백질이 IL-1 분비에 중요한 역할을 하는 것을 규명함.
‥만약에 두 유전자 중 하나만이라도 결핍이 되면 IL-1 분비와 염증반응이 문제가 되는 것을 규명함.
‥포도당을 처리하면 췌장세포에서 VDUP1이 증가되고 VDUP1과 NLRP3가 결핍이 된 췌장세포에서는 포도당에 의한 IL-1 분비가 감소되었음을 관찰함.
‥인슐린을 처리하면 베타세포에서 포도당에 의한 VDUP1의 발현을 억제하고 IL-1 생산이 억제되어, VDUP1-NLRP3 결합체는 베타세포에서의 포도당에 의한 IL-1 생산, 염증조절에 중요한 역할을 하는 것을 규명함.

활용사례 / 효과‥네이쳐 이뮤놀지(Nature Immunology)에 논문이 발표됨.
‥염증 조절, 염증과 당뇨병의 상관관계, 그리고 염증과 당뇨병 질병의 치료제를 개발하는데 중요한 기반이 될 것으로 기대함.



염증과 당뇨병의 관계
Metabolic stress 등에 의해 췌장세포가 자극을 받아 염증싸이토카인 (IL-1)을 분비하여 베타세포의 기능을 조절하여 인슐린 분비 등의 이상을 야기한다. IL-1 생산을 저해함으로 glucose의 양을 억제할 수 있다.





인슐린의 의한 VDUP1의 발현 억제
베타세포를 높은 농도의 glucose로 처리하면 VDUP1의 발현이 증가하고 인슐린을 처리하면 억제된다.
베타세포에서 VDUP1의 발현으로 보아 기능조절에 중요한 역할을 수행함을 알 수 있다.

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Thioredoxin-interacting protein links oxidative stress to inflammasome activation

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The NLRP3 inflammasome has a major role in regulating innate immunity. Deregulated inflammasome activity is associated with several inflammatory diseases, yet little is known about the signaling pathways that lead to its activation. Here we show that NLRP3 interacted with thioredoxin (TRX)-interacting protein (TXNIP), a protein linked to insulin resistance. Inflammasome activators such as uric acid crystals induced the dissociation of TXNIP from thioredoxin in a reactive oxygen species (ROS)-sensitive manner and allowed it to bind NLRP3. TXNIP deficiency impaired activation of the NLRP3 inflammasome and subsequent secretion of interleukin 1β (IL-1β). Akin to *Txnip*$^{-/-}$ mice, *Nlrp3*$^{-/-}$ mice showed improved glucose tolerance and insulin sensitivity. The participation of TXNIP in the NLRP3 inflammasome activation may provide a mechanistic link to the observed involvement of IL-1β in the pathogenesis of type 2 diabetes.

Active, mature interleukin 1β (IL-1β) is produced by cleavage of the inactive pro-IL-1β precursor by caspase-1, which is activated in a large multiprotein complex called the inflammasome[1,2]. The NLRP3 inflammasome, composed of the Nod-like receptor protein NLRP3 (also called cyopyrin or NALP3), CARDINAL, the adaptor protein ASC and caspase-1 (ref. 3), is vital for the production of mature IL-1β in response to a variety of signals. The NLRP3 inflammasome is activated by bacterial toxins[4] or pathogen-associated molecular patterns, such as muramyldipeptide[5]. NLRP3 can also detect endogenous stress-associated danger signals, such as ATP[4], monosodium urate crystals (MSU)[6] or β-amyloid[7]. Although reactive oxygen species (ROS), together with low cytoplasmic concentrations of potassium (K^+), are known to be prerequisites for activation of the NLRP3 inflammasome[8,9], the signaling pathways that lead to NLRP3 activation are still poorly understood.

Three distinct signaling pathways for inflammasome activation have been proposed. In one model, activators enter the cytoplasm

RESULTS

TXNIP is an NLRP3-binding protein

A yeast two-hybrid screen using the leucine-rich repeats (LRRs) of NLRP3 as bait has identified TXNIP[12,13] as a potential binding partner of NLRP3. We confirmed the interaction between TXNIP and NLRP3 in human embryonic kidney (HEK293) T cells. Overexpressed TXNIP (**Fig. 1a**) and endogenous TXNIP (**Fig. 1b**) bound full-length NLRP3 and the LRR region of NLRP3, as expected. The nucleotide-binding NACHT domain of NLRP3 also interacted with TXNIP. Endogenous TXNIP did not bind other members of the NLR family or other proteins containing LRRs (**Fig. 1c**), which suggested that the TXNIP interaction is a specific feature of NLRP3. TXNIP contains two arrestin domains and a carboxy (C)-terminal extension with no apparent homology to other proteins (**Fig. 1a**). The C-terminal arrestin domain 'preferentially' interacted with NLRP3 (**Fig. 1d**).

Activation of the NLRP3 inflammasome is dependent on the generation of ROS[14]. In fact, all known NLRP3 activators generate