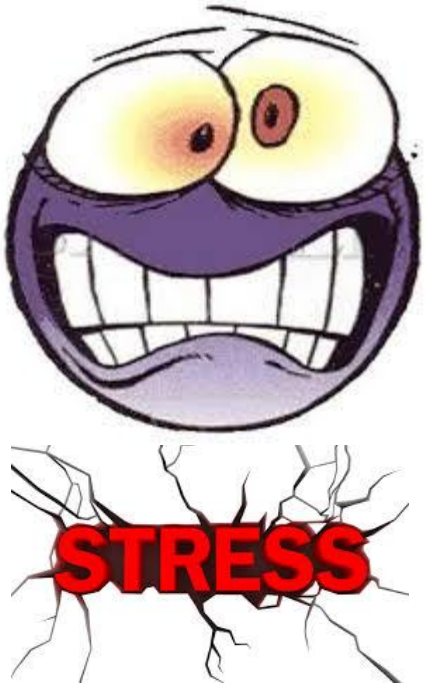
ER-stress in the pathogenesis of autoimmune diabetes

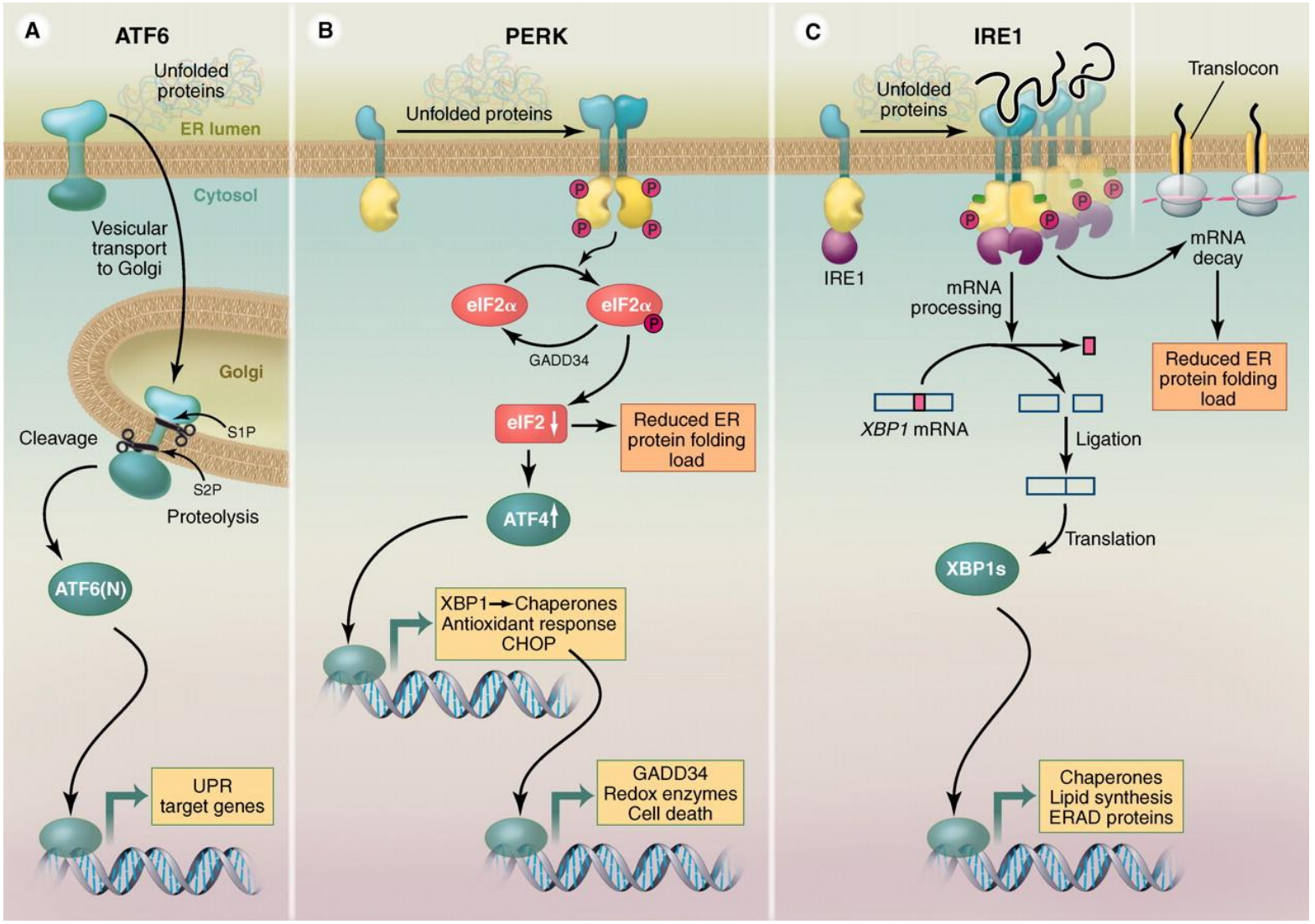


Armando

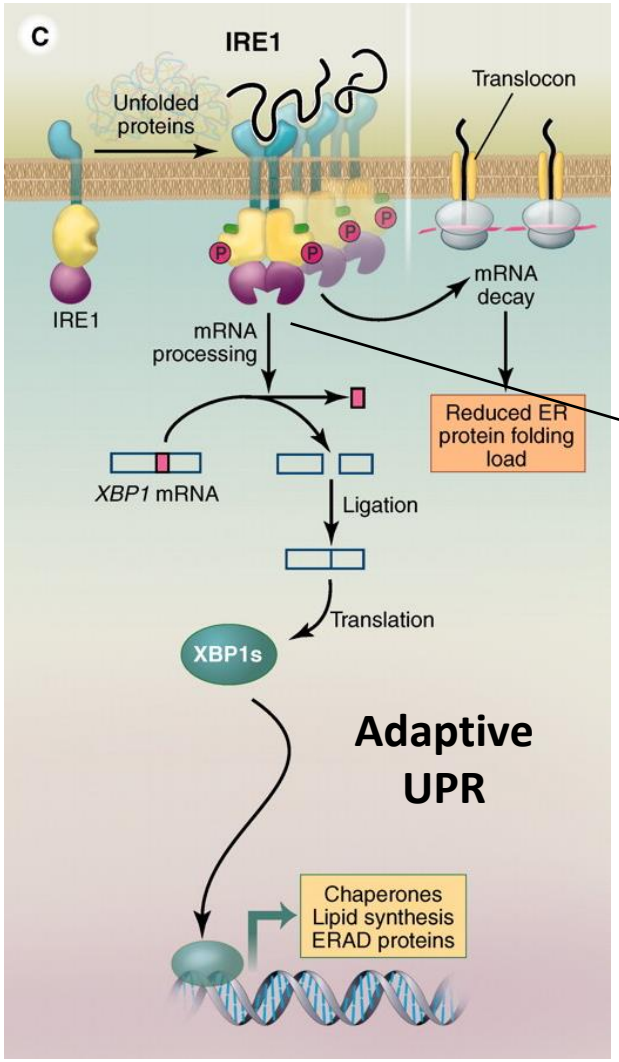
Lab meeting 2-26-14


STHENIC

The sensory systems of endoplasmic reticulum (ER) stress



Overview of IRE1α pathway



- **Increased IRE1α activity cleaves miR-17.**
- **Degradation of miR-17 removes repressive effect on TXNIP**
- **Increased TXNIP.**

miR-17

3’ **5’** **TXNIP mRNA**

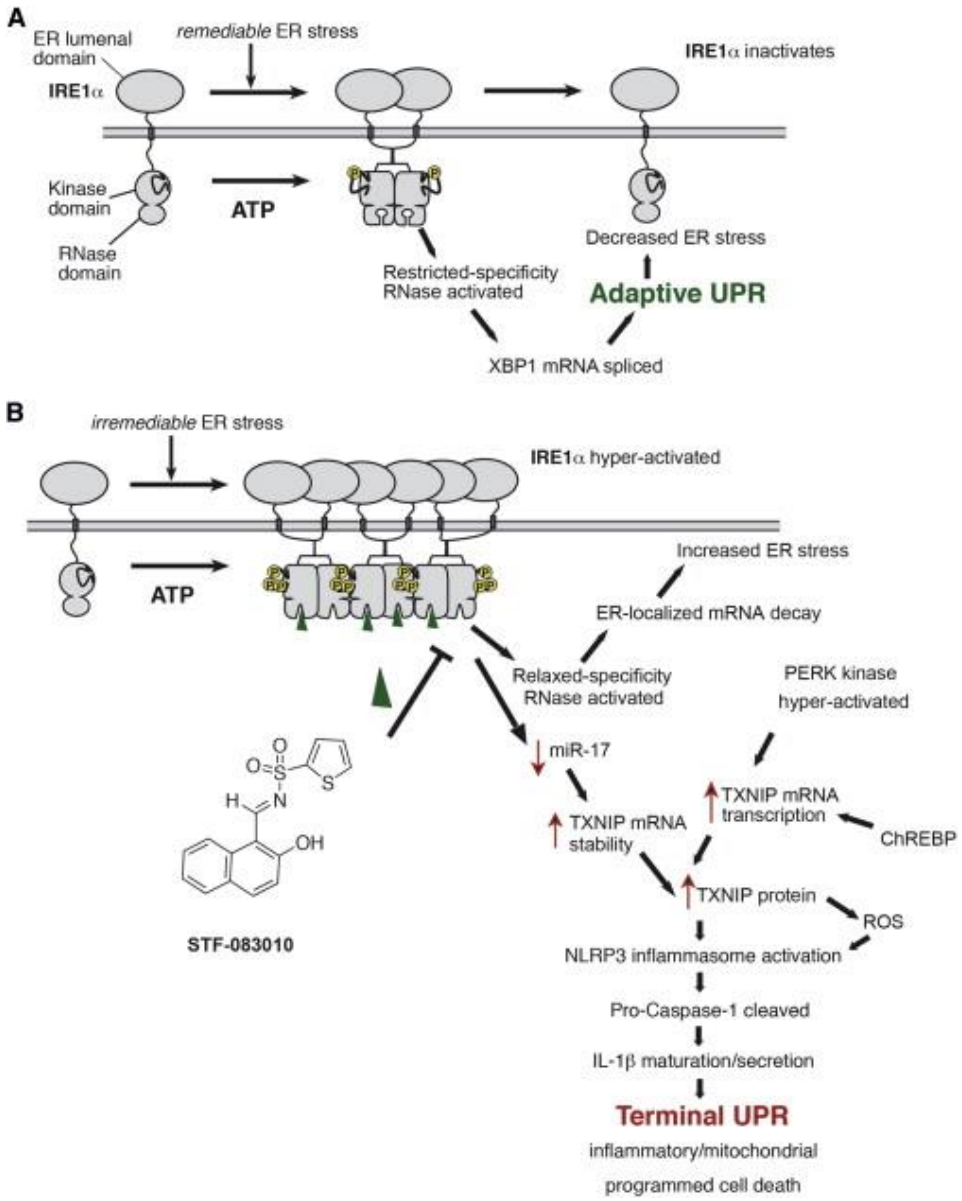
NRLP3 inflammasome activation

caspase

IL-1β

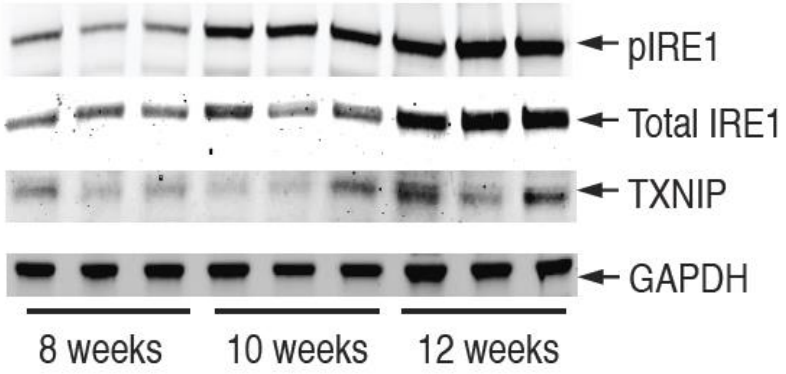
cell death

Adaptive vs Terminal UPR (homeostasis vs. cell death)

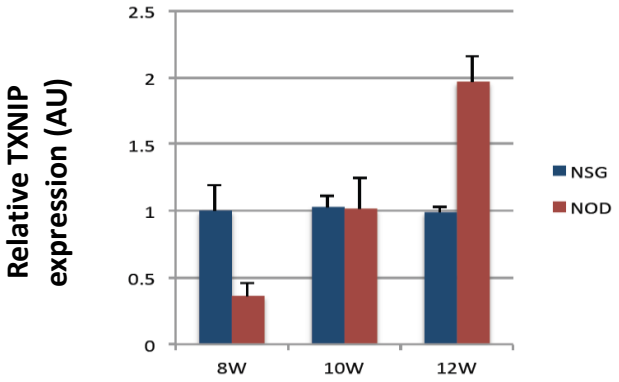


Activation of the IRE1 pathway in NOD mice precedes hyperglycemia

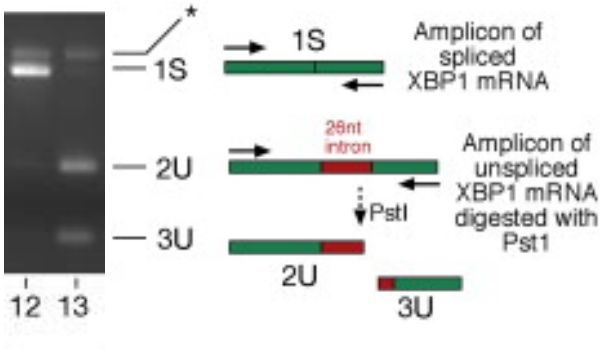
A

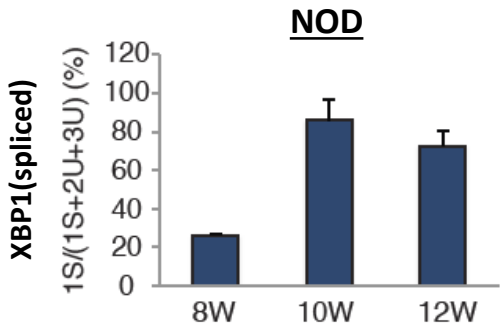


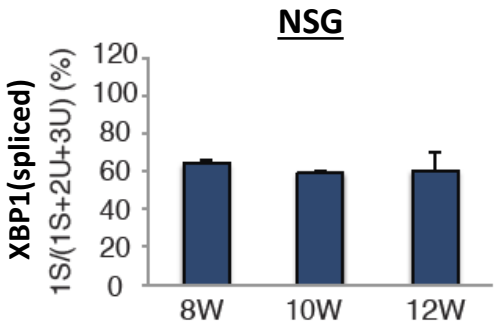
B



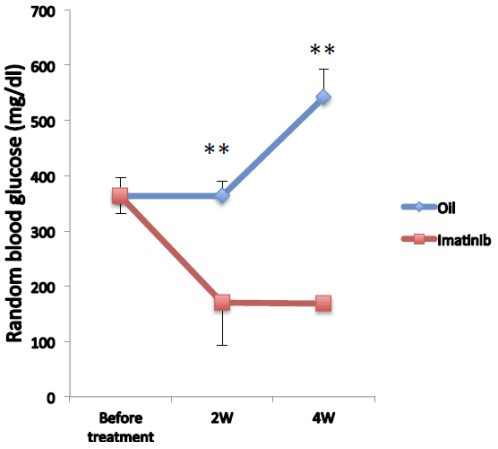
C

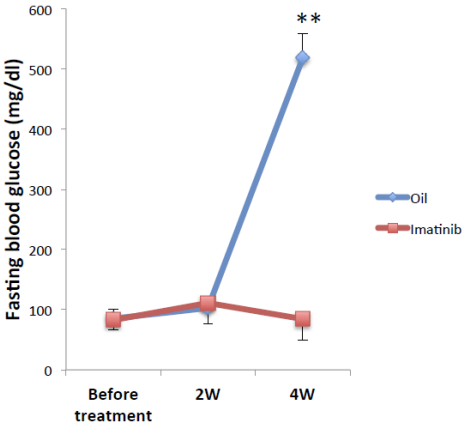




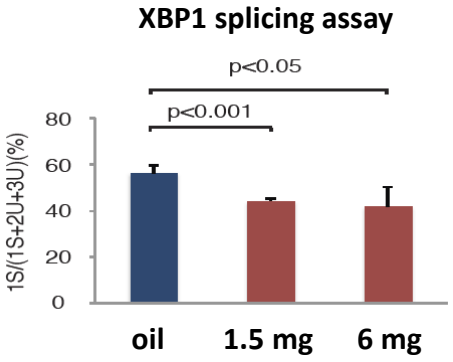


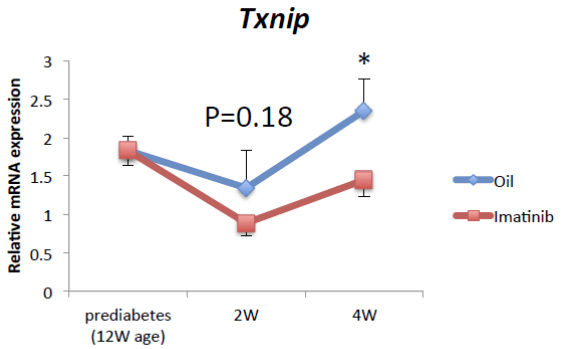
Imatinib attenuates ER-stress in the islets of diabetic NOD mice

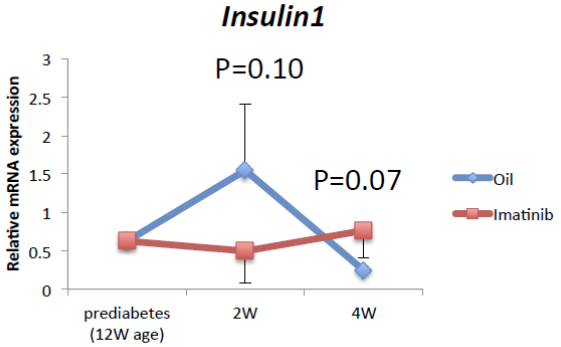




- *; <0.05, **; <0.001, vs. Imatinib treated group (n=3-5)
- Imatinib; 100mg/kg/day, p.o.

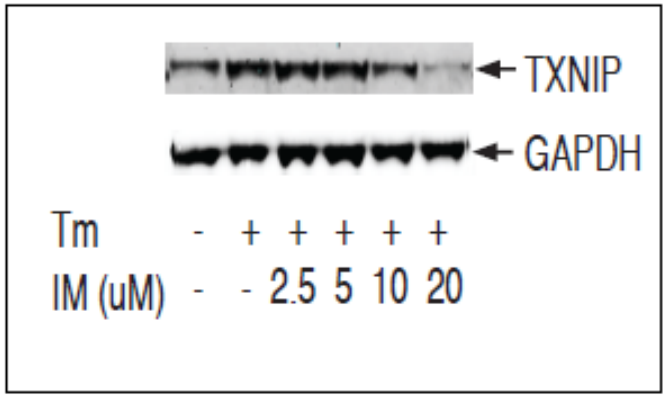


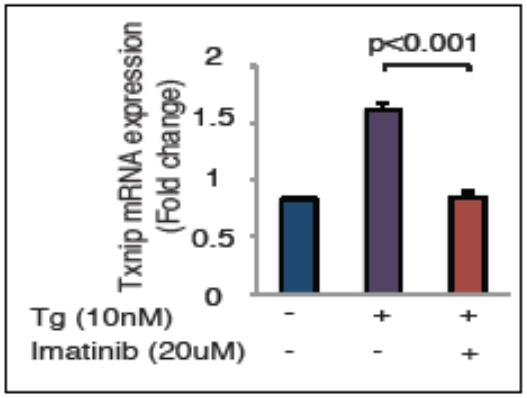




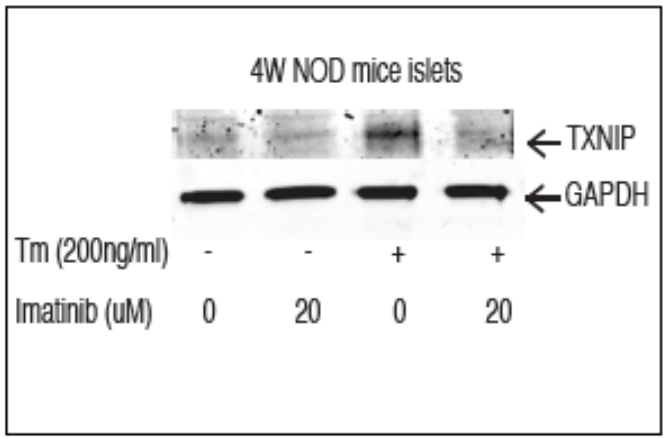
Imatinib inhibits experimentally-induced ER-stress in INS1 β-cells in NOD islets

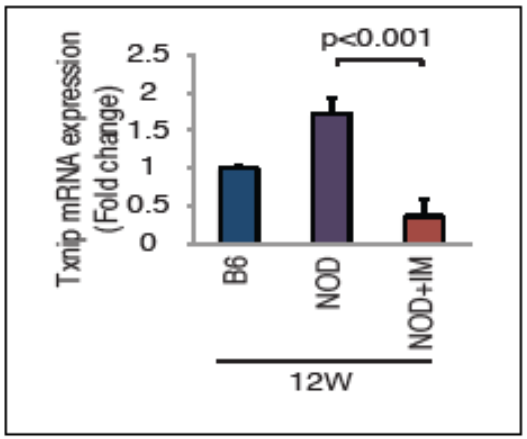
INS1 cells





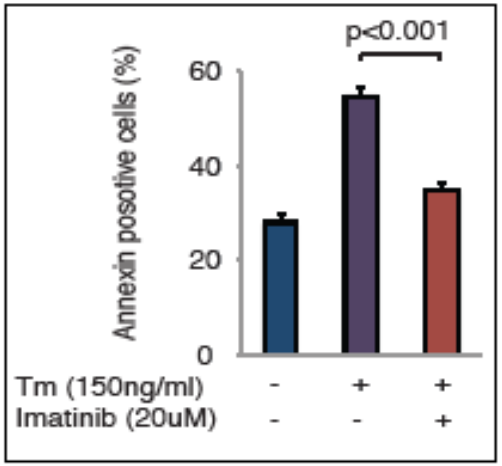
Islets





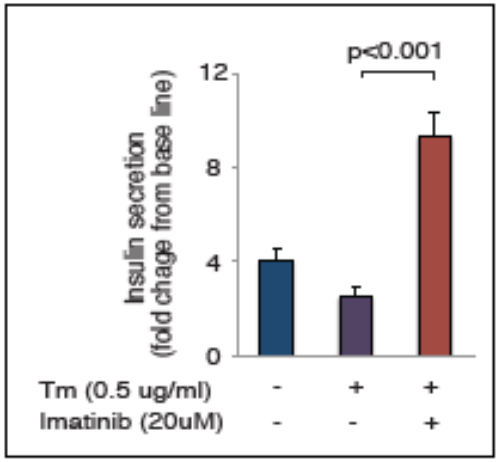
Imatinib inhibits ER-stress-mediated apoptosis and impairment of insulin secretion.

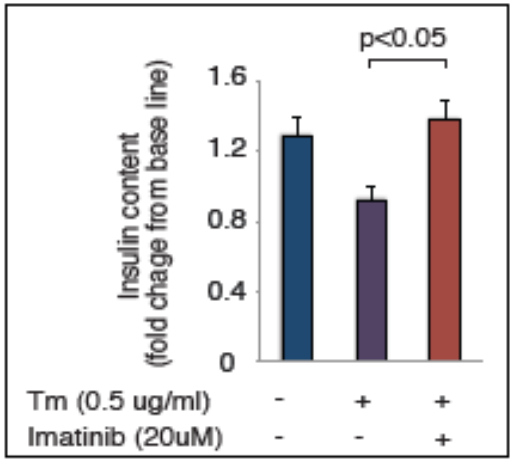
INS1 cells



Islets

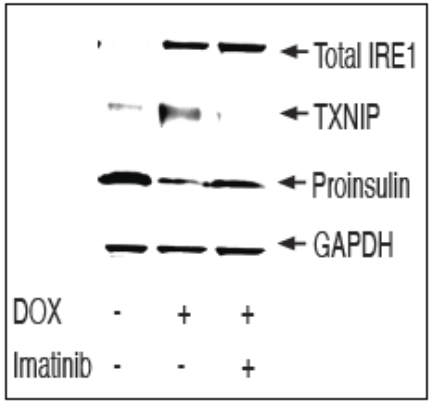
(B6)

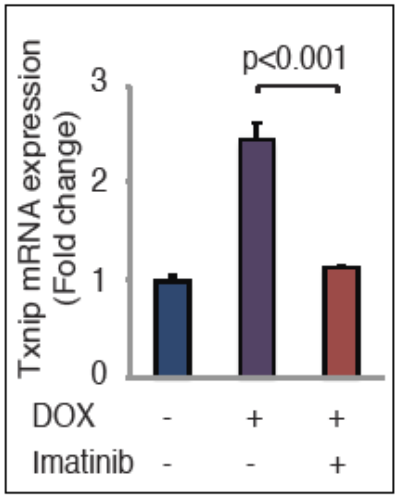


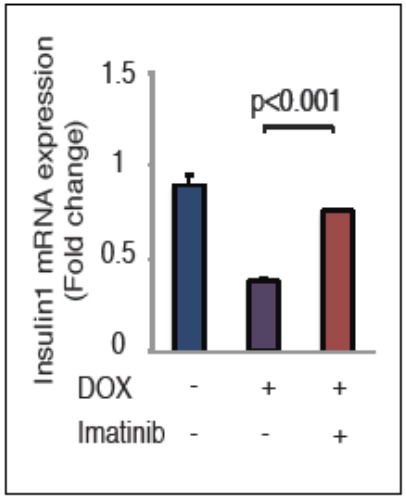


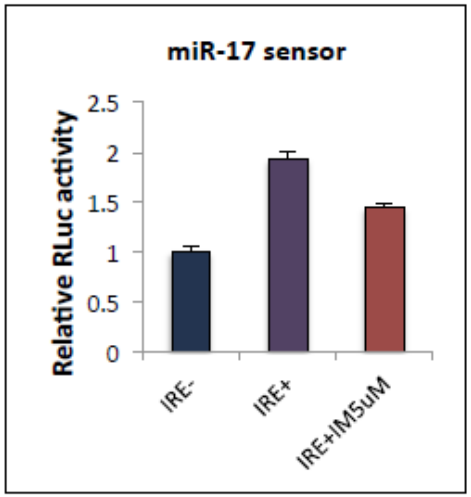
Imatinib inhibits ER-stress-mediated apoptosis and impairment of insulin secretion.

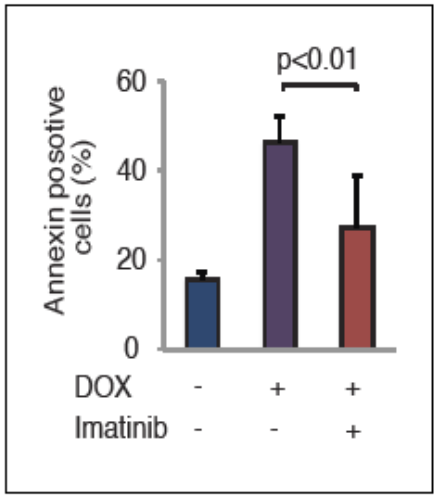
INS-1 cells :: $P_{CMV/2X\ TetO_2}$ → IRE1 α





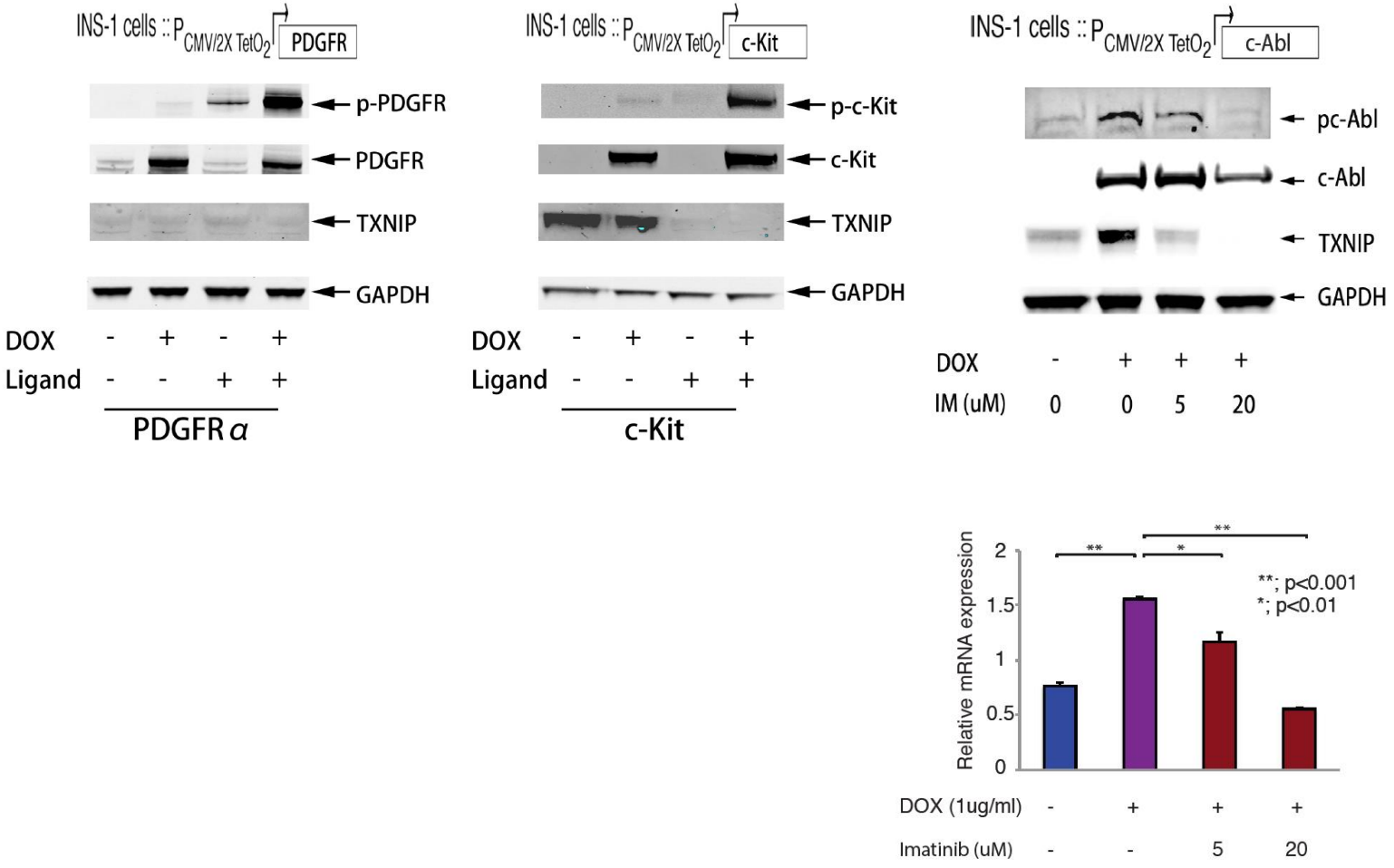






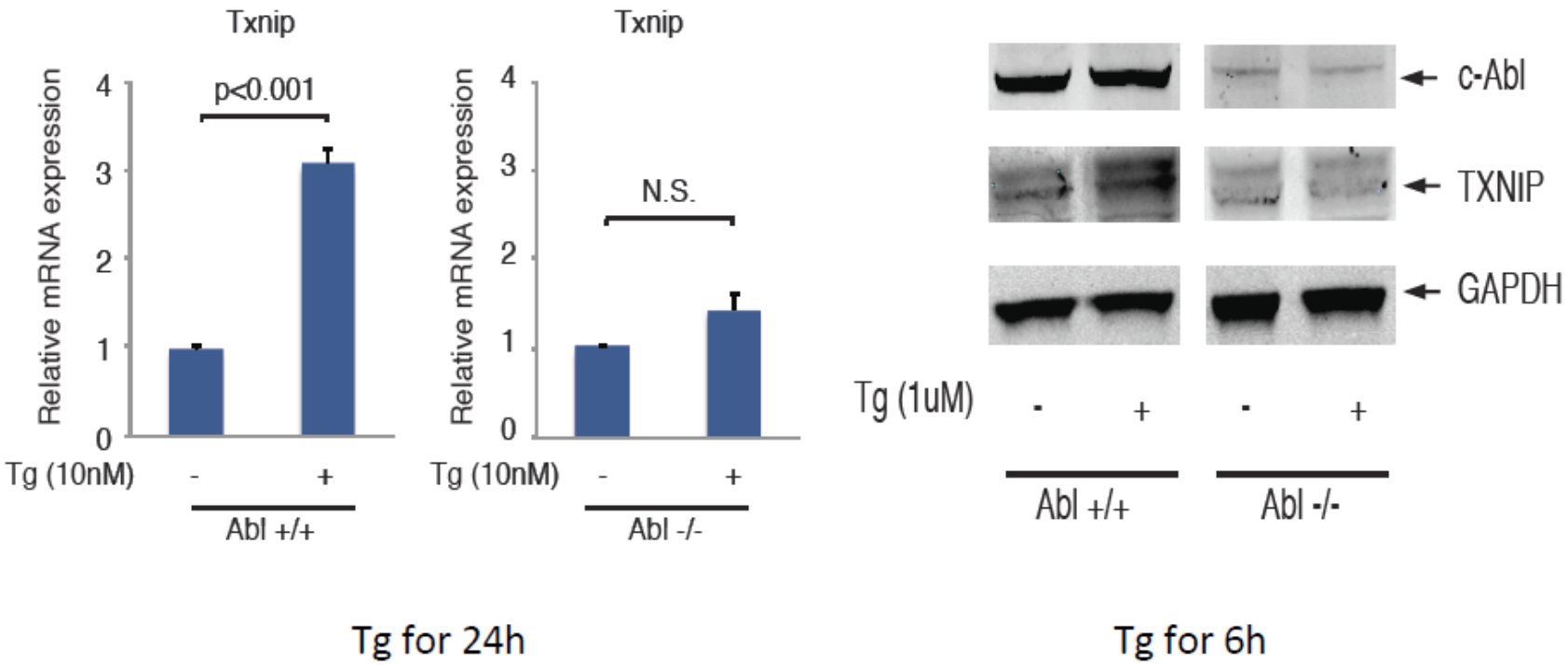
How does this assay work again?

Overexpression of c-abl in INS-1 cells induces TXNIP expression.

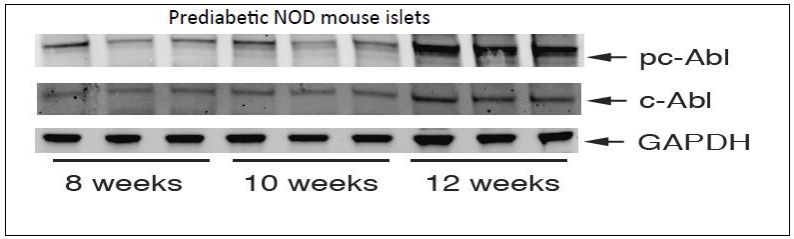


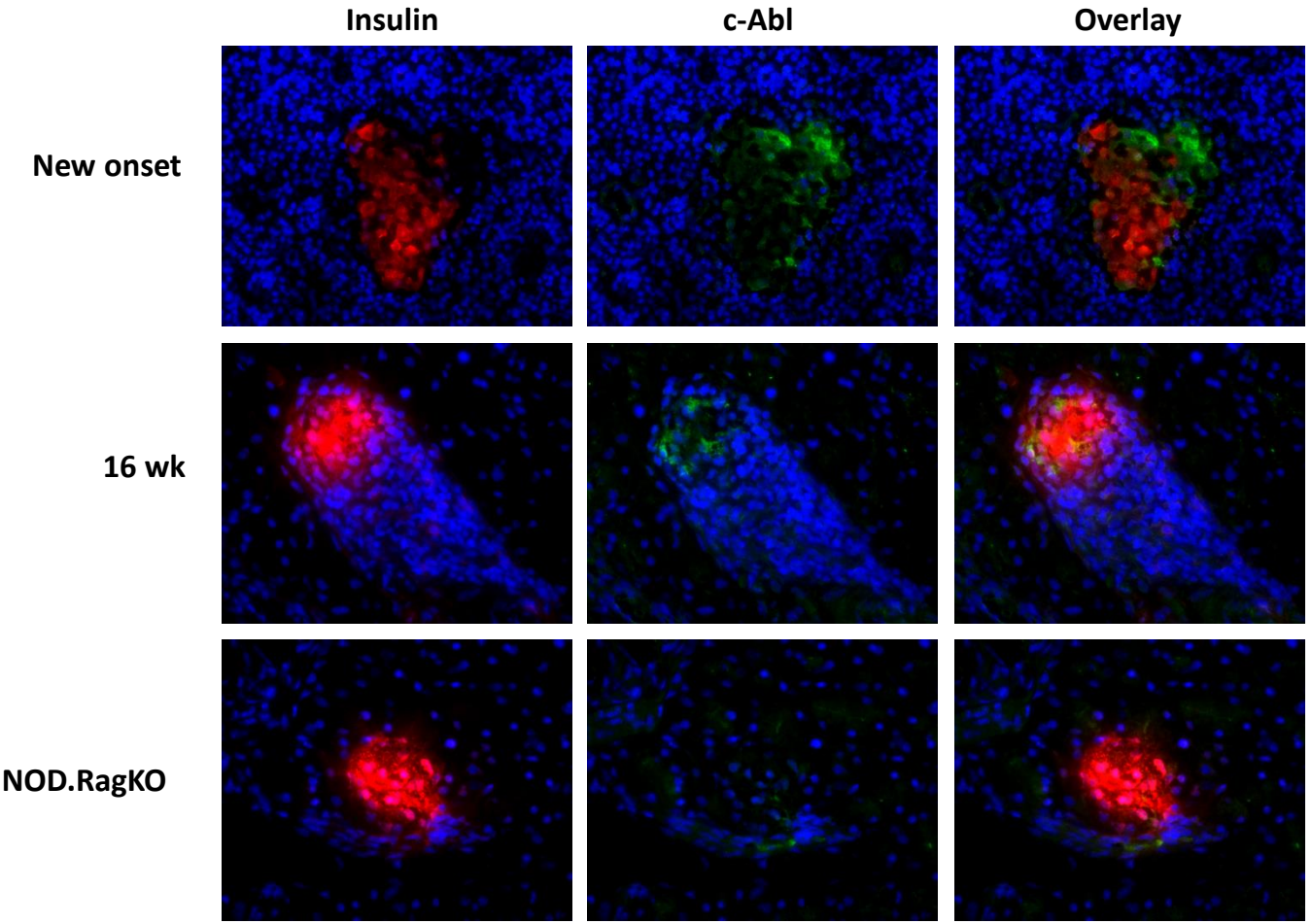
Thapsigargin-dependent induction of TXNIP is c-abl dependent.

Mouse embryonic fibroblasts (MEFs).

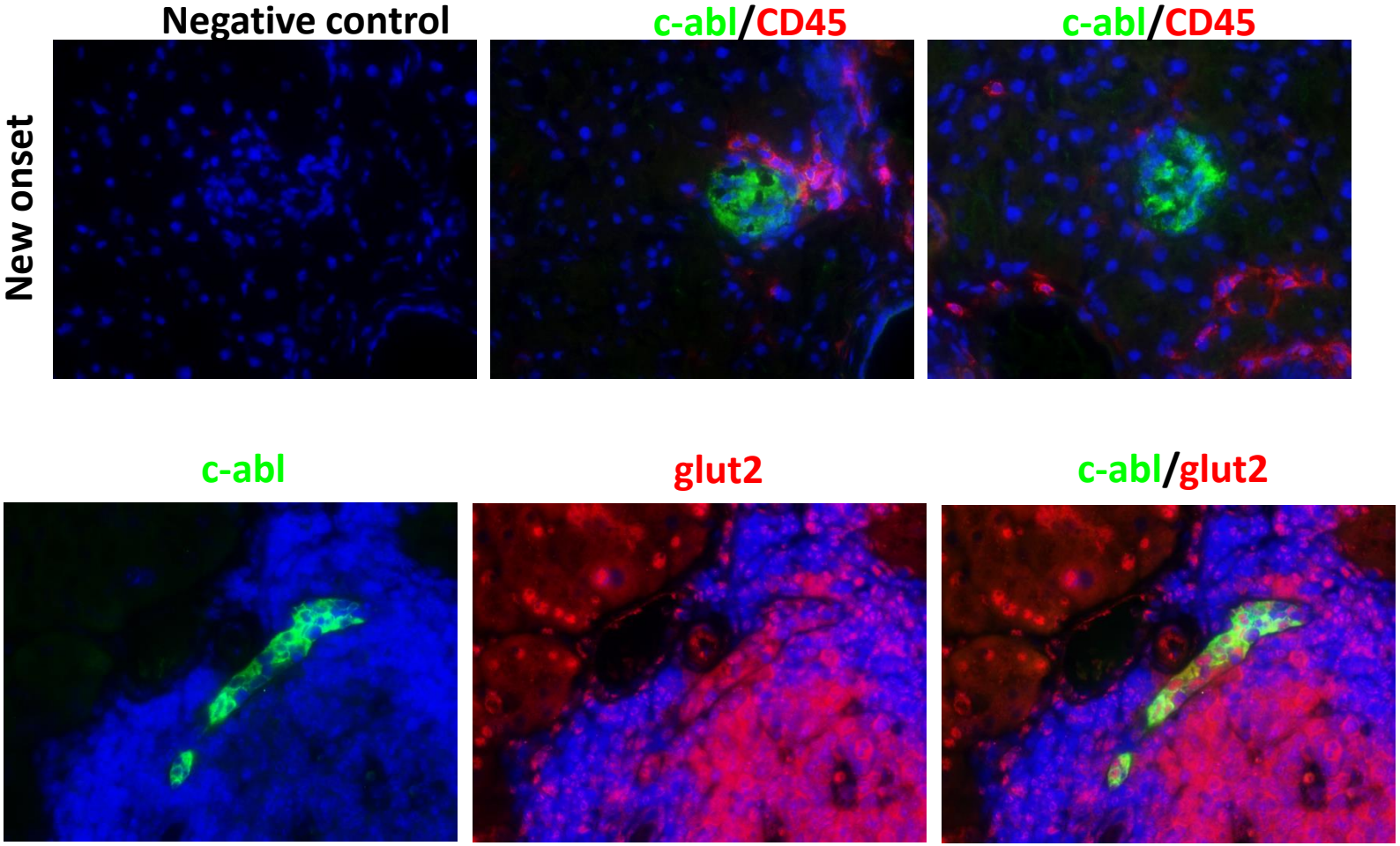


Induction of c-abl in NOD islets is dependent on inflammation.

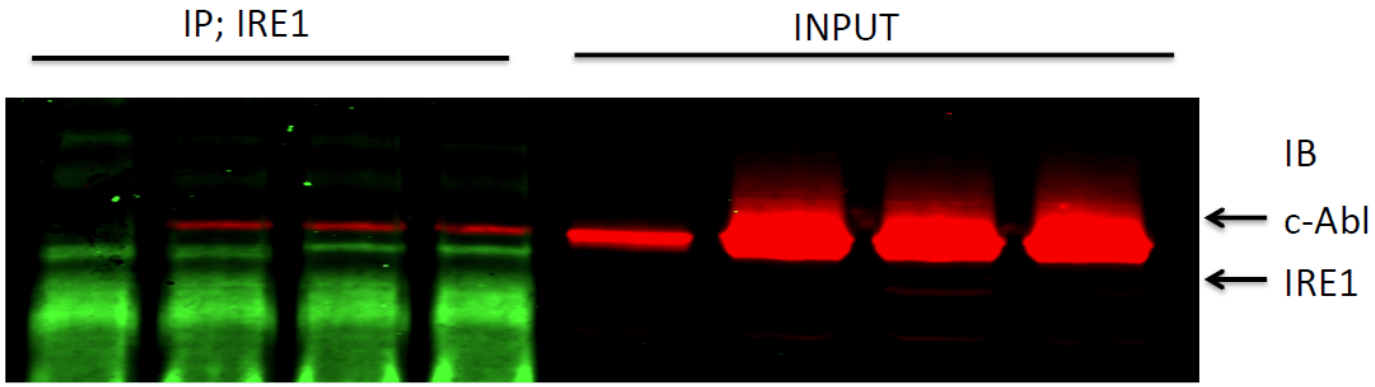


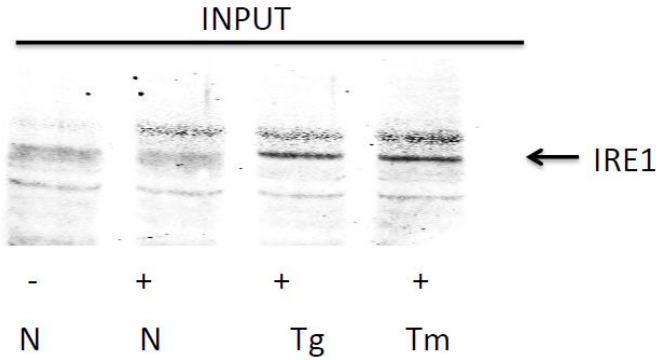


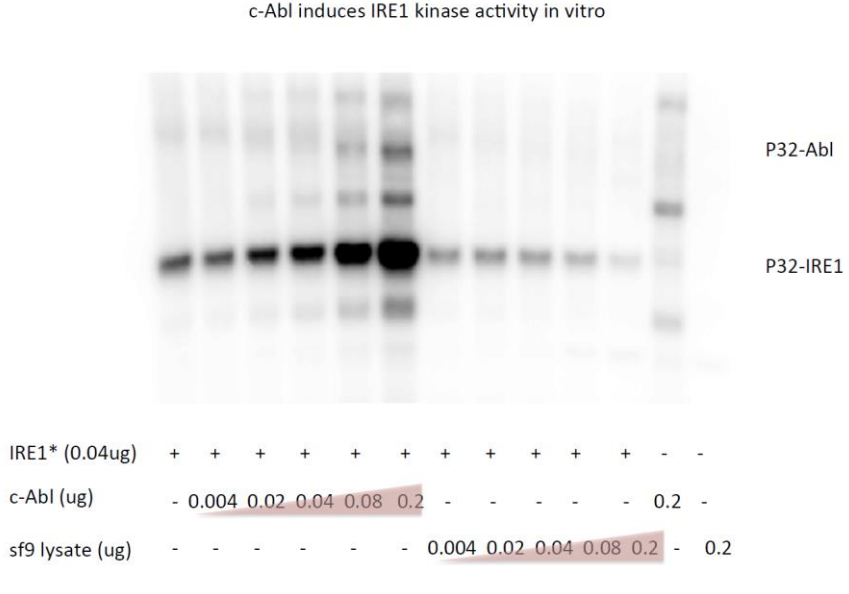
C-abl^{+} islets cells express GLUT-2



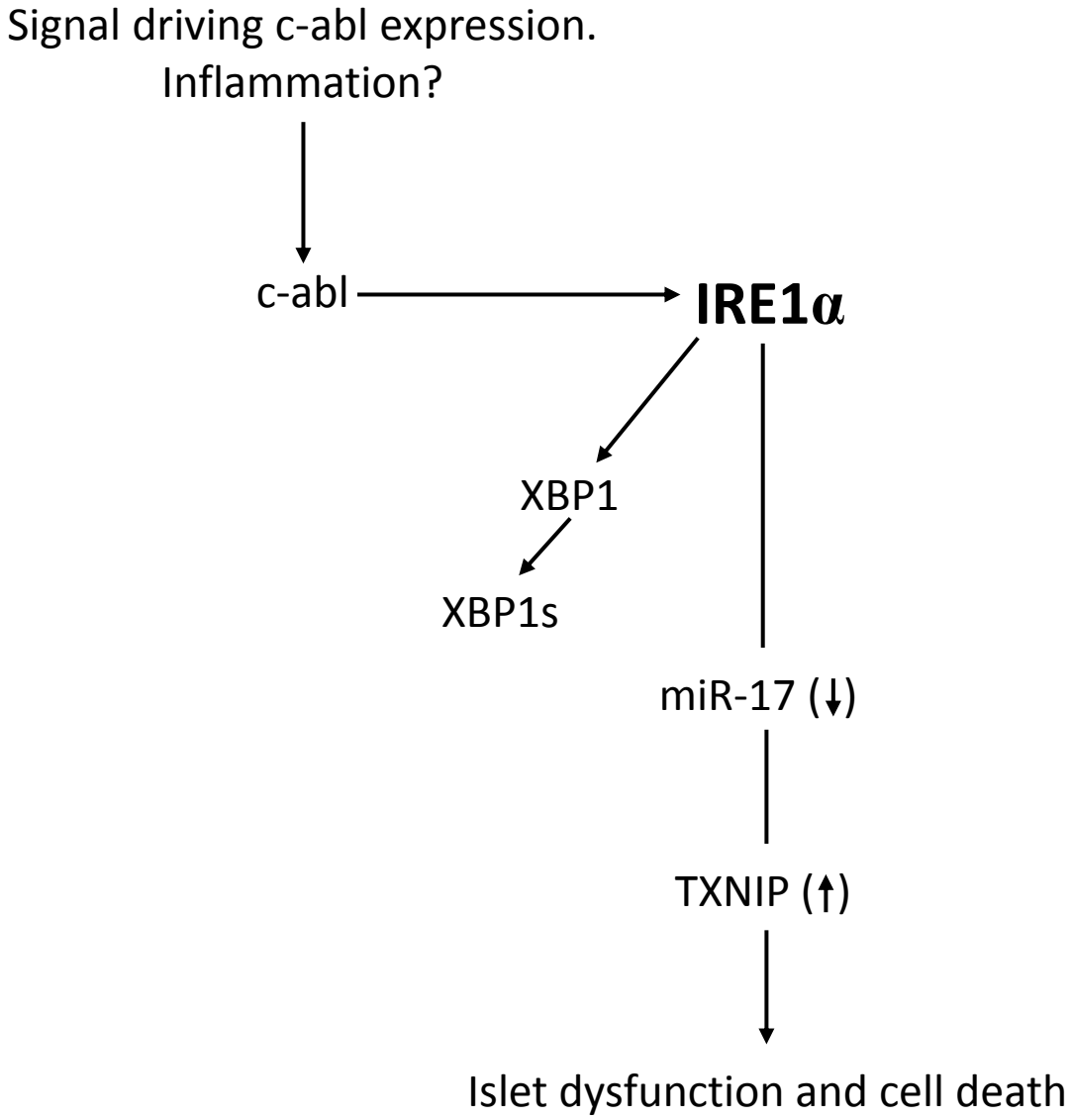
A potential c-abl and IRE1α complex that promotes activation of IRE1α.







Working Model



Acknowledgements:

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Wendy Rosenthal

Feroz Papa
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Rajarshi Ghosh
Aeid Igbaria

Evidence for the IRE1α sensing of ER stress in the immune system.

Plasma cell differentiation and the unfolded protein response intersect at the transcription factor XBP-1

Neal N. Iwakoshi[1]*, Ann-Hwee Lee[1]*, Prasanth Vallabhajosyula[1], Kevin L. Otipoby[2], Klaus Rajewsky[2] and Laurie H. Glimcher[1,3]

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Research article Related Commentary, page 224

The unfolded protein response sensor IRE1α is required at 2 distinct steps in B cell lymphopoiesis

Kezhong Zhang,[1] Hetty N. Wong,[1] Benbo Song,[2] Corey N. Miller,[1] Donalyn Scheuner,[2] and Randal J. Kaufman[1,2]

[1]Department of Biological Chemistry and [2]Howard Hughes Medical Institute, University of Michigan Medical Center, Ann Arbor, Michigan, USA.

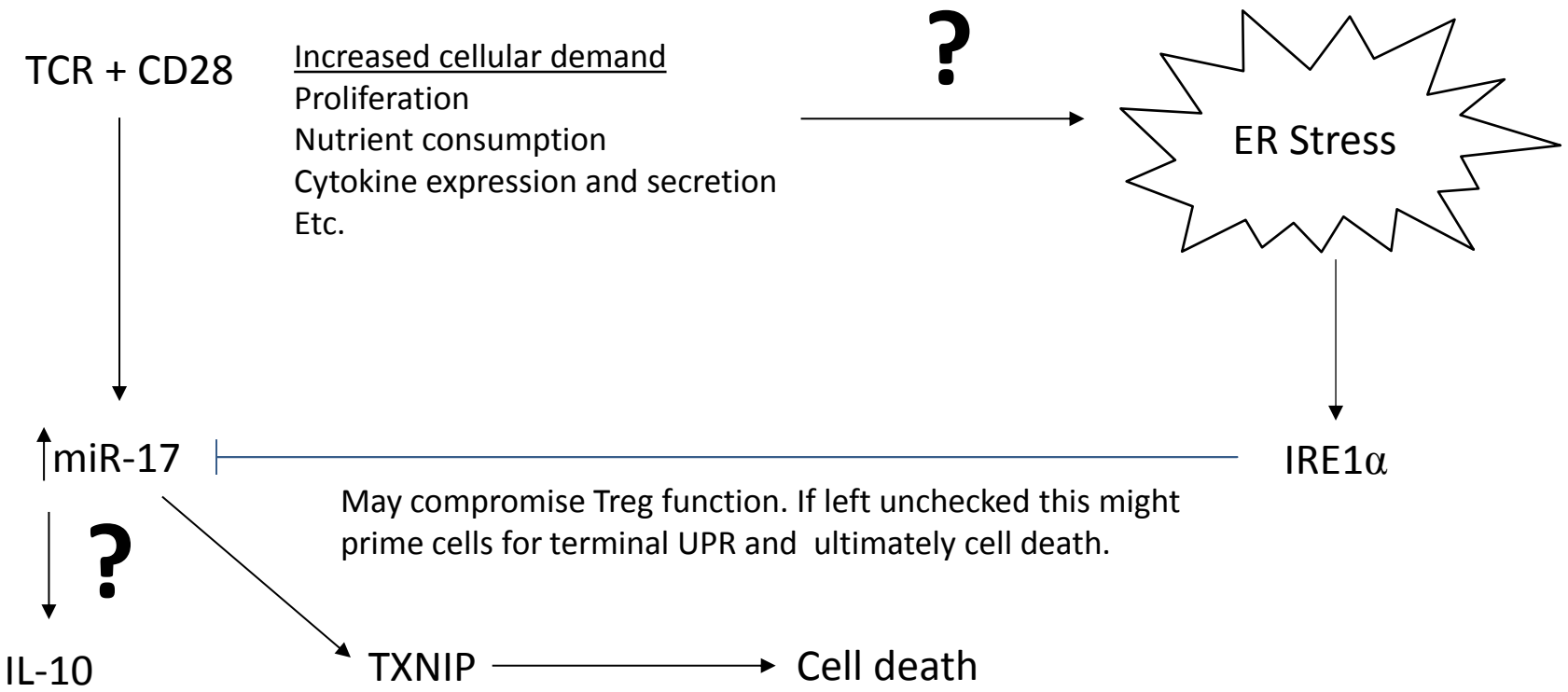
The transcription factor XBP-1 is essential for the development and survival of dendritic cells

Neal N. Iwakoshi,[1,2] Marc Pypaert,[3] and Laurie H. Glimcher[1,4]

[1]Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA 02115
[2]Department of Surgery, Emory School of Medicine, Atlanta, GA 30322
[3]Department of Cell Biology, Yale University School of Medicine, New Haven, CT 06520
[4]Department of Medicine, Harvard Medical School, Boston, MA 02115

microRNA-17–92 Regulates IL-10 Production by Regulatory T Cells and Control of Experimental Autoimmune Encephalomyelitis

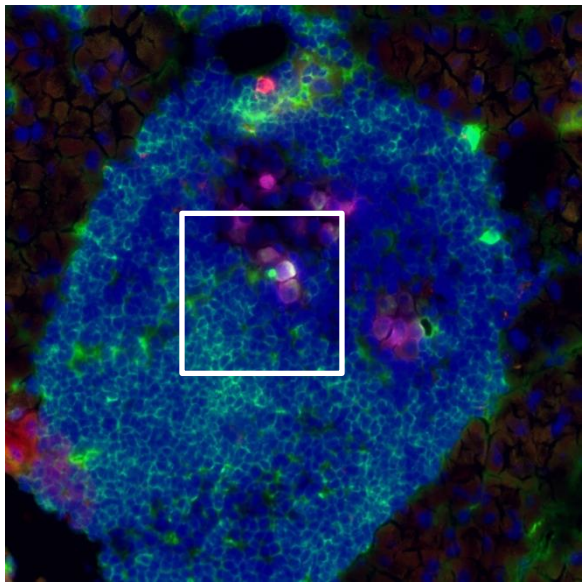
Dimitri de Kouchkovsky,* Jonathan H. Esensten,* Wendy L. Rosenthal,* Malika M. Morar,* Jeffrey A. Bluestone,*,†,1 and Lukas T. Jeker*,†,1



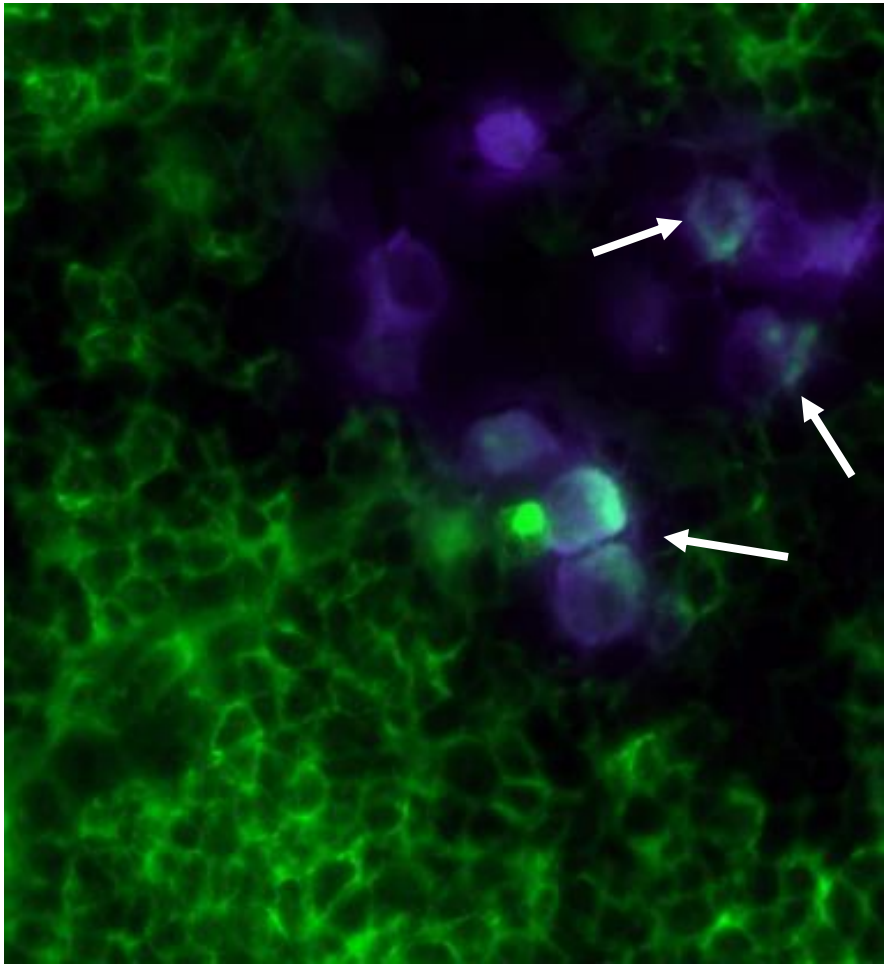
TXNIP is expressed by multiple cell types in NOD islets.

New onset diabetic

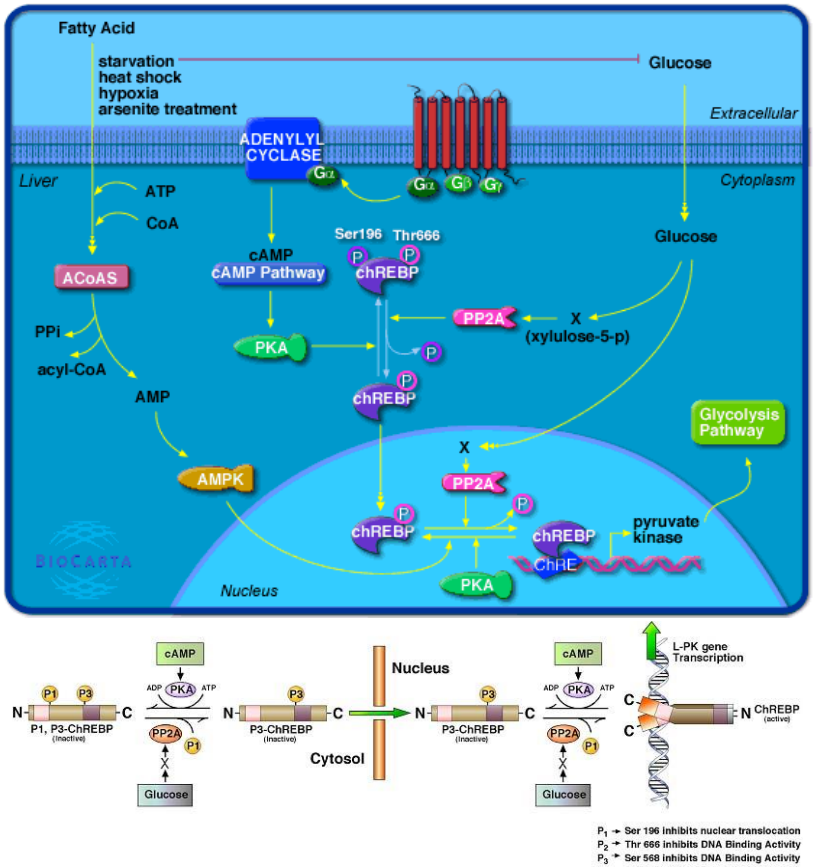
DAPI/GLUT-2/Insulin/TXNIP

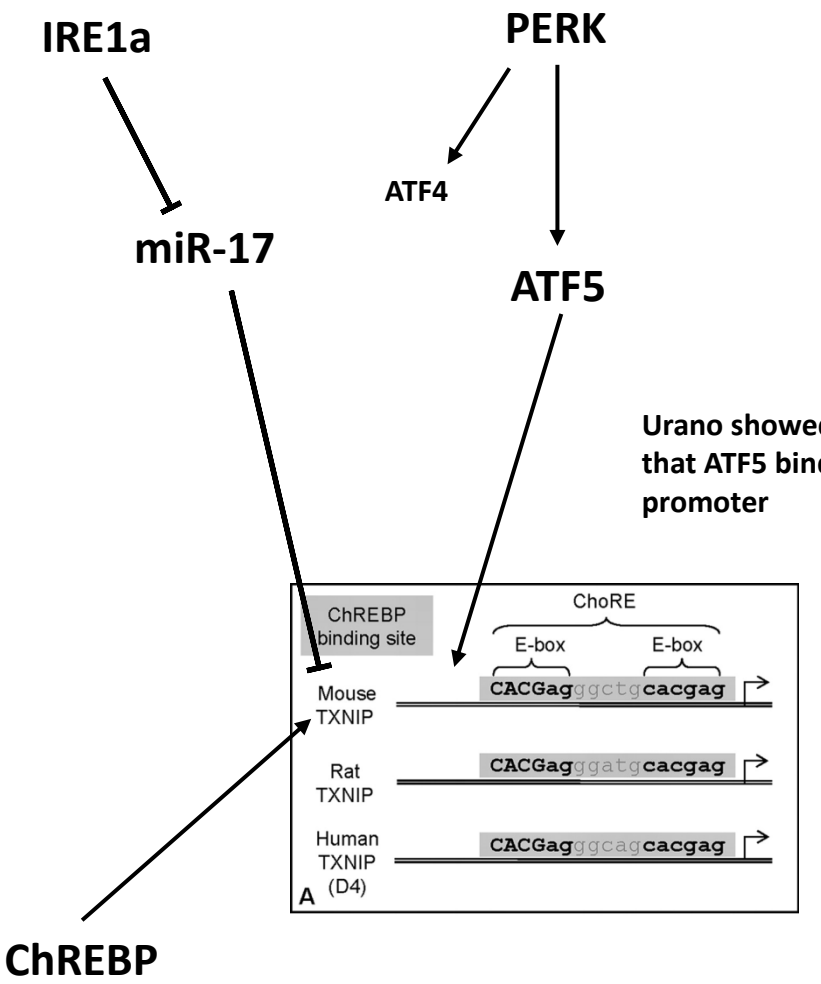


Insulin/TXNIP



Pathways regulating TXNIP

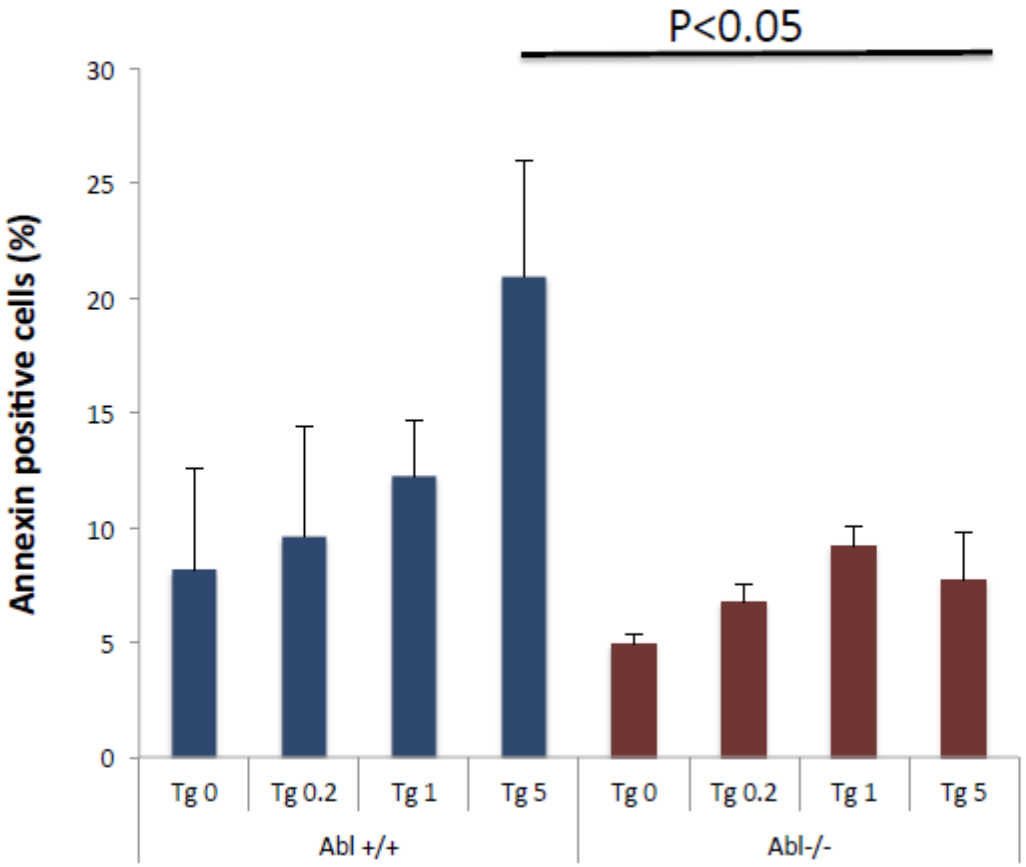




Urano showed by ChIP that ATF5 binds TXNIP promoter

ER stress-induced apoptosis is c-Abl dependent

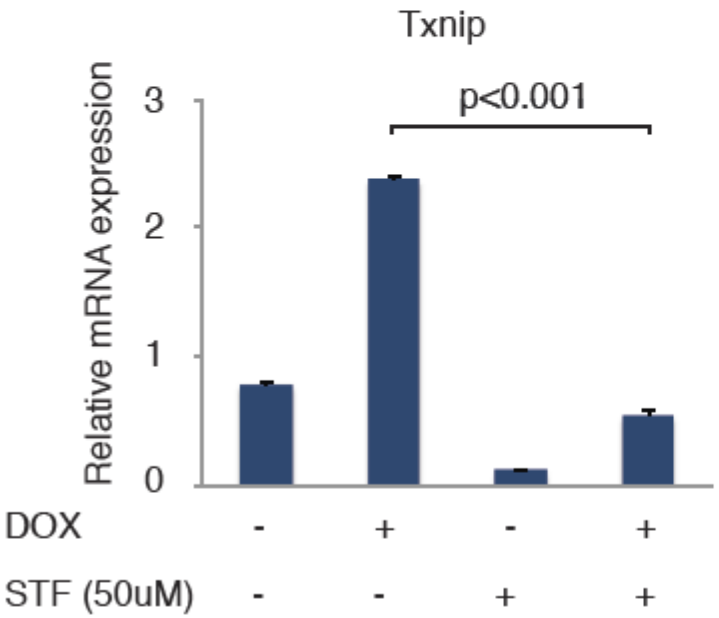
Done in MEFs

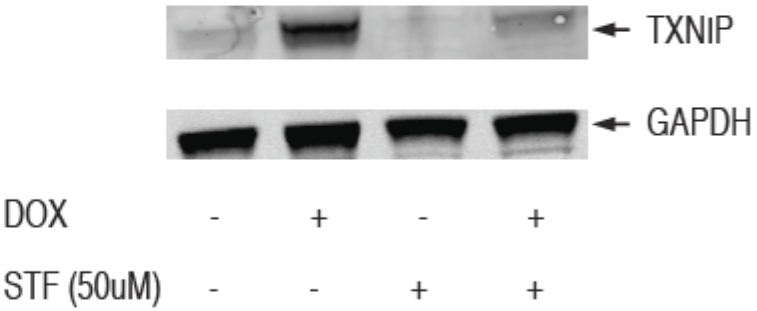


Tg (uM) for 8h

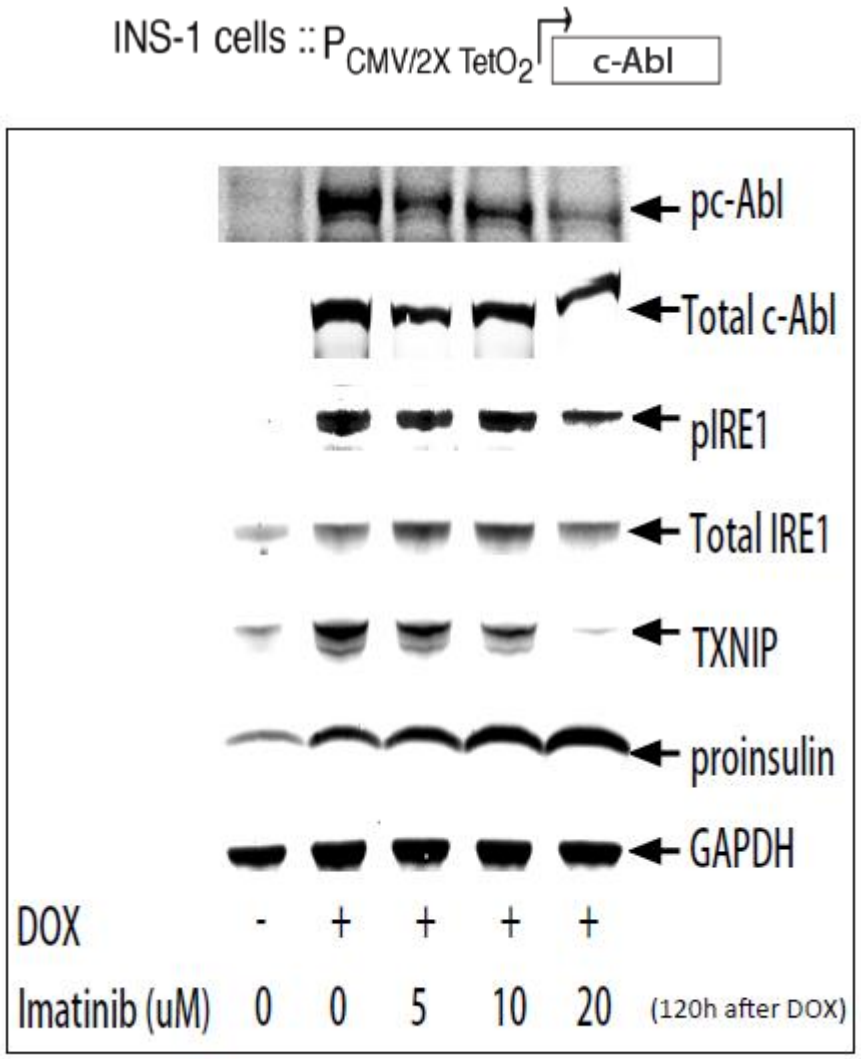
STF reduces c-Abl-induced TXNIP expression

INS-1 cells :: $P_{CMV/2X\ TetO_2}$ c-Abl





DOX, STF for 72h


INS-1 cells :: P CMV/2X TetO2
c-Abl
pc-Abl
Total c-Abl
pIRE1
Total IRE1
TXNIP
proinsulin
GAPDH
DOX - + + + +
Imatinib (uM) 0 0 5 10 20
(120h after DOX)