Overview of the Unfolded Protein Response

13th International Myeloma Workshop
6-3-2011

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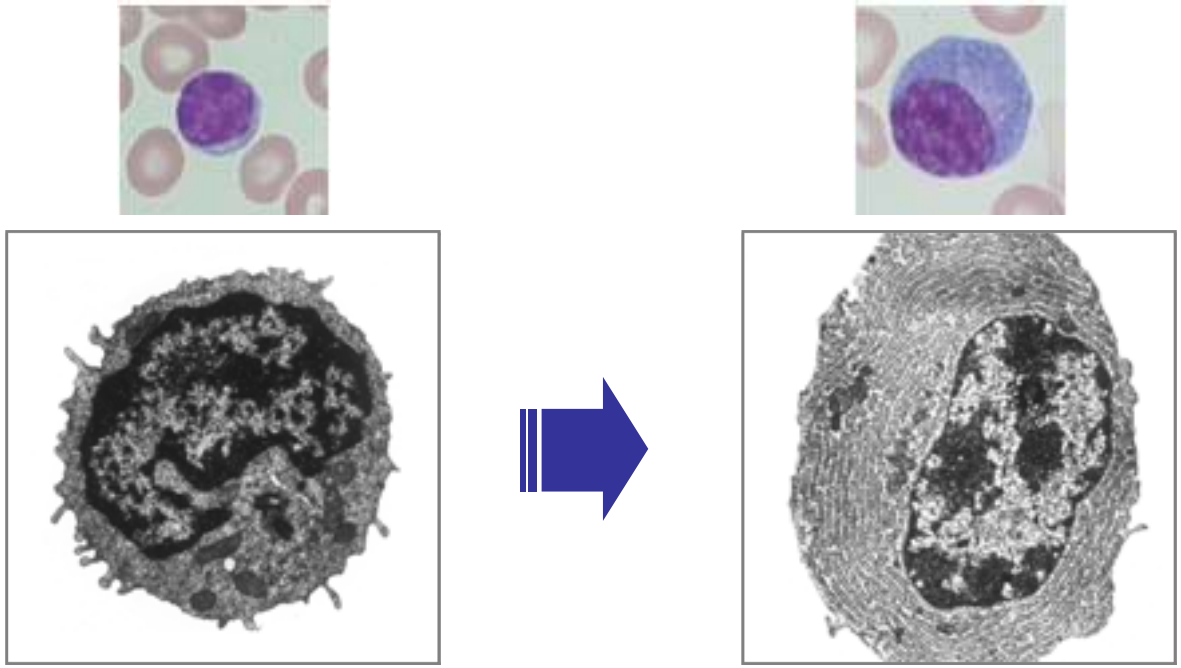
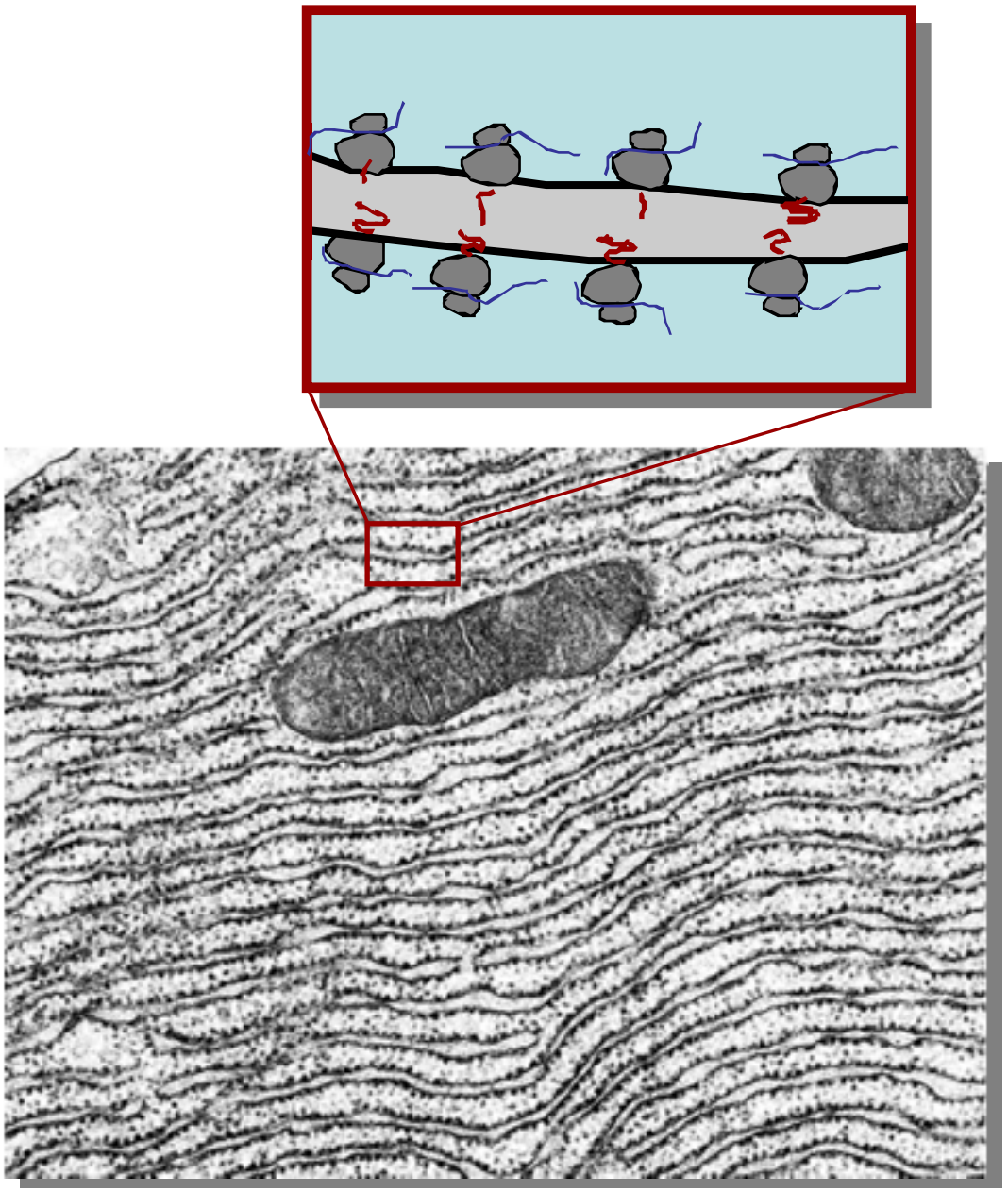
Hallmark feature of plasma cell differentiation



Resting B cell

Active B cell
(Plasma cell)



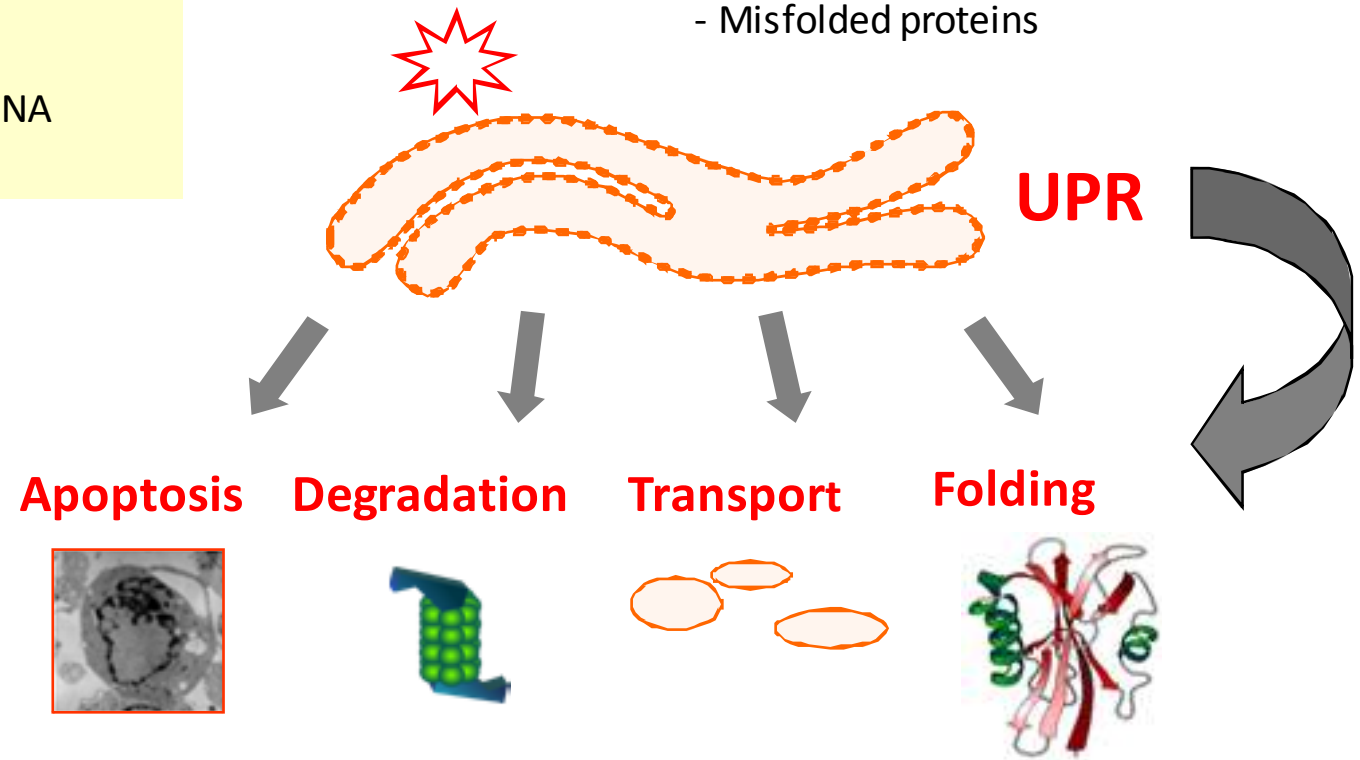
Maturation of secretory and transmembrane proteins

Lipid membrane biogenesis

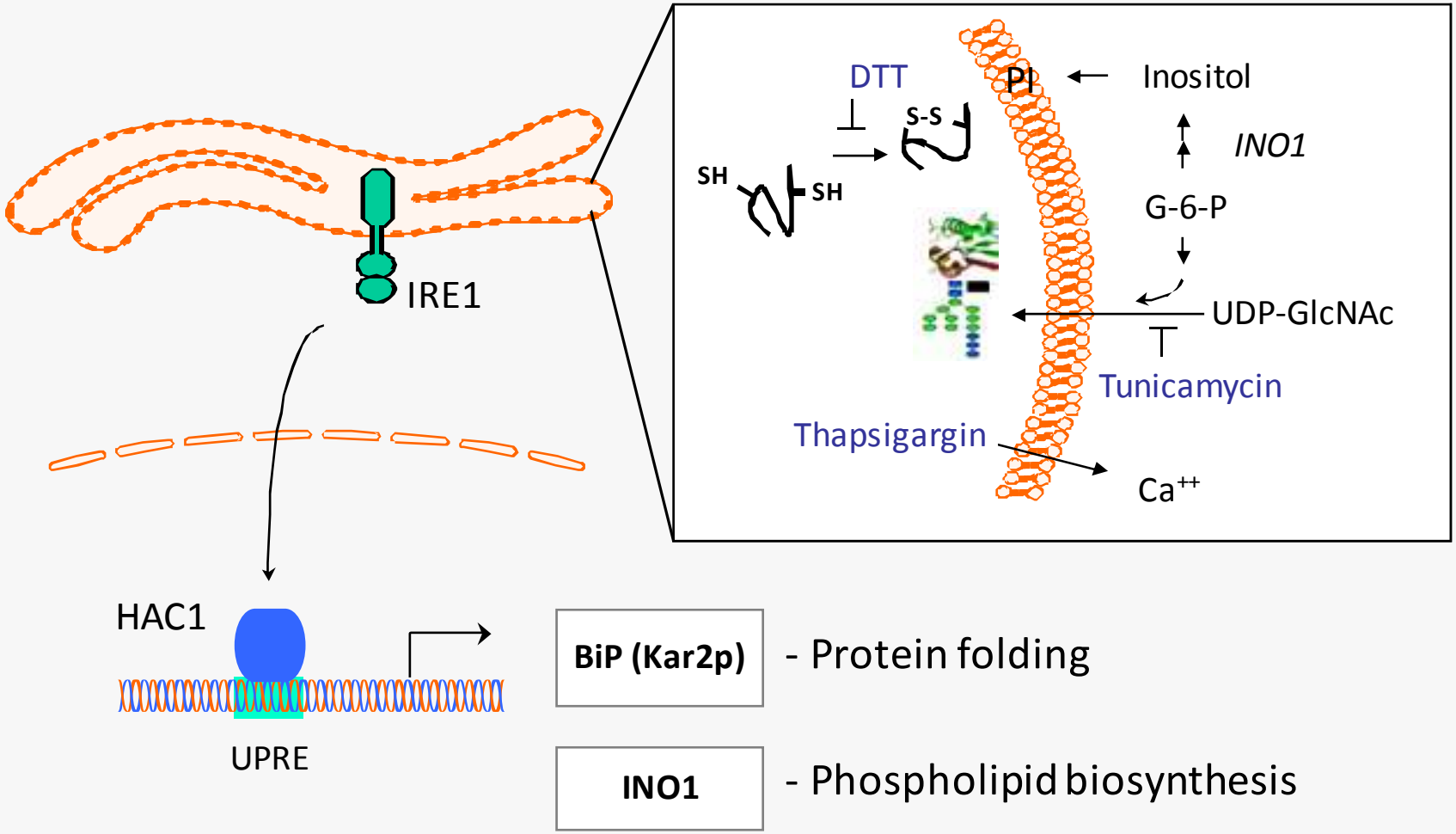
Major calcium storage

UPR is activated by ER stress

- Pharmacological
  - -Tunicamycin, DTT, etc
- Physiological
  - - Secretory proteins (Immunoglobulins)
- Pathological
  - - Misfolded proteins



UPR signaling pathway - *Saccharomyces cerevisiae*



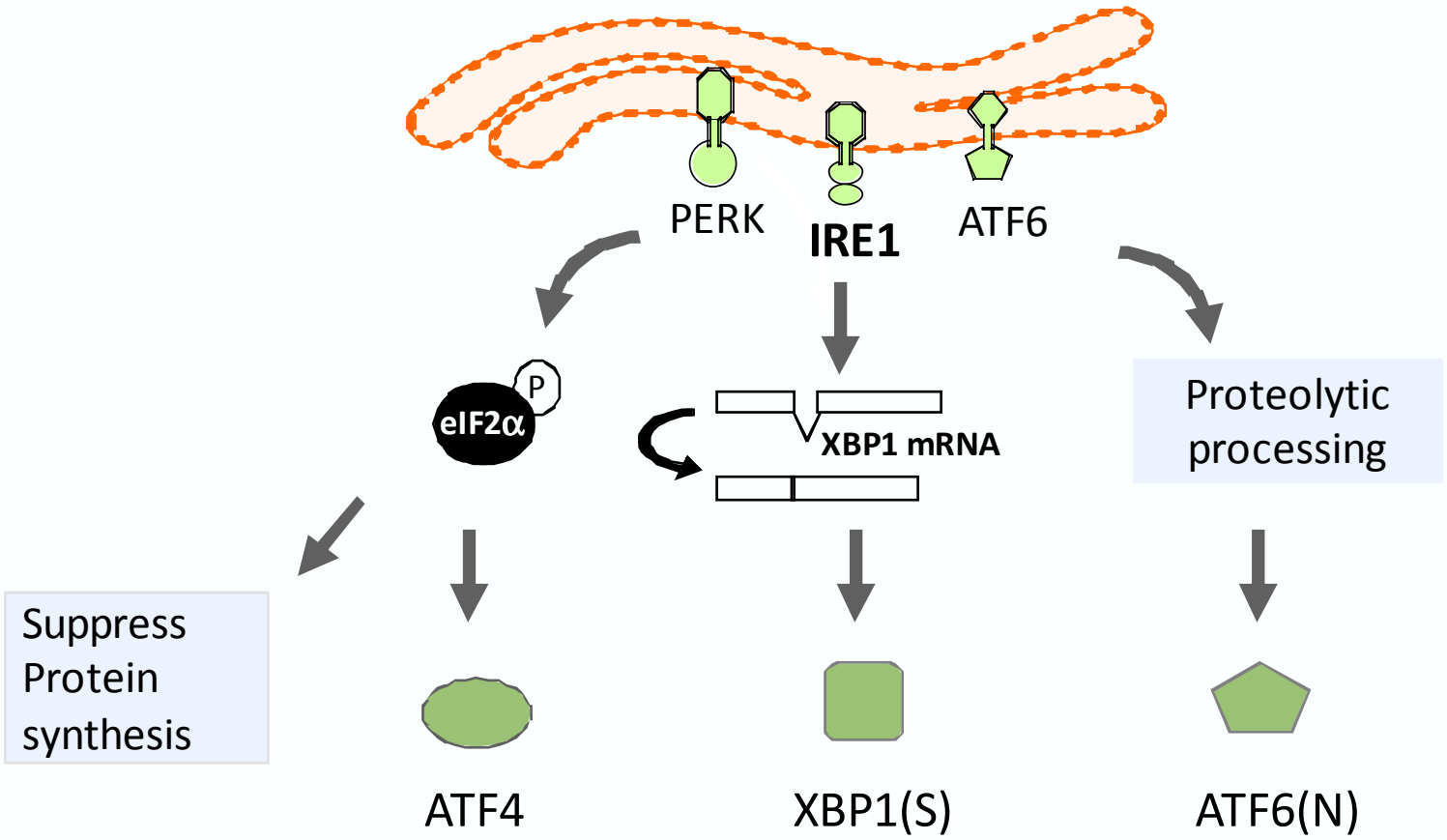
BiP (Kar2p) - Protein folding

INO1 - Phospholipid biosynthesis

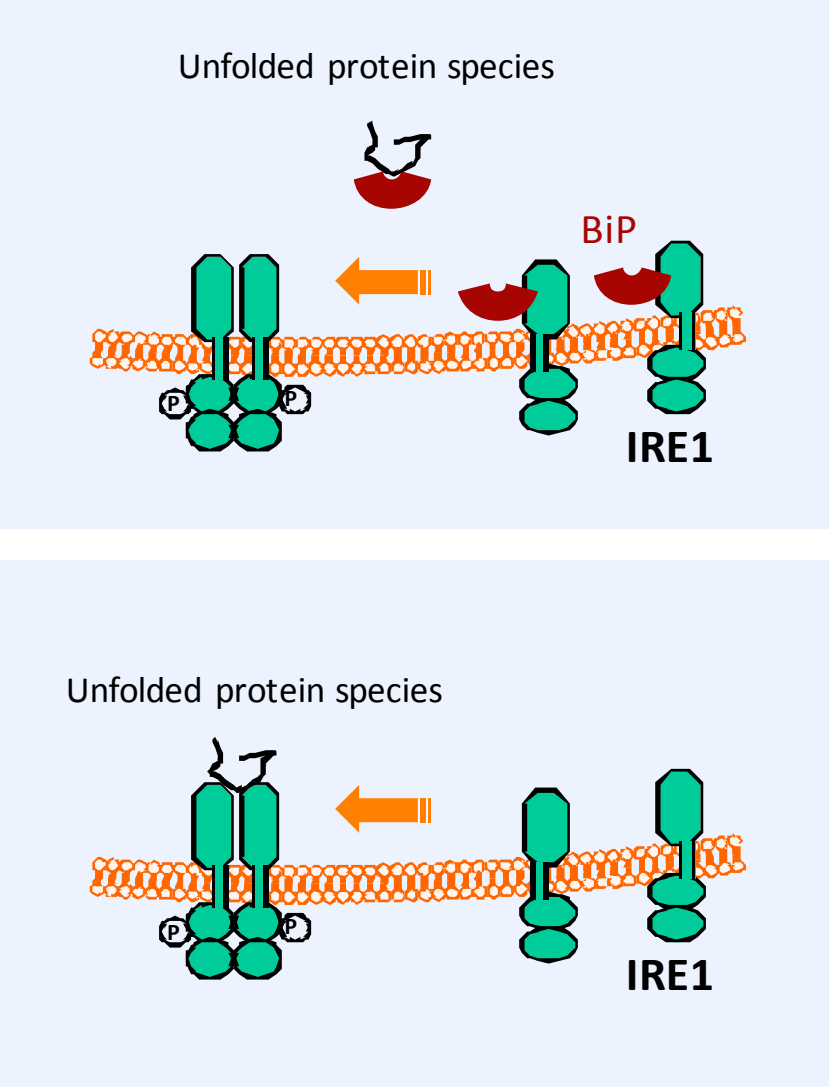
IRE1 : Nikawa J, Yamashita and S, Mol Microbiol., 1992
Mori K and J. Sambrook J, Cell, 1993

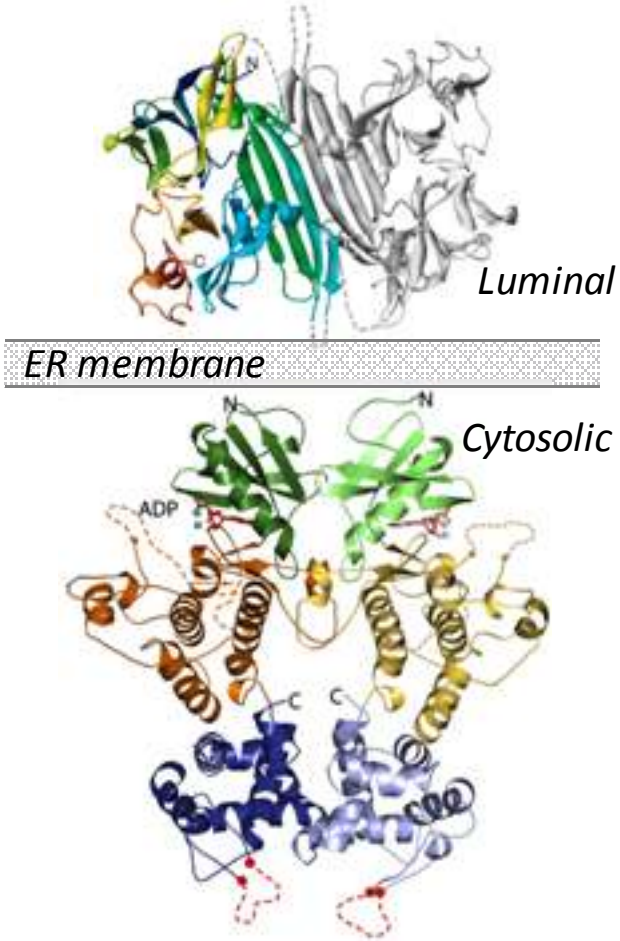
HAC1 : Cox J and Walter P, Cell, 1993

Mammalian UPR signaling pathway



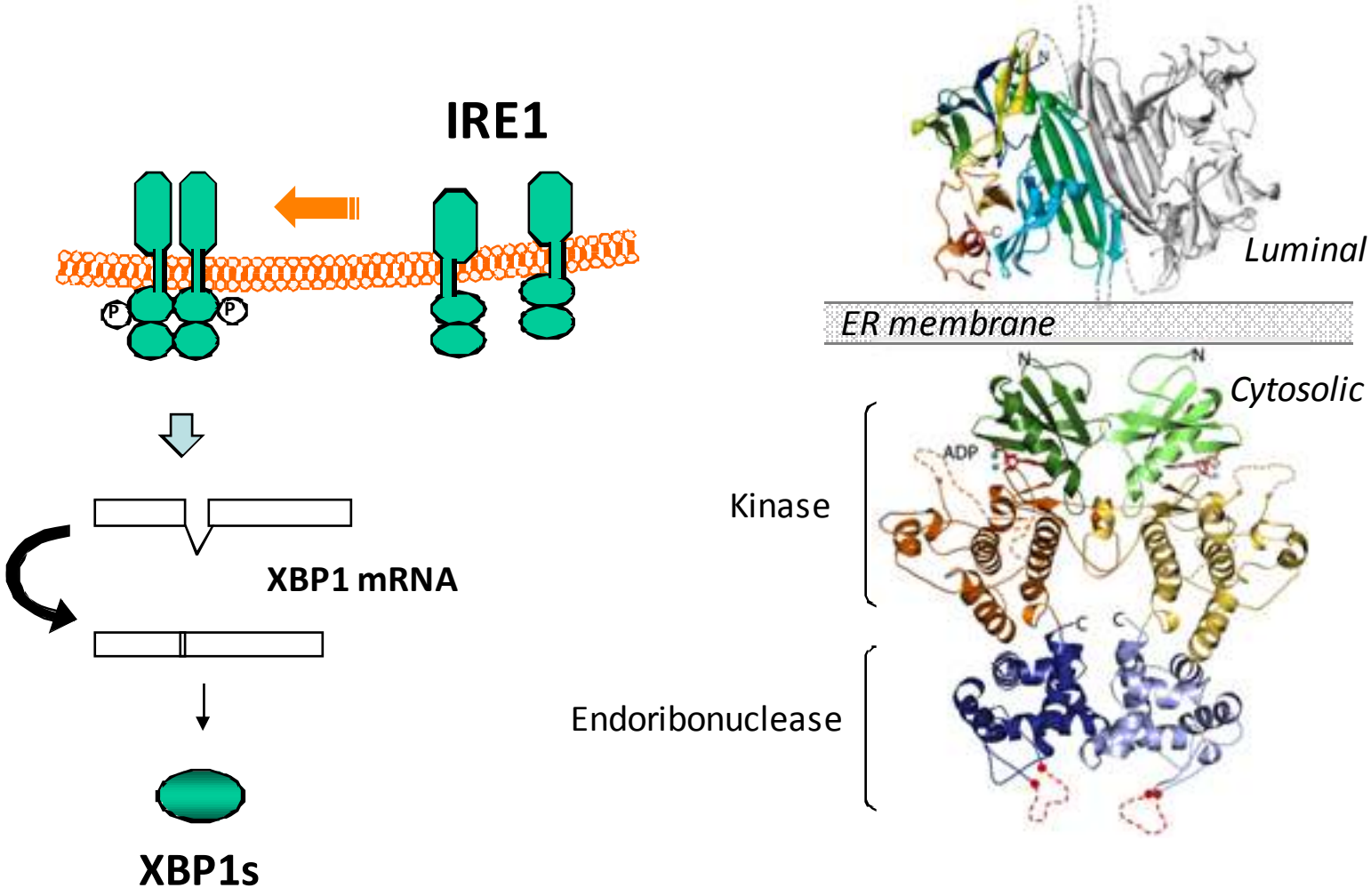
IRE1/XBP1 signaling pathway



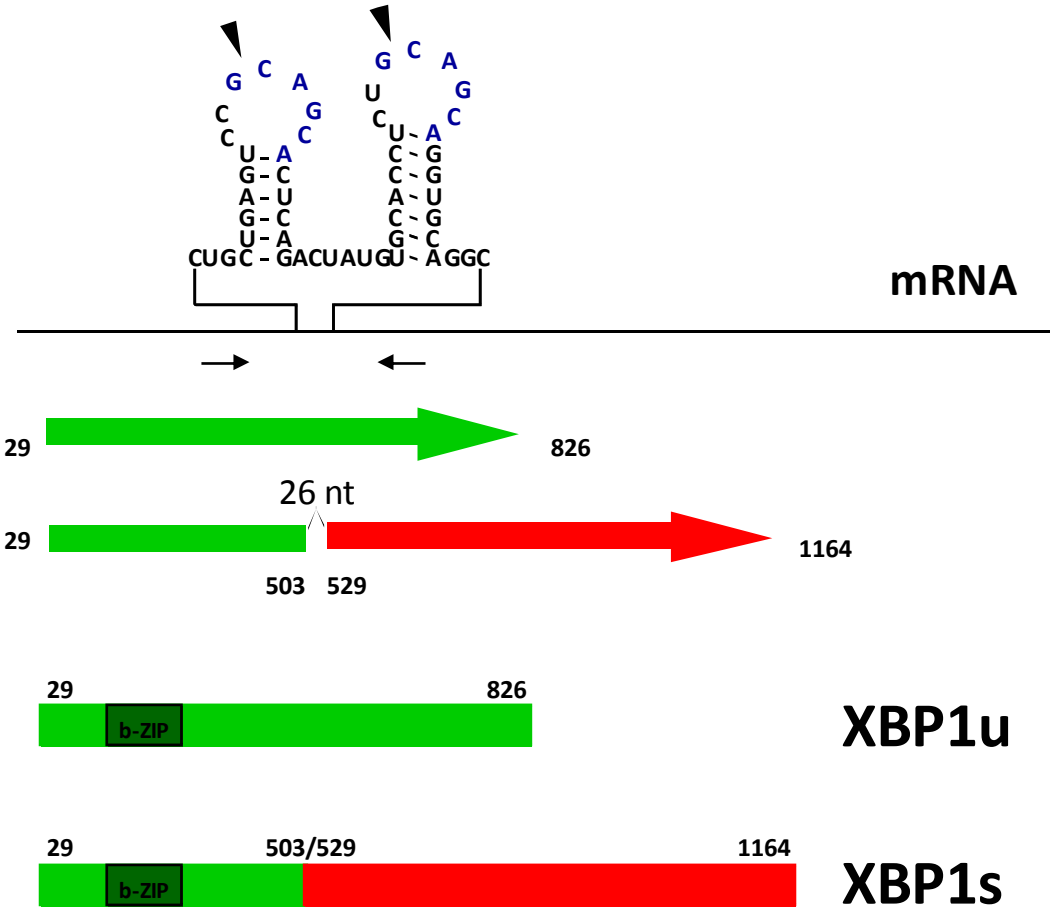


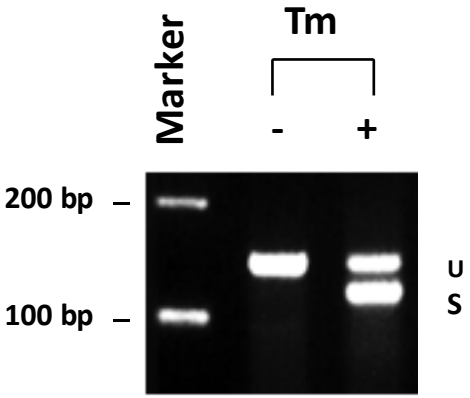
Credle et al., Proc. Natl. Acad. Sci. USA. 2005
Zhou et al., Proc. Natl. Acad. Sci. USA. 2006
Lee et al., Cell. 2008
Korennykh, et al., Nature. 2009
Ali et al., EMBO 2011

IRE1/XBP1 signaling pathway

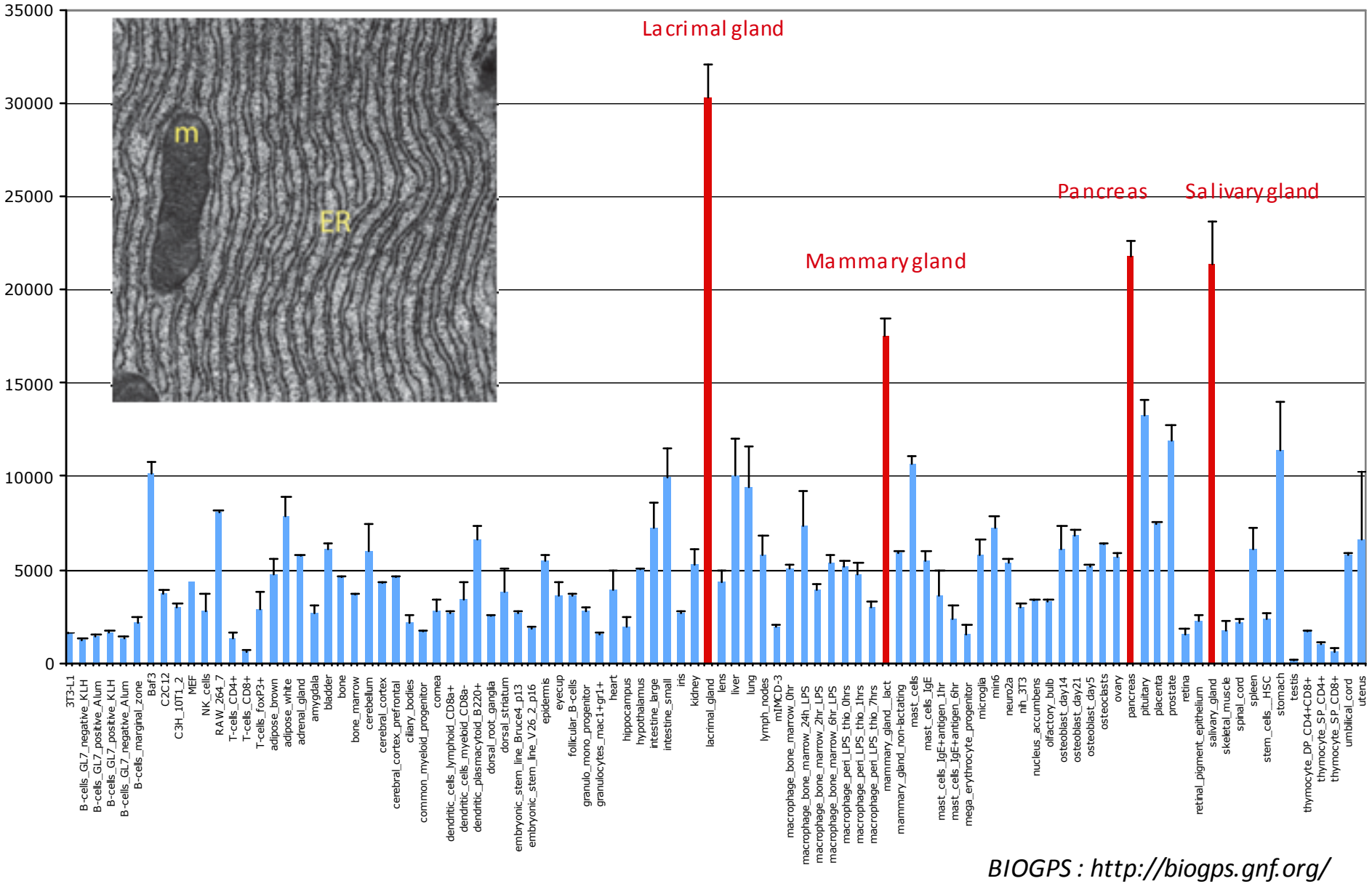


Splicing of XBP1 mRNA by IRE1



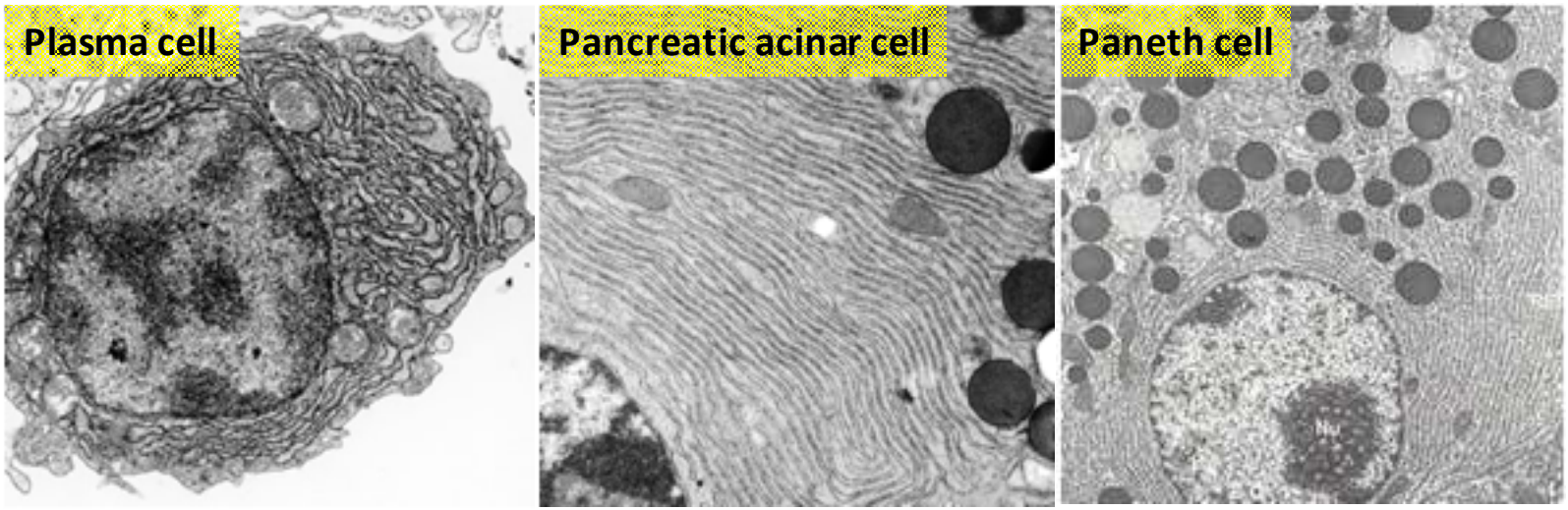


XBP1 is highly expressed in secretory organs



BIOGPS : http://biogps.gnf.org/

Role of XBP1 in development of secretory cells

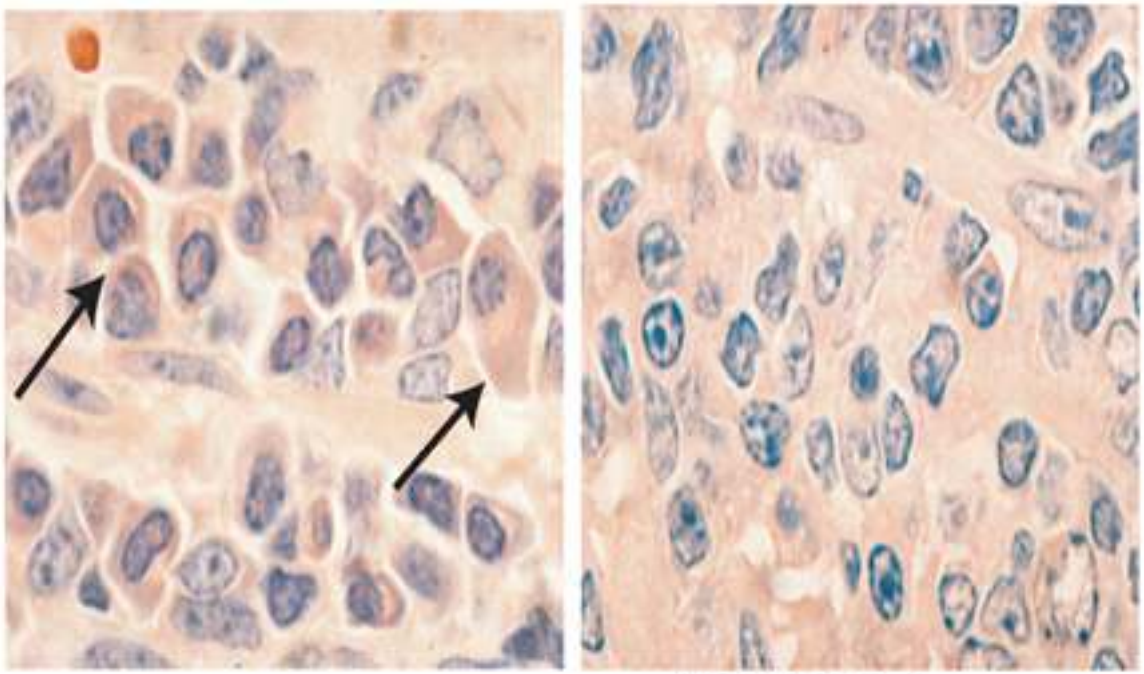


Reimold et al, Nature, 2001

Lee et al, EMBO 2005

Kaser et al, Cell 2008

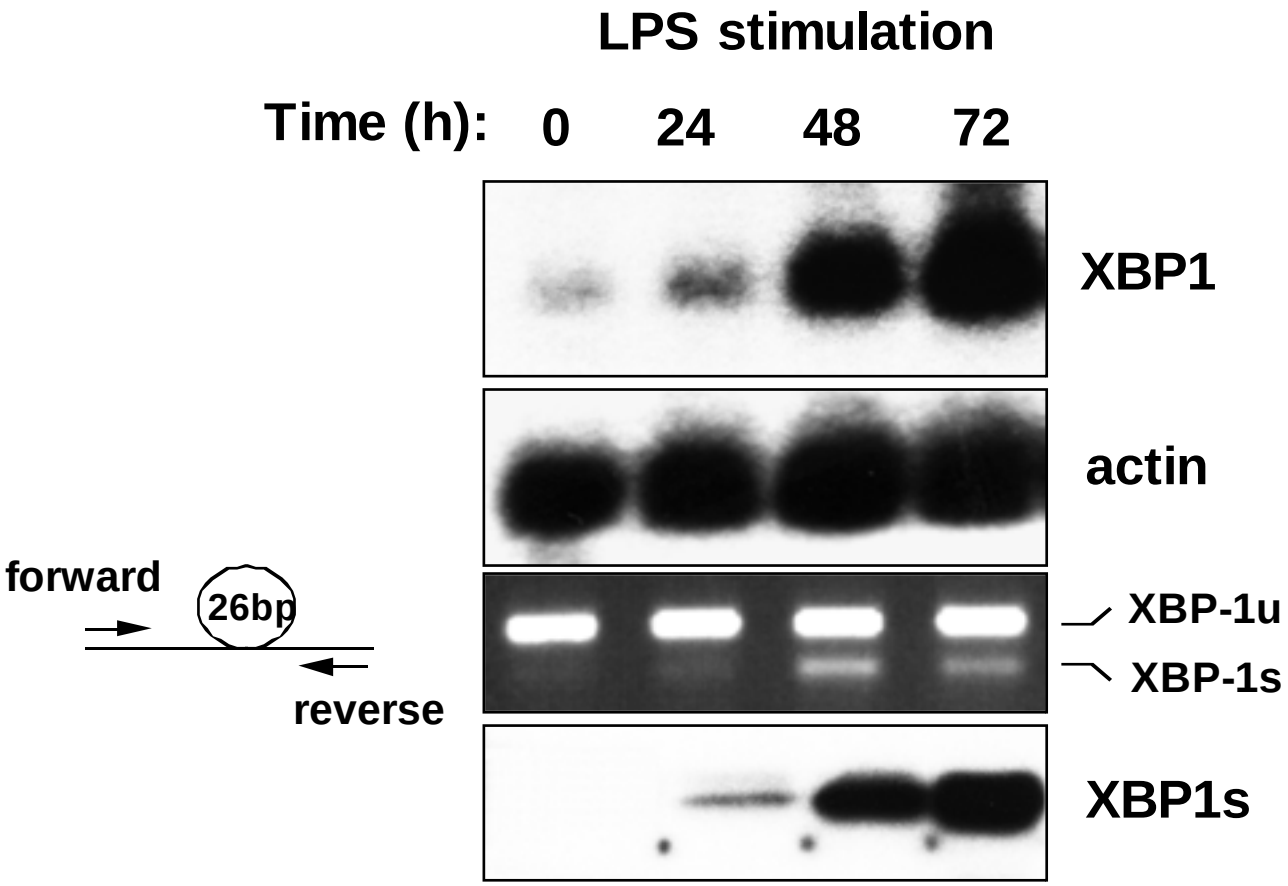
Severely impaired plasma cell generation in the absence of XBP1 and greatly diminished immunoglobulin



Wild type

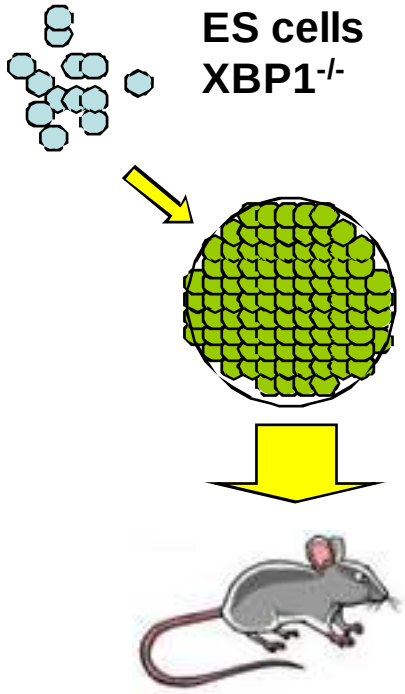
XBP/RAG -/-

Induction and IRE1α-mediated splicing of XBP1 mRNA during plasma cell differentiation

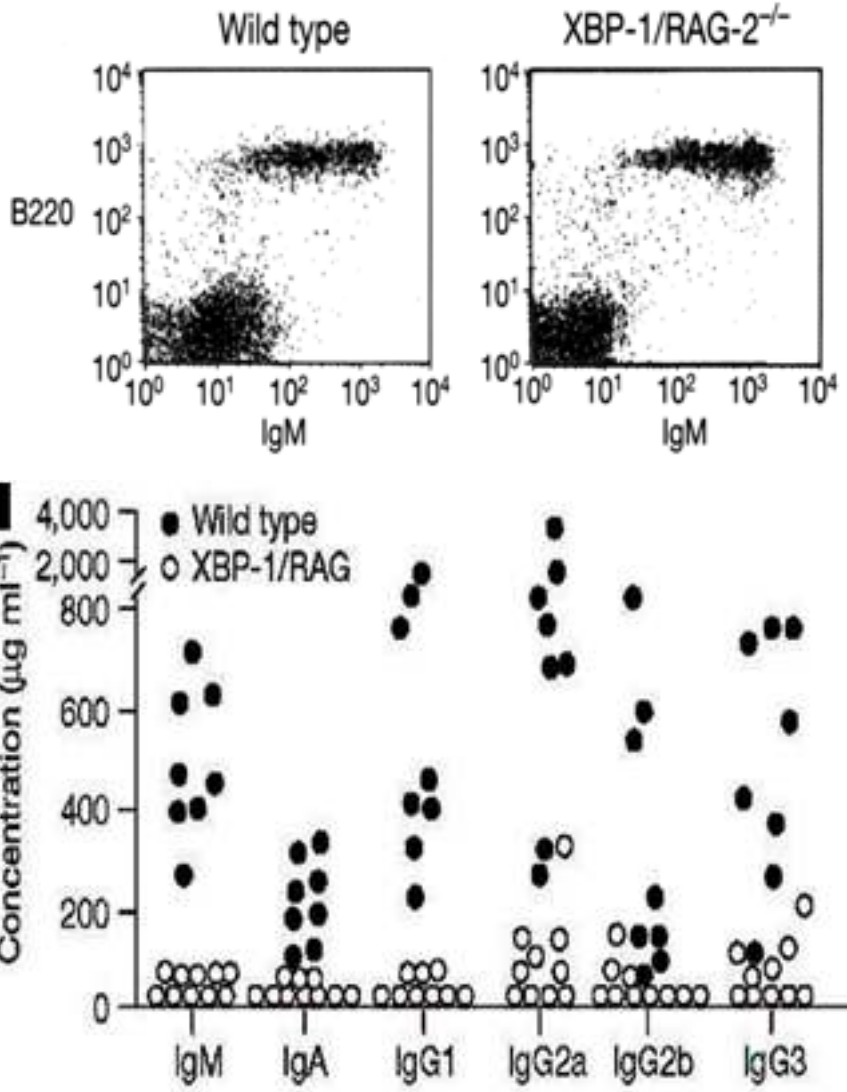


Iwakoshi et al. Nat. Immunol. (2003)

Impaired immunoglobulin production from XBP1 deficient B cells

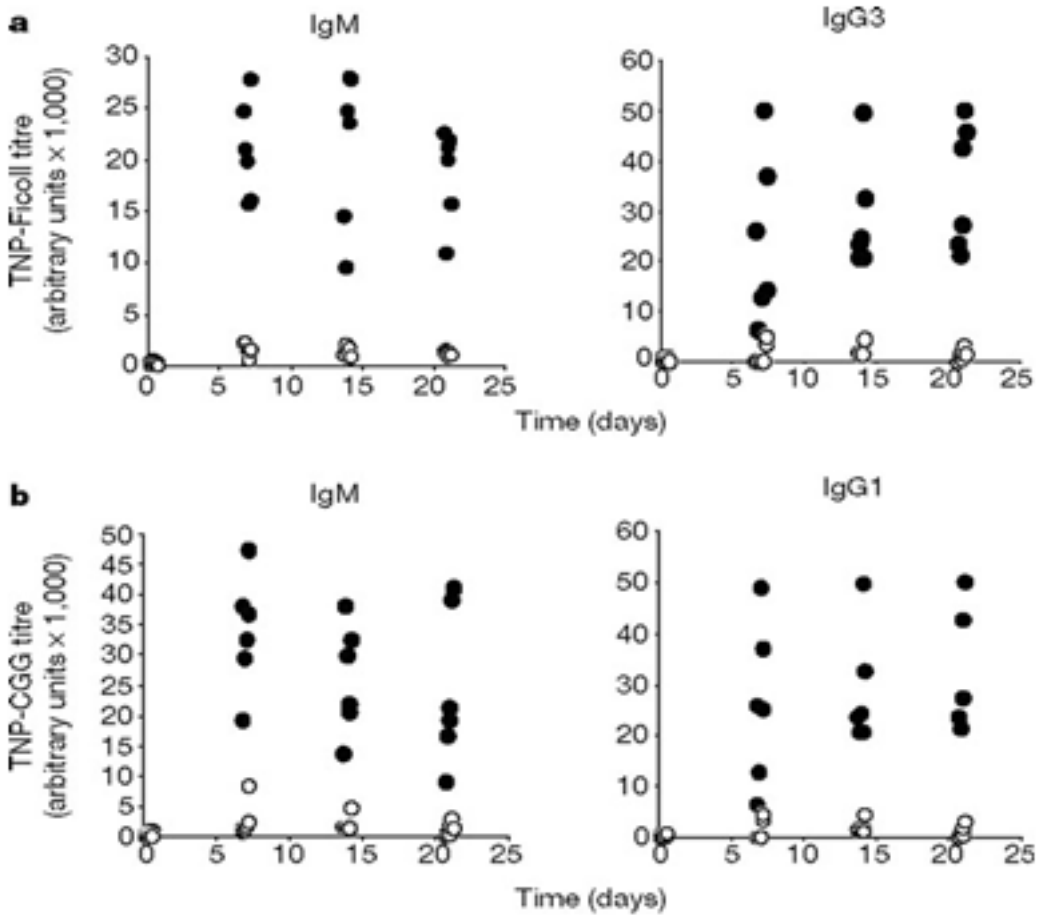


Lymphoid cells : XBP1$^{-/-}$
Liver : Rag2$^{-/-}$
Others : Mixture of Rag2$^{-/-}$ and XBP1$^{-/-}$



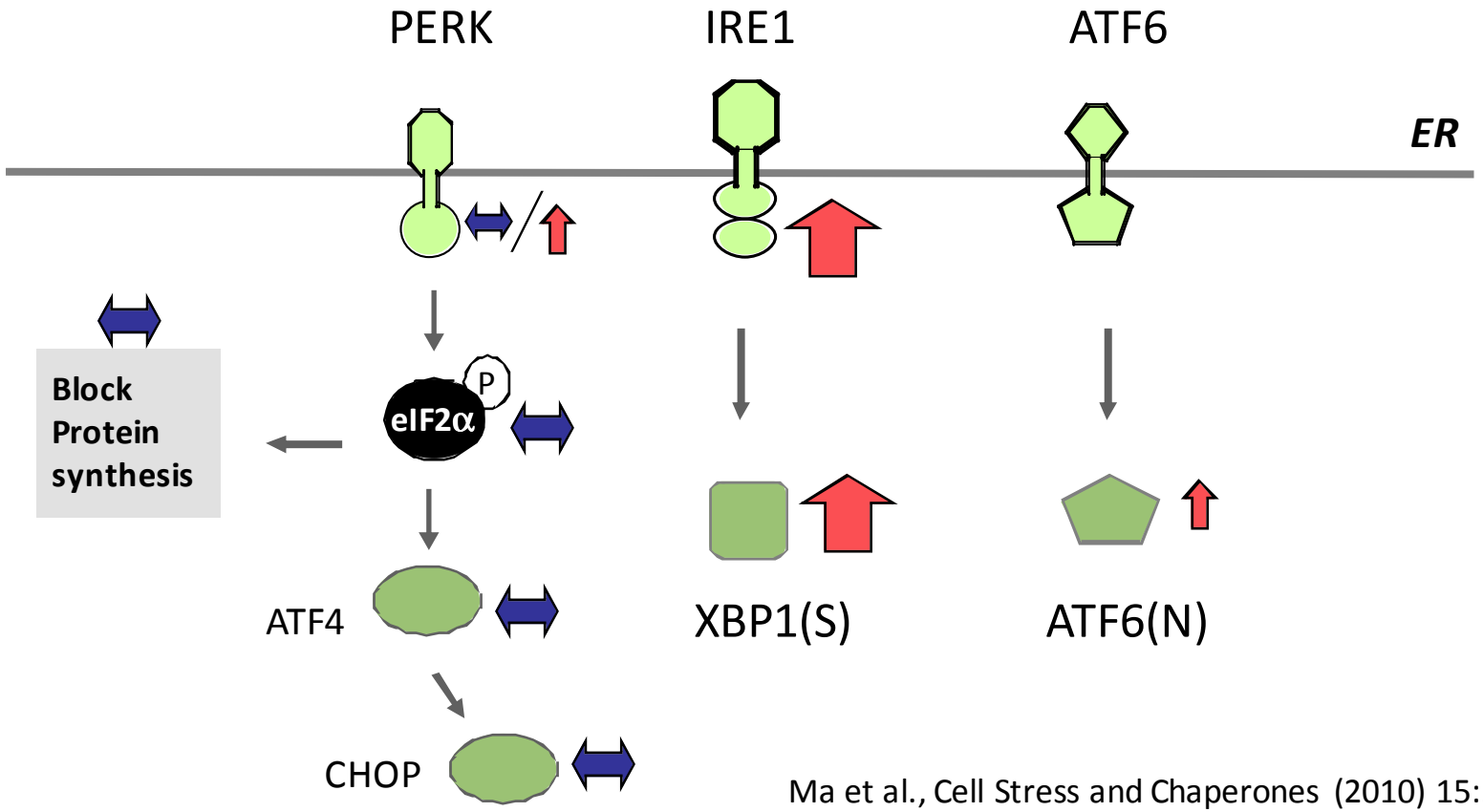
Reimold et al., Nature, 2001

XBP1$^{-/-}$ Rag chimeras fail to mount an immune response



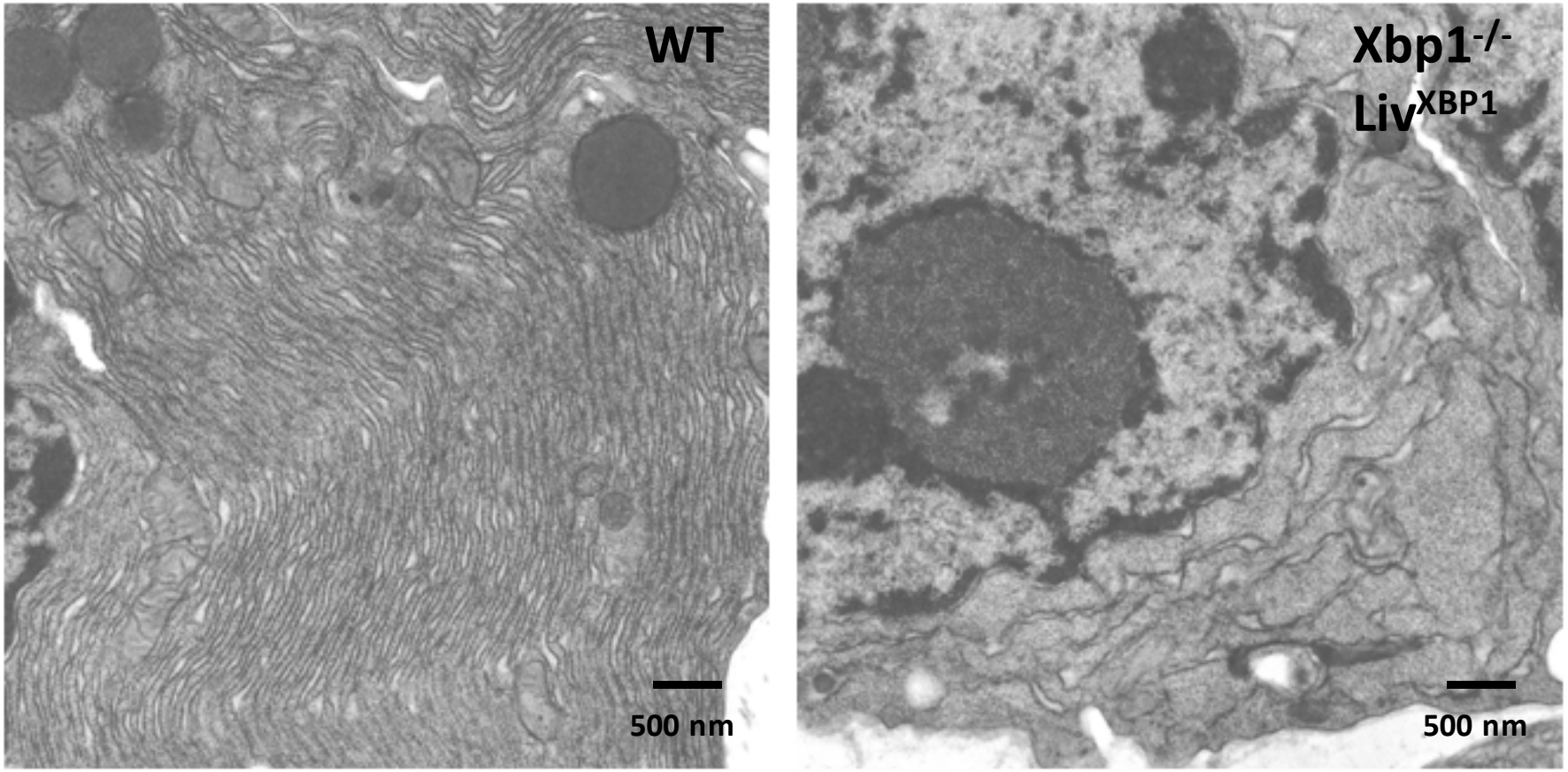
Reimold et al., Nature, 2001

UPR activation during plasma cell differentiation



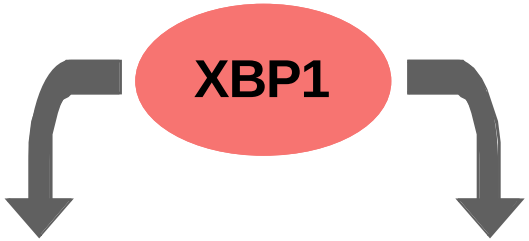
Ma et al., Cell Stress and Chaperones (2010) 15:281–293
Gass et al., Molecular Immunology 45 (2008) 1035–1043
Gass et al., J Biol Chem 277 (2002) 49047–49054
Zhang et al., J Clin Invest. 115 (2005) 268–281
Iwakoshi et al. Nat. Immunol. 4 (2003) 321-329

XBP1 is essential for the development of pancreatic acinar cells



Lee et al. EMBO (2005)

XBP1 induces ER expansion and activates genes in protein secretory pathway



Phospholipid Synthesis

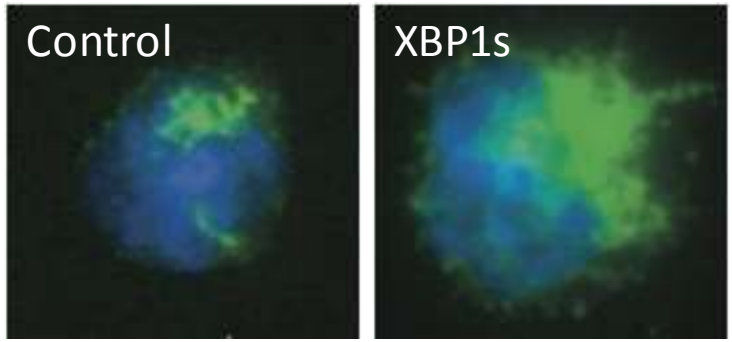
ER expansion

Secretory Pathway

Translocation
Sec61α
Derl1

Degradation
EDEM
Herp
Hrd1
Mannosidase I

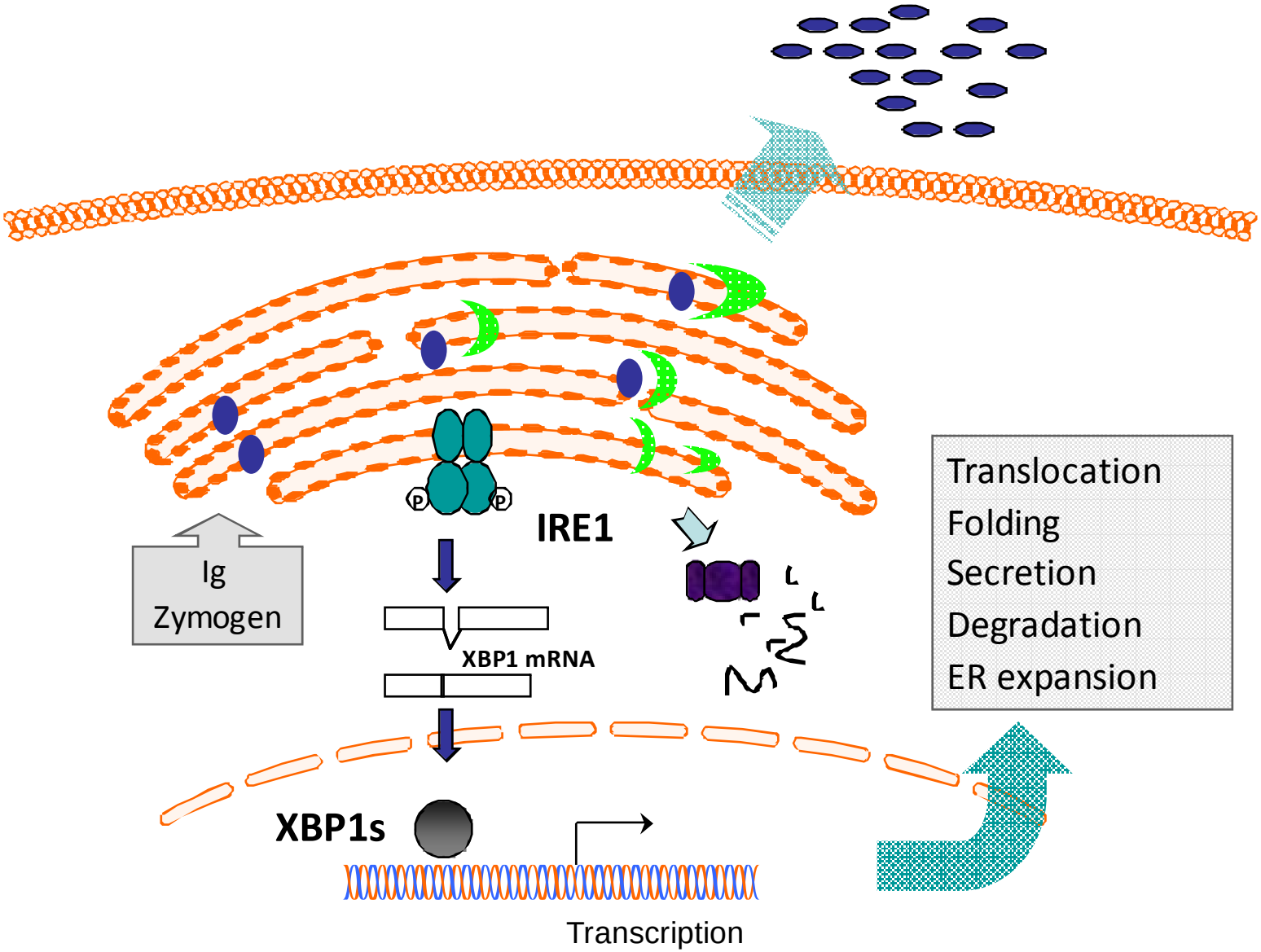
Folding
ERdj3
p58^{IPK}
ERdj4
Grp78
Grp94
PDIs



Shaffer et al Immunity 2004
Sriburi et al J. Cell Biol 2004

Lee et al Mol. Cell. Biol. 2003
Shaffer et al Immunity 2004
Acosta-Alvear et al Mol. Cell 2007

Critical function of XBP1 in biogenesis of cellular secretory machinery

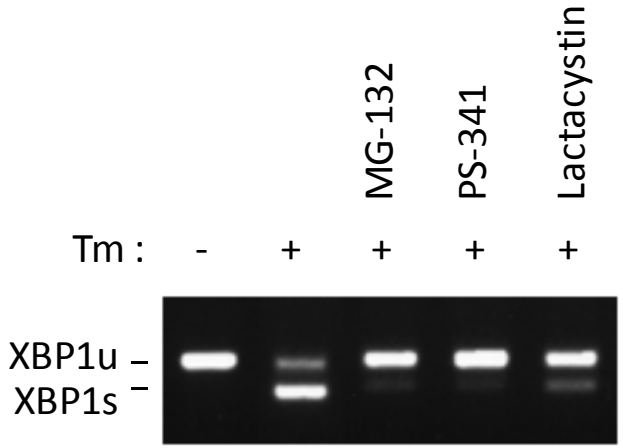


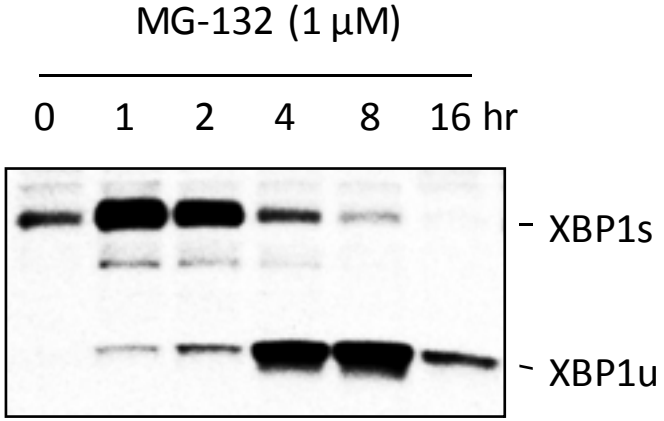
Is XBP1 also required for the survival of myeloma cells?

What is the role of XBP1 in myeloma cells treated with proteasome inhibitors (Velcade)?

Proteasome inhibitors target IRE1/XBP1

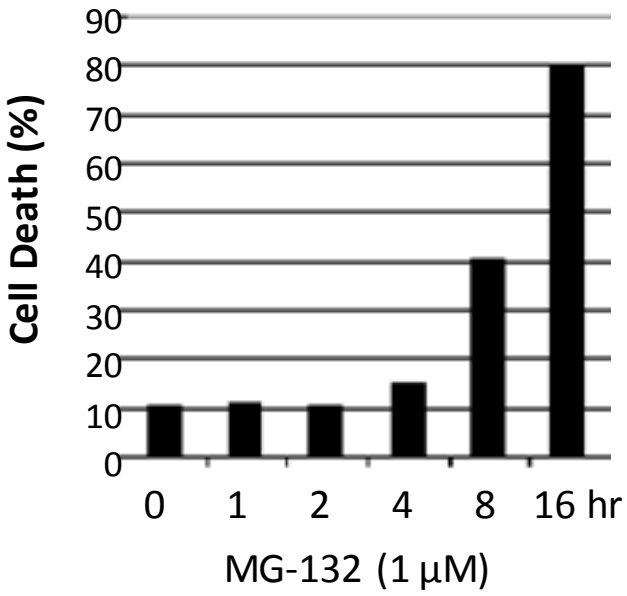
- Inhibit IRE1 driven XBP1 mRNA splicing
- Stabilize XBP1u protein that acts as a dominant negative

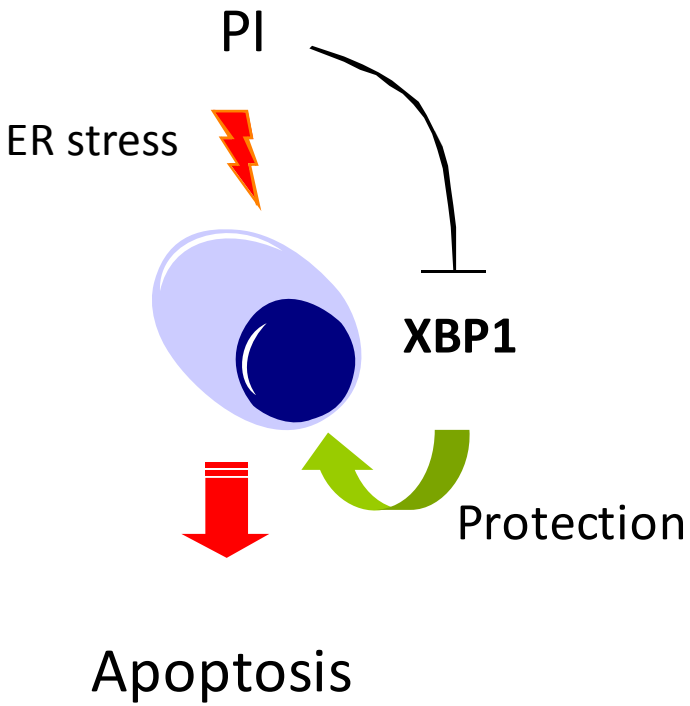




Lee et al. PNAS (2003)

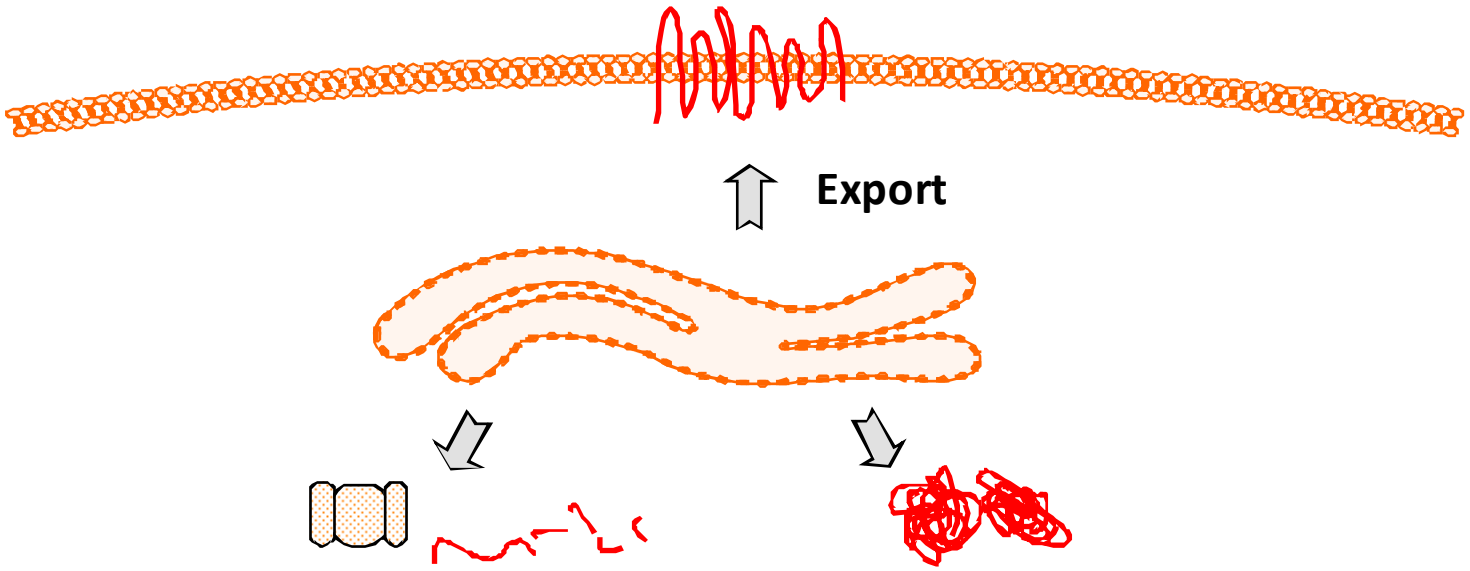
Inhibition of IRE1/XBP1 by proteasome inhibitors correlates with apoptosis of myeloma cells





Does XBP1 have a protective role in human diseases associated with aggregation of misfolded proteins?

Diseases associated with protein misfolding in the ER



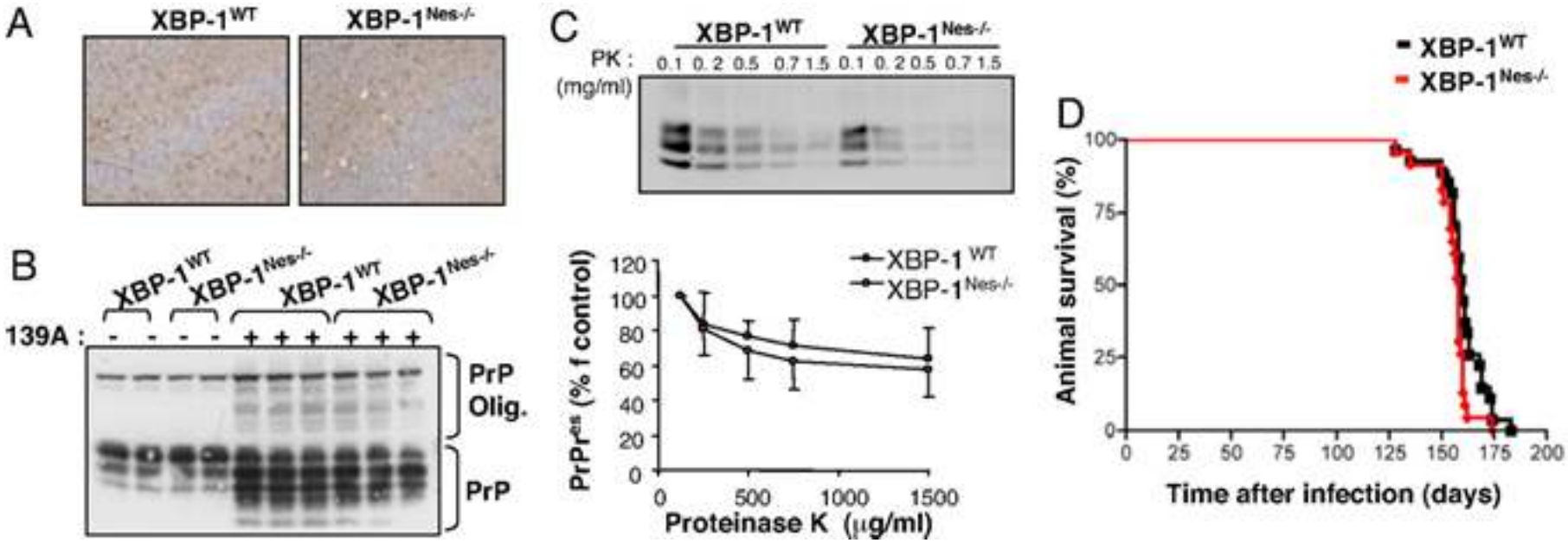
Degradation
No functional protein

Cystic fibrosis
Hereditary emphysema
Hereditary hemochromatosis
Duchenne muscular dystrophy

Aggregation
Accumulation of misfolded protein

Alzheimer disease
Prion diseases
Neonatal Diabetes

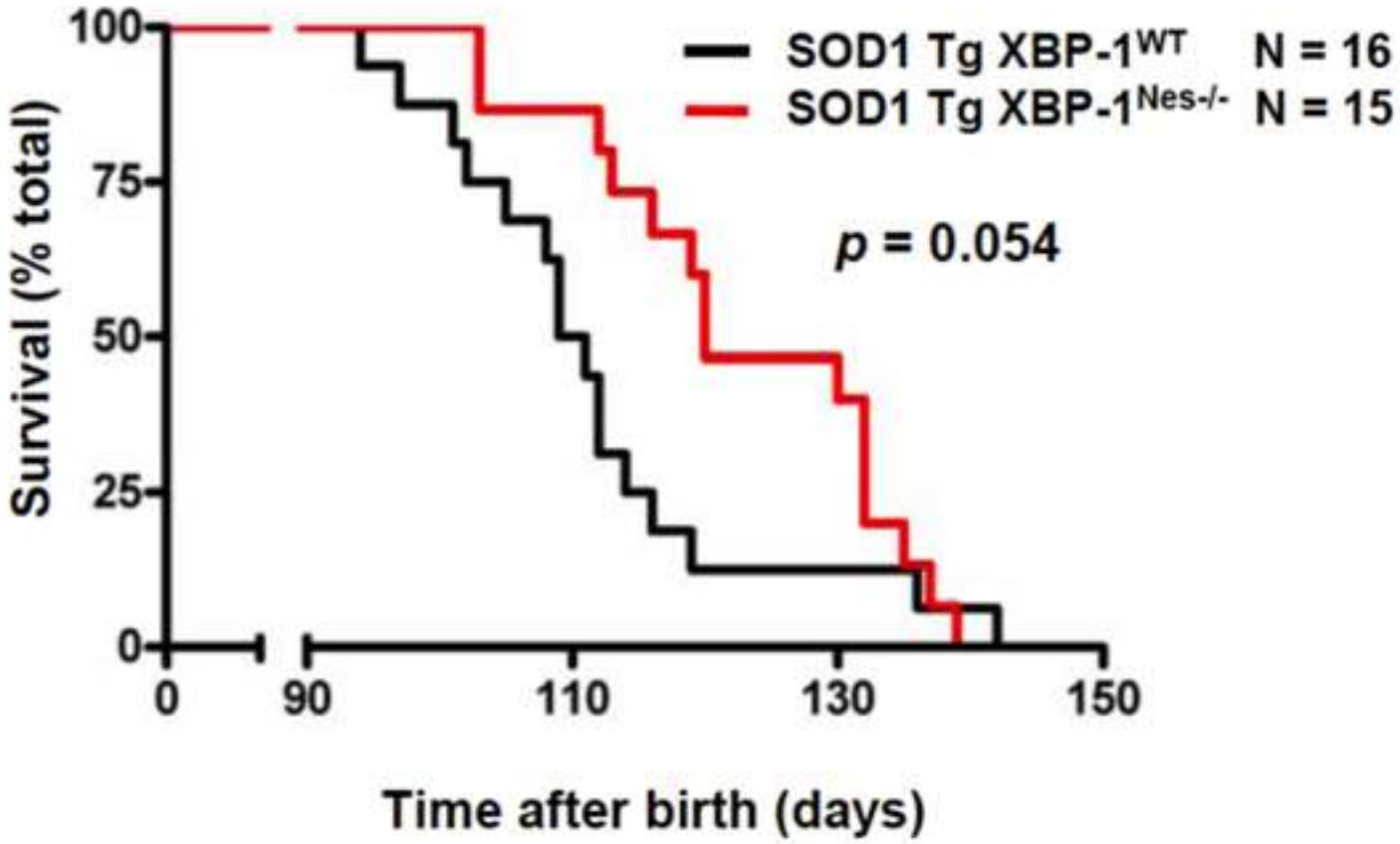
XBP1 does not affect prion pathogenesis



Hetz C. et.al. PNAS 2008;105:757-762

PNAS

Delayed Amyotrophic Lateral Sclerosis by XBP1 deletion in brain



Hetz et al, Genes and Dev.(2010)

Role of UPR in other organ system

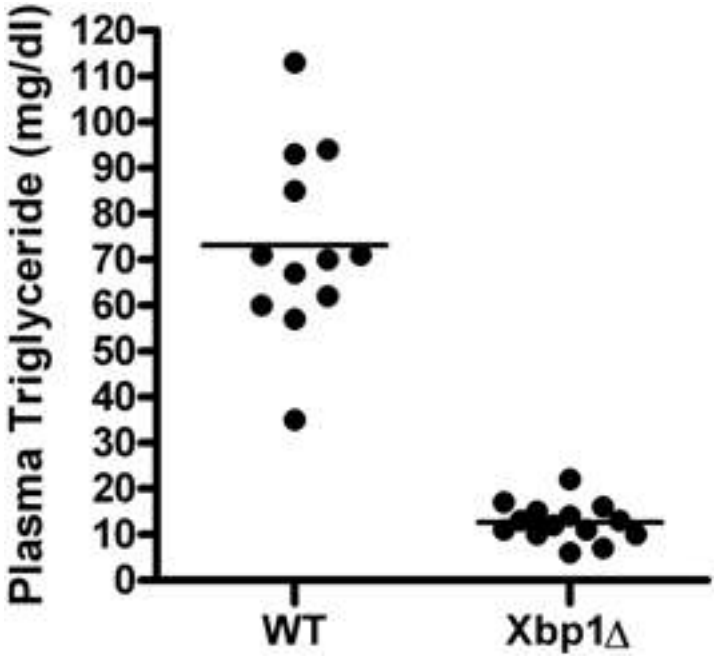
- Liver - lipid metabolism
- Dual roles of IRE1α

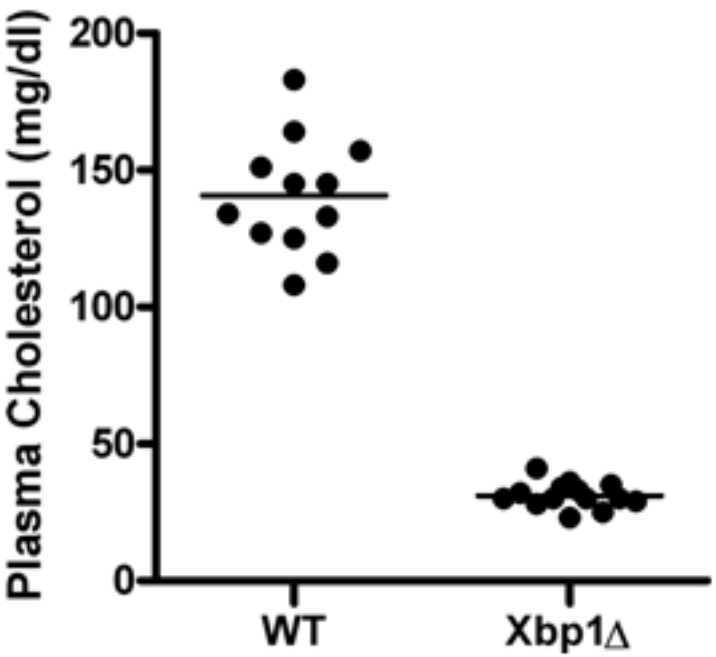
Low plasma lipid levels in XBP1Δ mice

4 weeks after Xbp1 deletion (polyIC injection)

WT, n = 12

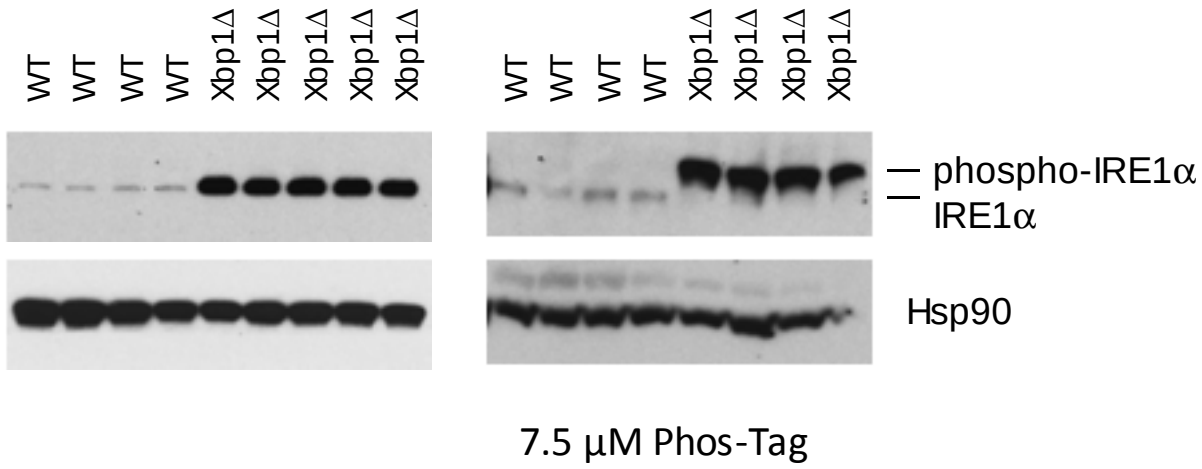
Xbp1Δ, n = 14



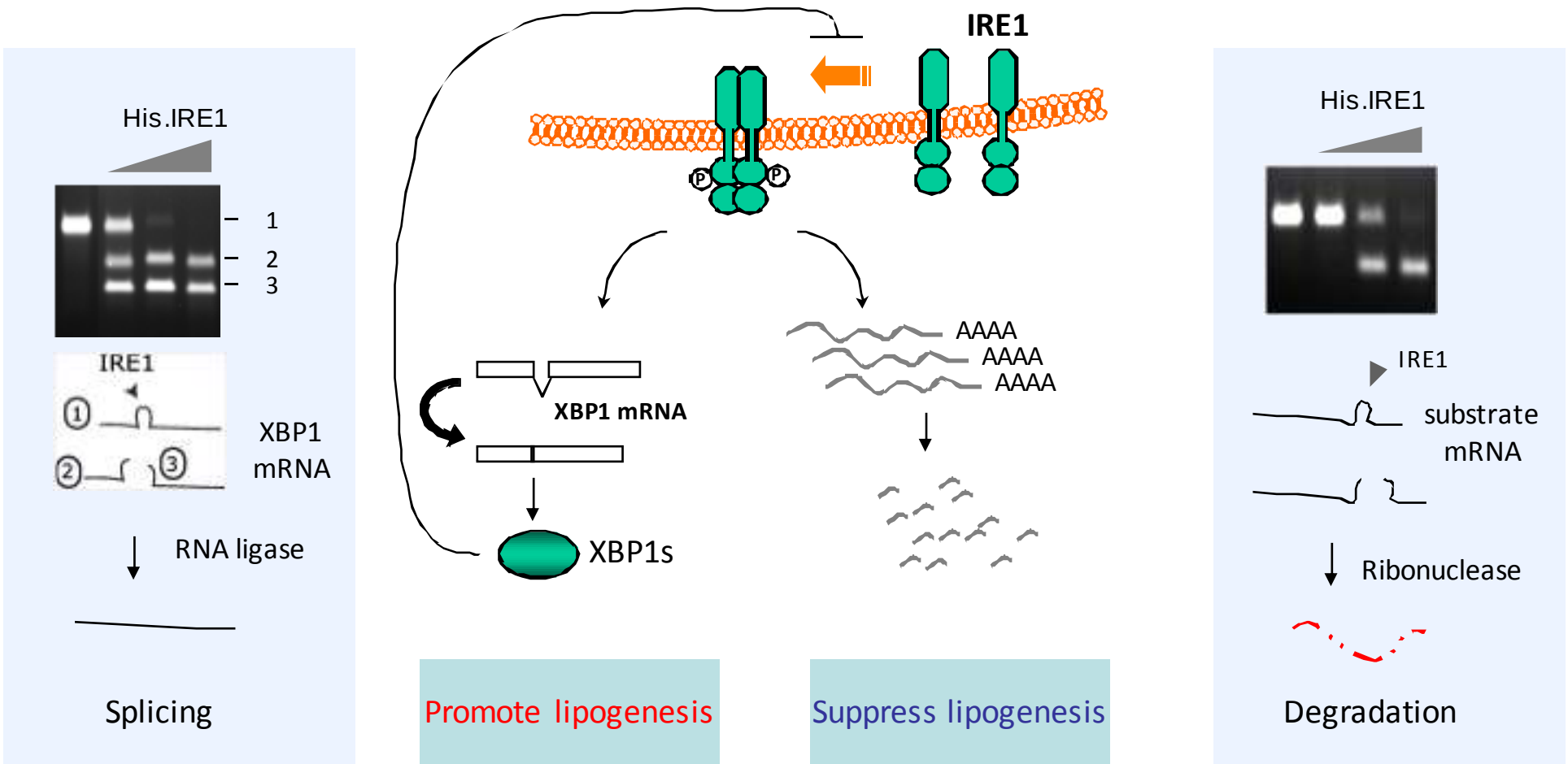


Lee et al. Science (2008)

Induction and hyperactivation of IRE1α by XBP1 deficiency in liver



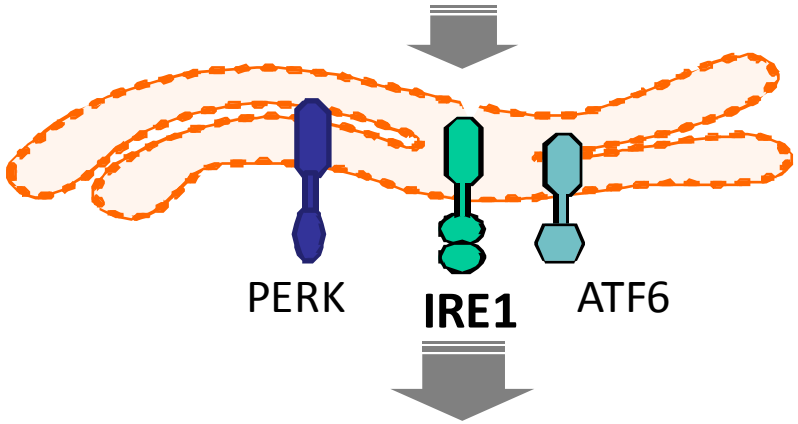
Dual roles of IRE1α/XBP1 UPR signaling in hepatic lipid metabolism



Physiological functions of the UPR

ER stress
Phamacological (Tunicamycin, DTT)
Physiological ER stress (secretory protein, ?)

ER signaling
TLR activation - macrophage
High glucose - liver
Feedbak regulation



UPR/Stress response	Development	Lipogenesis	Inflammtion
Protein folding homeostasis	ER expansion ER chaperones in secretory cells	Lipogenic enzymes	Cytokines

Acknowledgements

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Laurie H.Glimcher
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