



**Meta-Inflammation Responsible for the Progression
from Obesity to Metabolic Syndrome
Originates in the Endoplasmic Reticulum Stressed Tissues**

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Meta-Inflammation Research Institute

Flow Chart

from **HFD** to **CardioMet & Autoimmune Diseases**



**HFD, Obesity
(caloric imbalance)**



**ERS-UPR, Mt Dysfunction
Autophagy Deficiency**



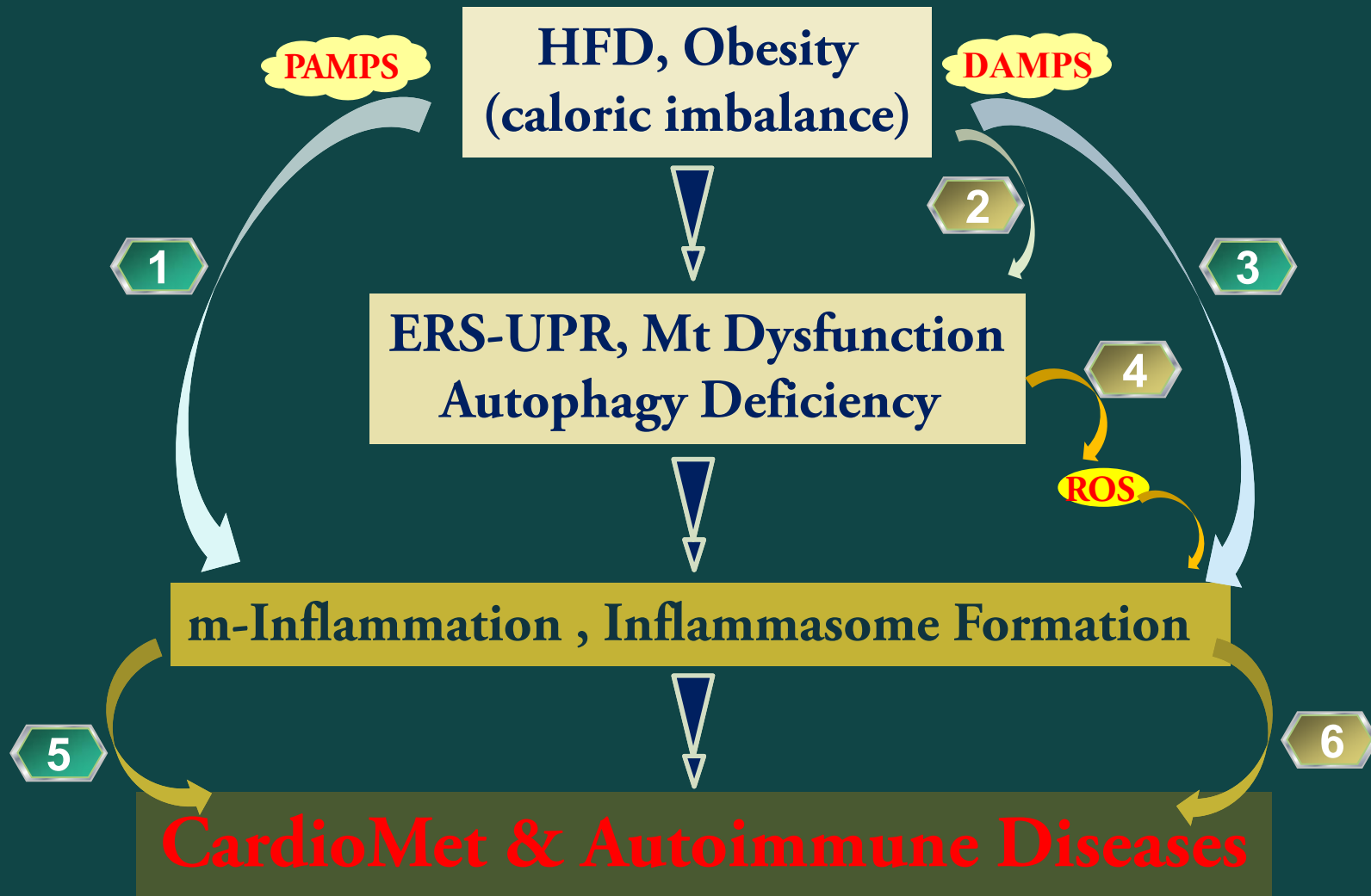
m-Inflammation , Inflammasome Formation



CardioMet & Autoimmune Diseases

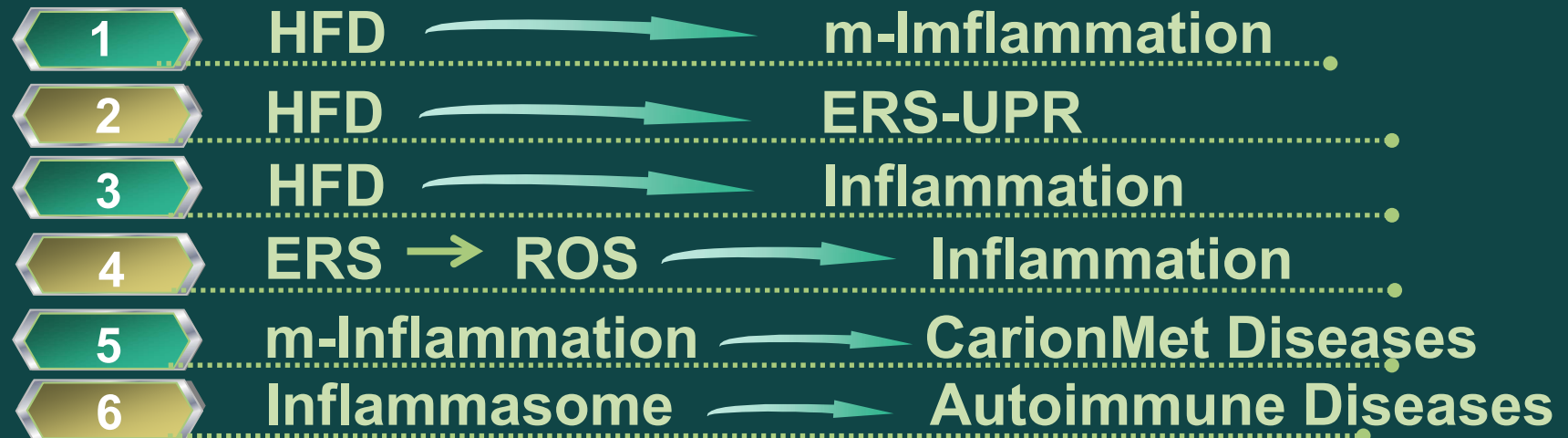
Flow Chart (1)

from **HFD** to **CardioMet & Autoimmune Diseases**



Flow Chart (2)

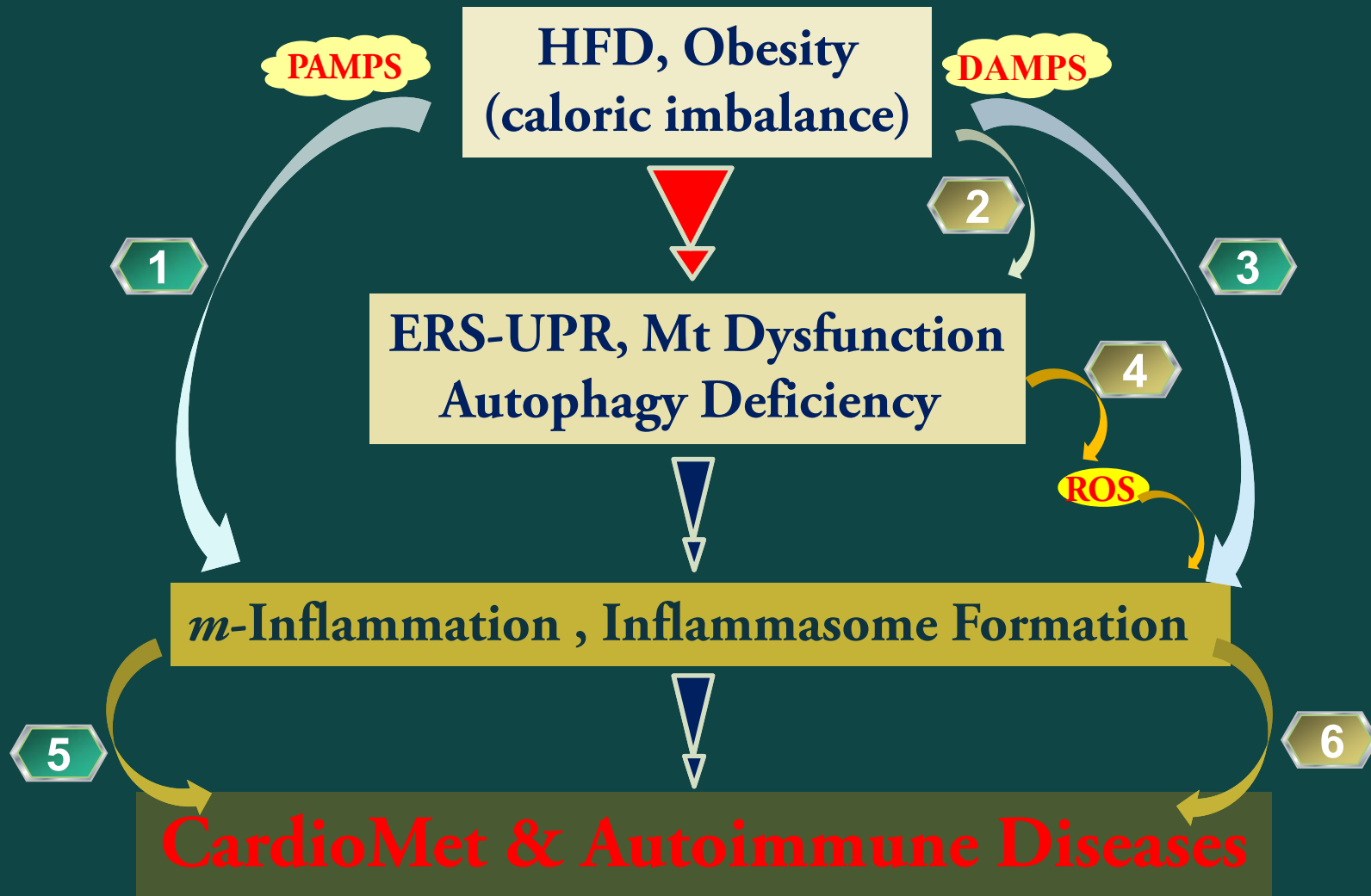
from **HFD** to **CardioMet & Autoimmune Diseases**



1. Nutrient sensing and inflammation in metabolic diseases,
Nat. Rev. 8:923-934, 2008 (Hotamisligil GS and Erbay E.)
2. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes,
Science 306:457-461, 2004 (Ozcan U. et al.)
3. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance,
Nat. Med. 17:179-188, 2011 (Vandanmagsar B. et al.)
4. Thioredoxin-interacting protein links oxidative stress to inflammasome activation
Nat. Immunol. 11:136-140, 2010 (Zhou R. et al.)
5. Targeting IL-1 β in disease; the expanding role of NALP3 inflammasome
Euro. J. Inter. Med. 21:157-163, 2010 (Mitroulis I. et al.)
6. A mutation in the Nlrp3 gene causing inflammasome hyperactivation potentiates Th17 cell-dominant immune responses.
Immunity, 30: 860-874, 2009 (Meng G et al.)

Flow Chart (3)

from **HFD** to **CardioMet & Autoimmune Diseases**



Flow Chart (4)

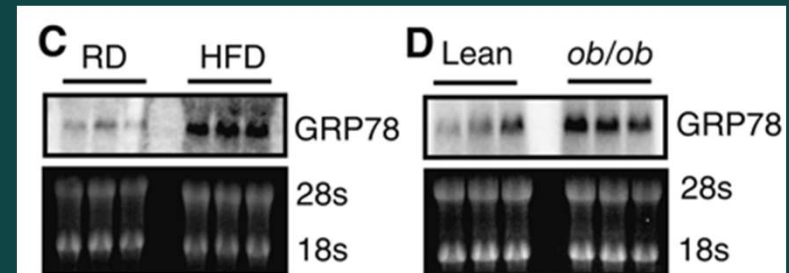
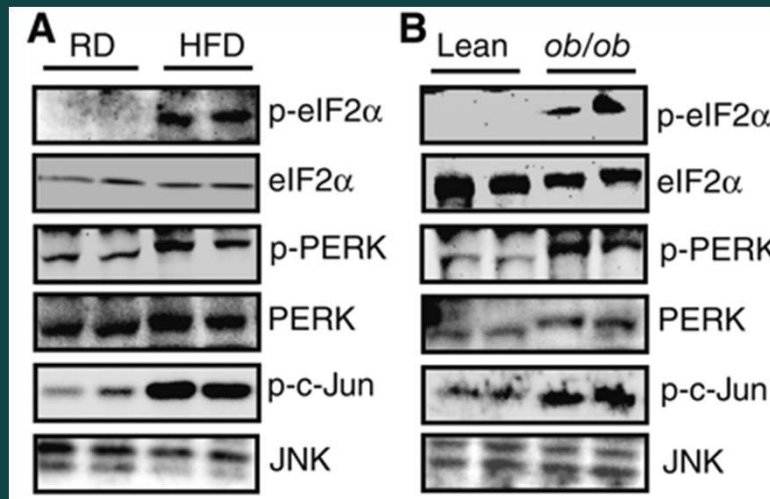
from **HFD** to **CardioMet & Autoimmune Diseases**



**HFD, Obesity
(caloric imbalance)**



**ERS-UPR, Mt Dysfunction
Autophagy Deficiency**

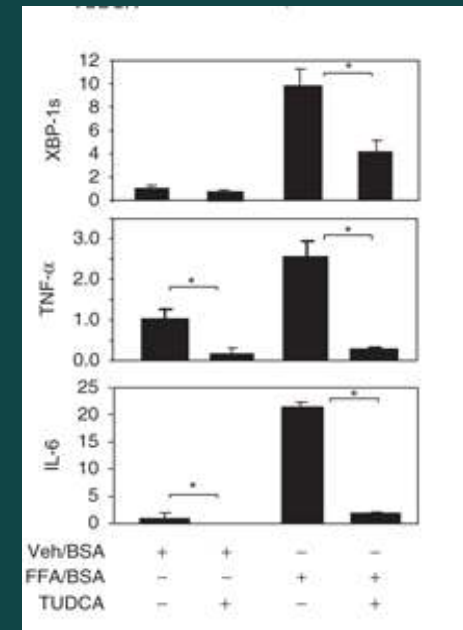
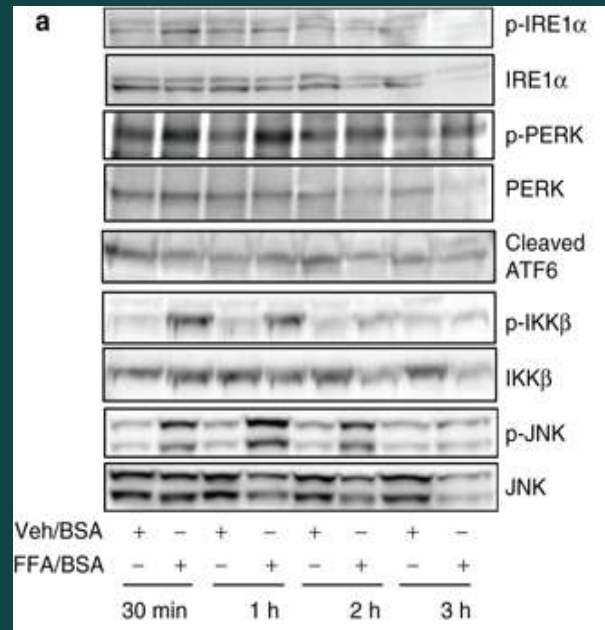
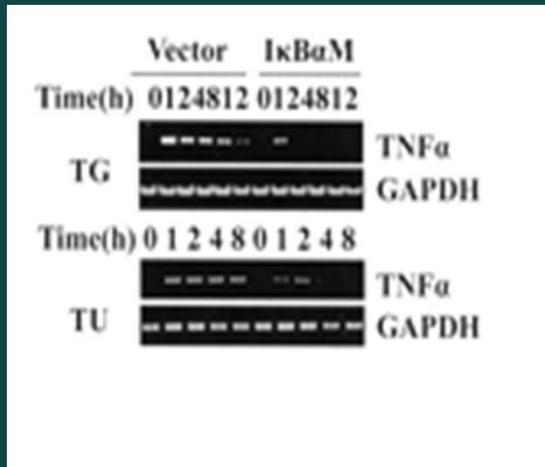


**Endoplasmic Reticulum Stress Links Obesity, Insulin Action,
and Type 2 Diabetes**

Science 15 October 2004: Vol. 306 no. 5695 pp. 457-461

Flow Chart (5)

from **HFD** to **CardioMet** & **Autoimmune Diseases**



Mol Cell Biol. 2006 Apr;26(8):3071-84

Obesity (2011) 19(3), 483-491

Flow Chart (6)

from **HFD** to **CardioMet** & **Autoimmune Diseases**



**HFD, Obesity
(caloric imbalance)**



**ERS-UPR, Mt Dysfunction
Autophagy Deficiency**



m-Inflammation , Inflammasome Formation

**ER stress-mediated interleukin 1 β production
via NF- κ B and inflammasome activation**

From Endoplasmic reticulum stress to the assembly of Inflammasome (1)



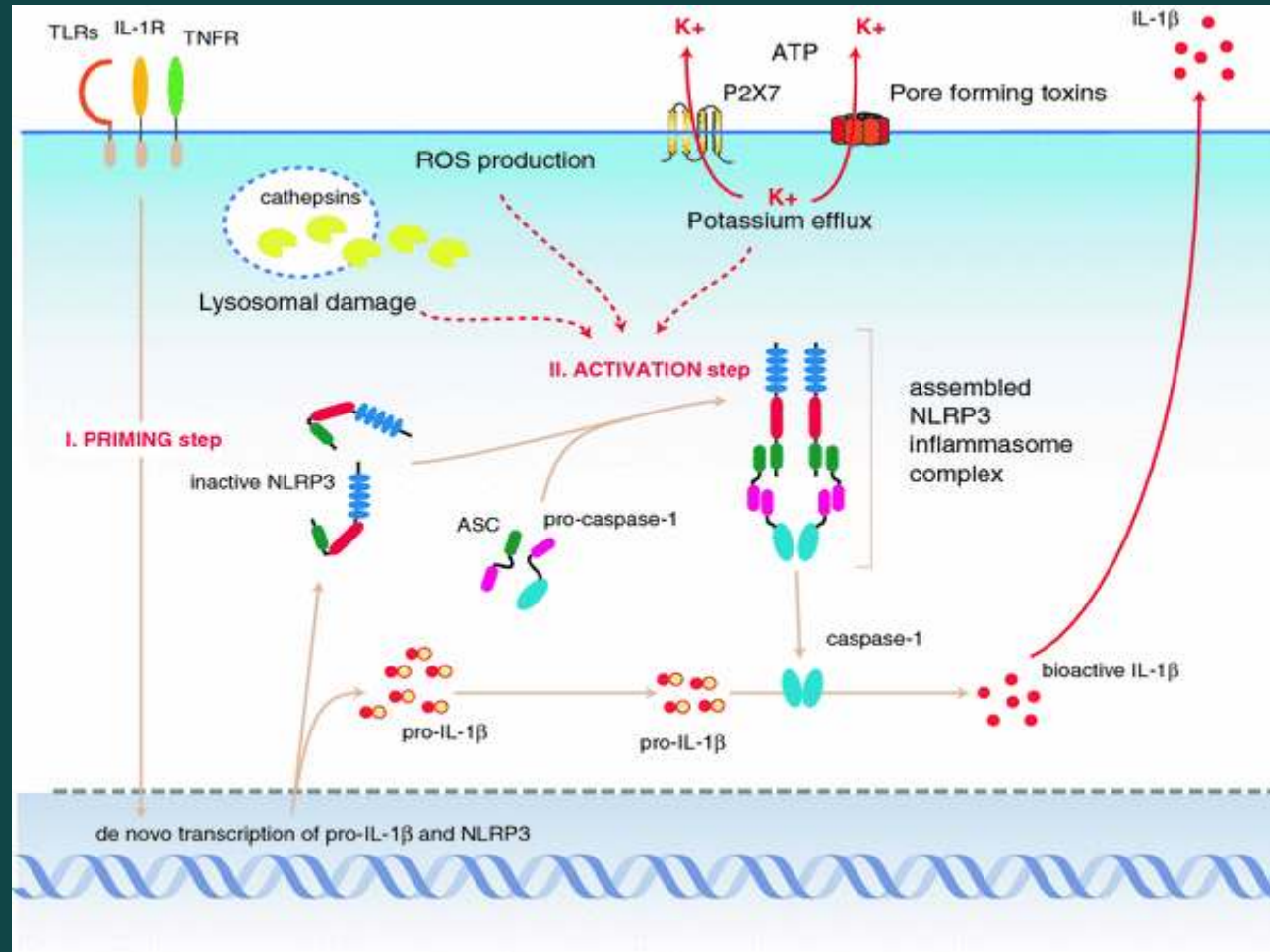
1. Priming Step: transcription of pro-IL- β and NLRP3

- (1) NLRP3 expression by NF- κ B activating pattern recognition or TNF- α
- (2) pro-IL-1 β expression by IL-1R, TNFR and TLRs
- (3) **ER stress induced TNF- α as well as pro-IL-1 β**

2. Activation step: assembly of NLRP3 inflammasome

- (1) Efflux of potassium by pore-forming toxins
- (2) Lysosomal disintegration-induced cathepsin B release
- (3) production of ROS releases TXNIP to bind to NLRP3
- (4) **ERS produced enough ROS to release TXNIP to bind to NLRP3**

From Endoplasmic reticulum stress to the assembly of Inflammasome (2)



[Cell Mol Life Sci.](#) 2011 Mar;68(5):765-83. Epub 2010 Oct 31.

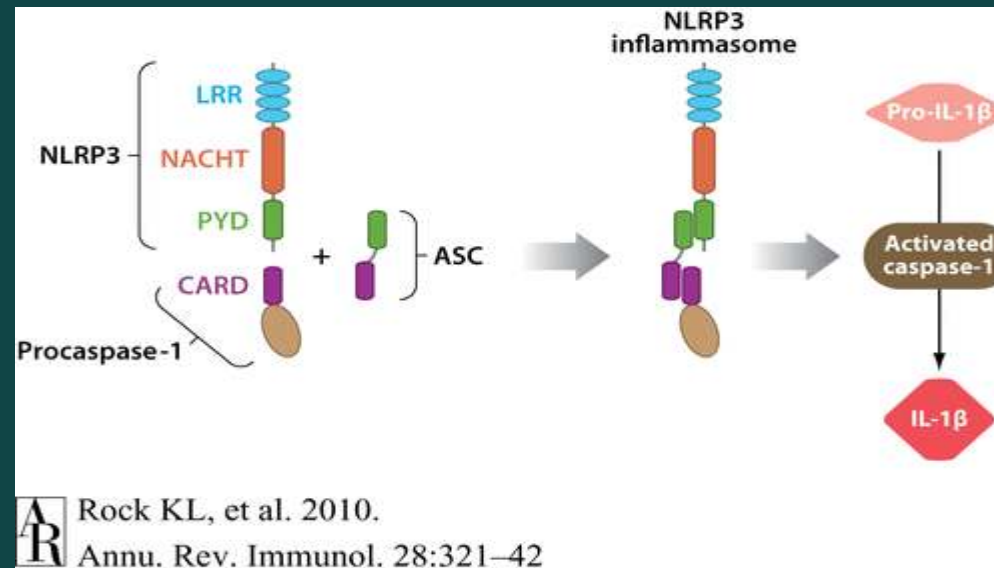
From Endoplasmic reticulum stress to the assembly of Inflammasome (3)



Nlrp3 Inflammasome

(A cytosolic heterotrimeric protein complex)

- (1) Nlrp3; the regulatory subunit
- (2) Asc; the adaptor subunit
- (3) Procaspase-1; the effector subunit

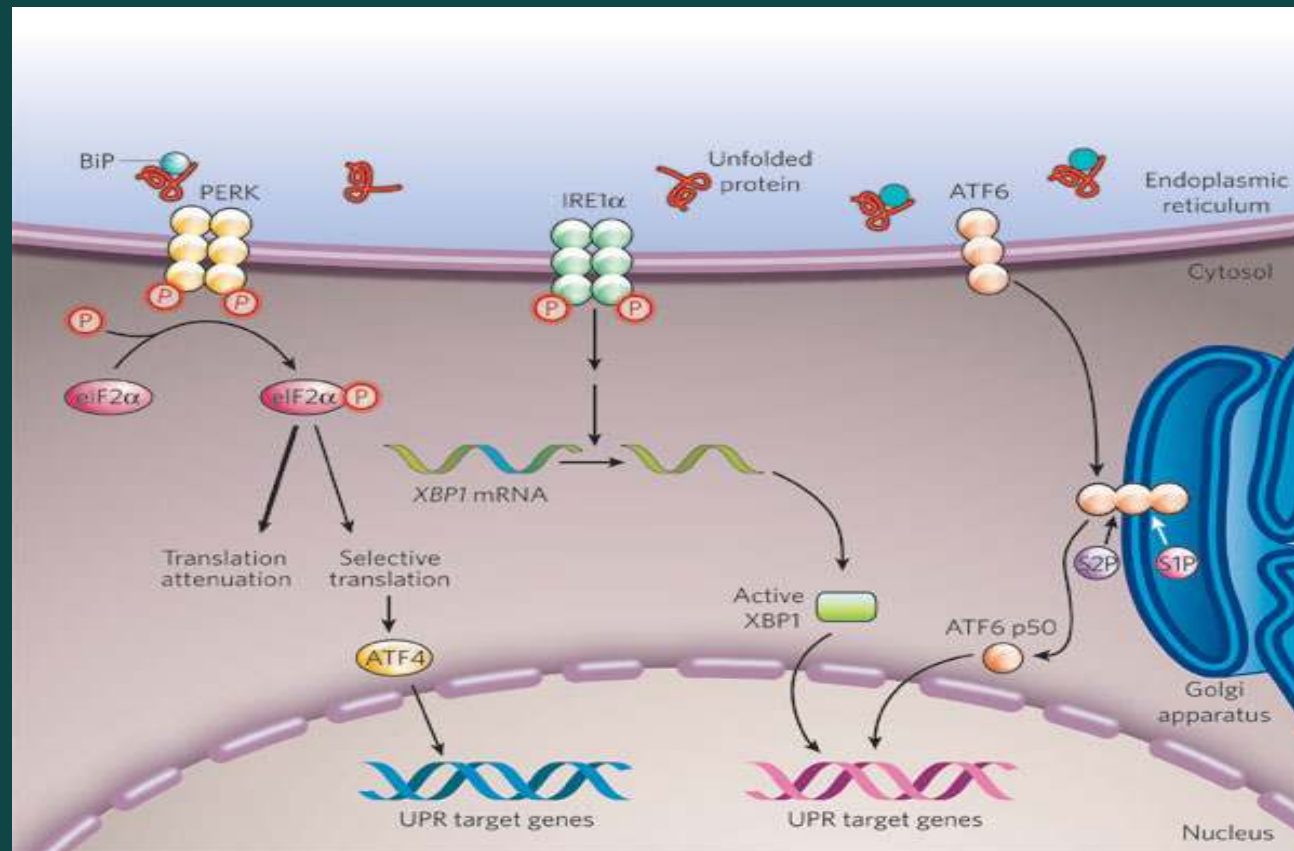


Nlrp3 inflammasome is activated by 'danger signals' and important in 'sterile inflammation'

From Endoplasmic reticulum stress to the assembly of Inflammasome (4)



The Mammalian UPR Pathways

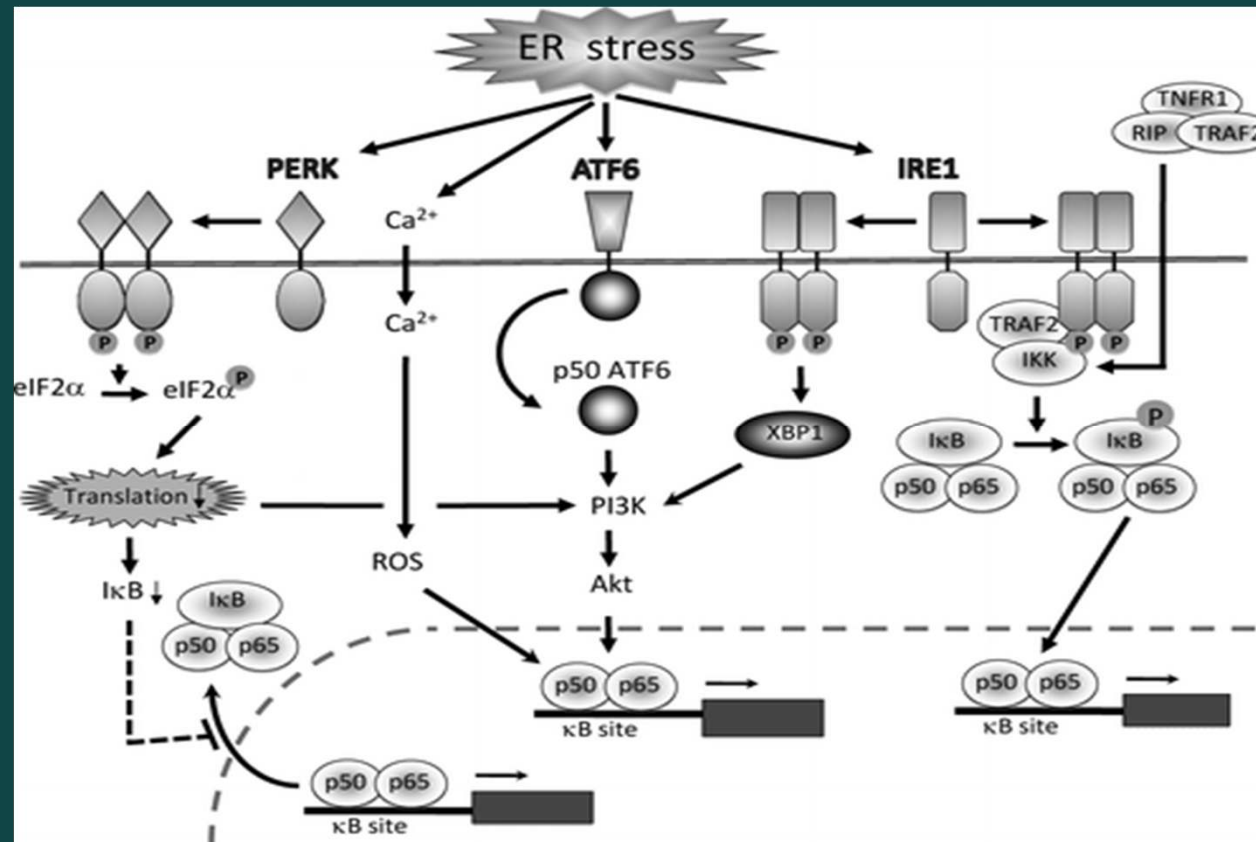


Nature 454, 455-462(24 July 2008)

From Endoplasmic reticulum stress to the assembly of Inflammasome (5)



ER-Induced UPR Activates **NF- κ B**

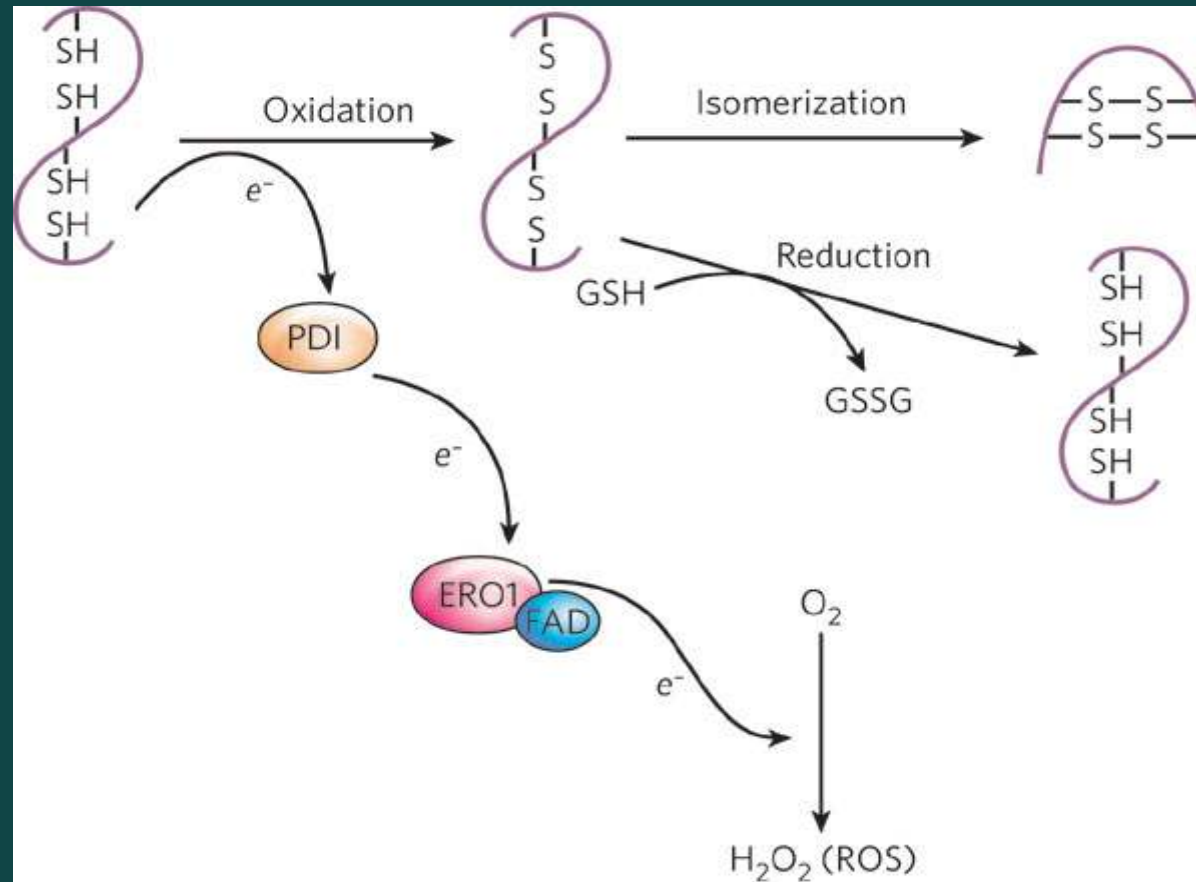


[Antioxid Redox Signal.](#) 2009 Sep;11(9):2353-64

From Endoplasmic reticulum stress to the assembly of Inflammasome (6)



ERS Accumulates ROS during Oxidative Protein Folding



Nature 454, 455-462(24 July 2008)

ERS · UPR induces Inflammasome induces IL-1 β



***m*-Inflammation Responsible for the Progression from Obesity to Metabolic Syndrome Originates in the ER Stressed Tissues**

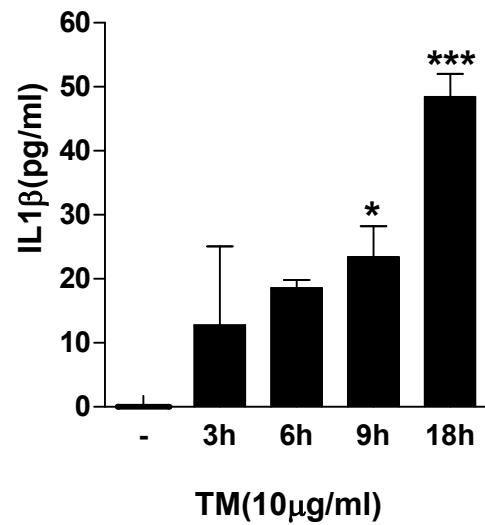
- **ERS induces IL-1 β through UPR**
- **Priming of inflammasome assembly via NF- κ B activation**
- **Chemical chaperone inhibits IL-1 β production**
- **ERS-induced NLRP3 activation via ROS production**
- **HO-1/CO system inhibits IL-1 β secretion**

ERS · UPR induces Inflammasome induces IL-1 β

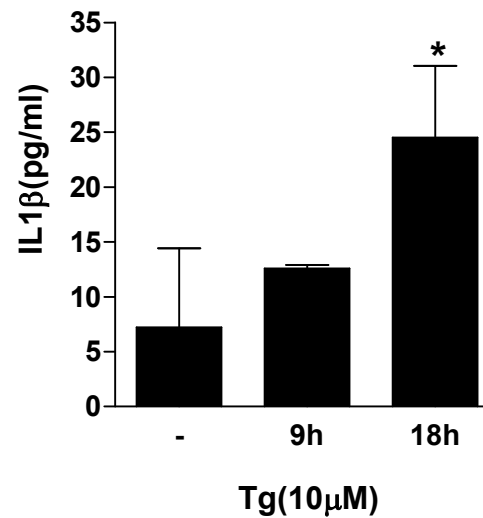
ERS induces IL-1 β through UPR



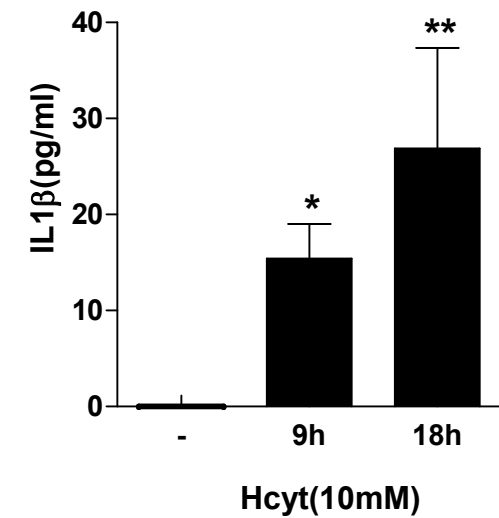
A. U937



B. U937



C. U937

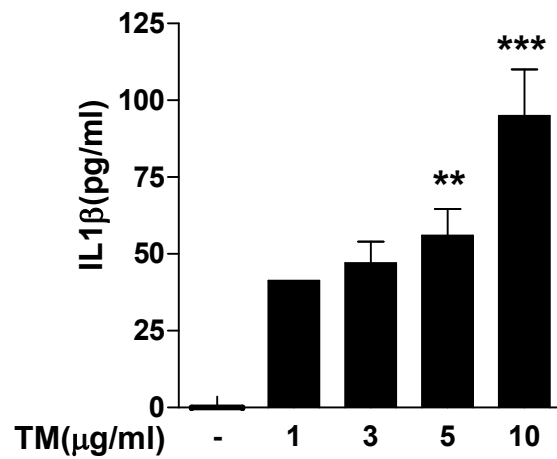


ERS · UPR induces Inflammasome induces IL-1 β

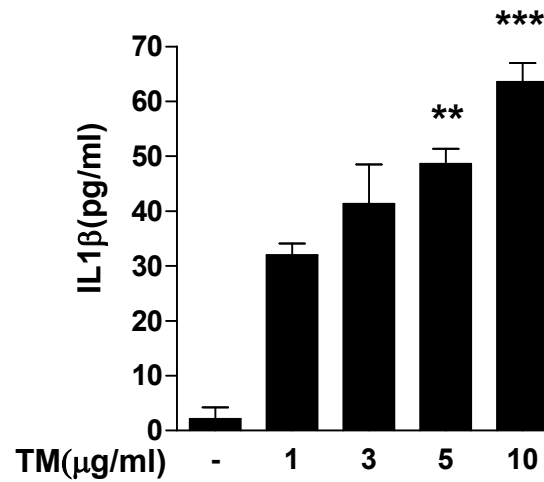
ERS induces IL-1 β through UPR



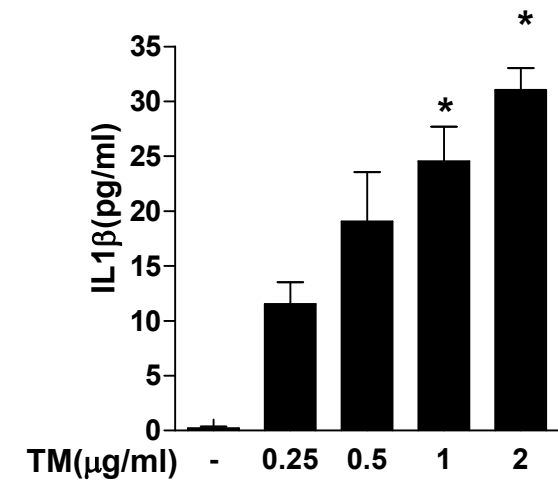
D. Peritoneal macrophage



E. BMDM

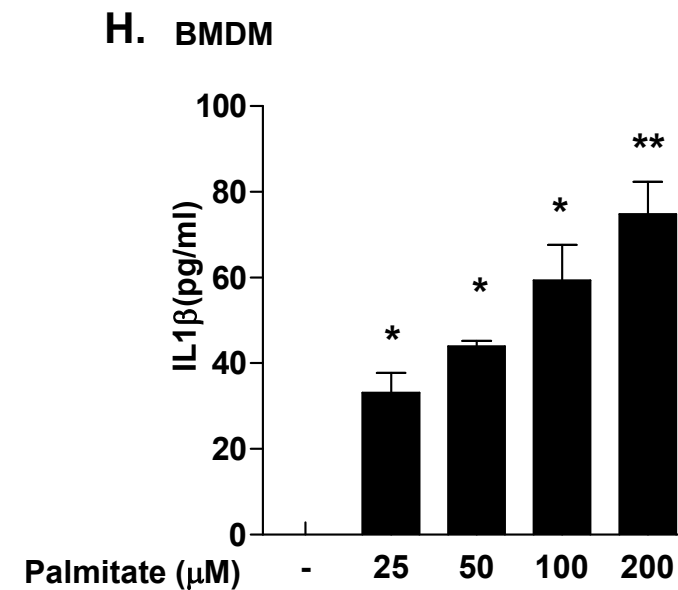
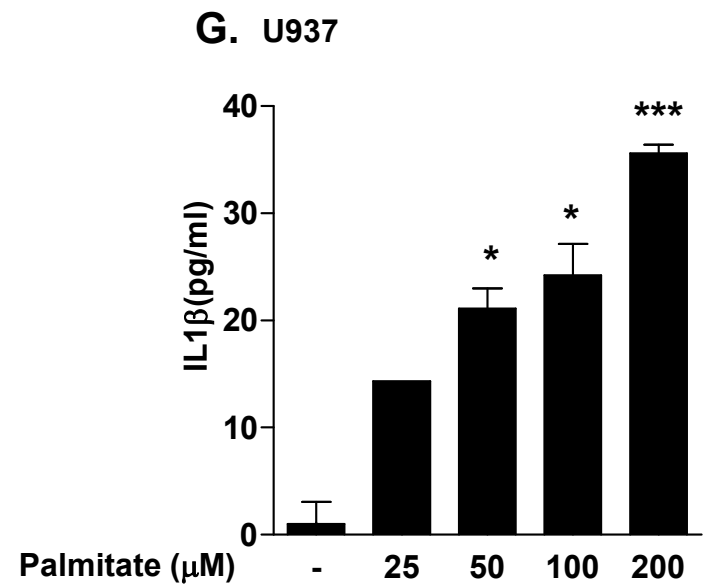


F. Adipocyte



ERS · UPR induces Inflammasome induces IL-1 β

ERS induces IL-1 β through UPR

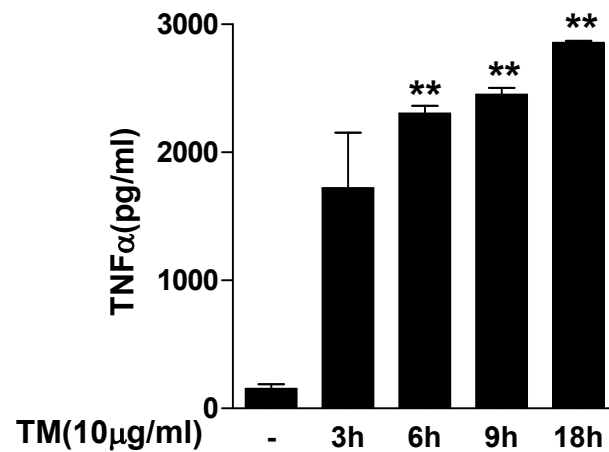


ERS · UPR induces Inflammasome induces IL-1 β

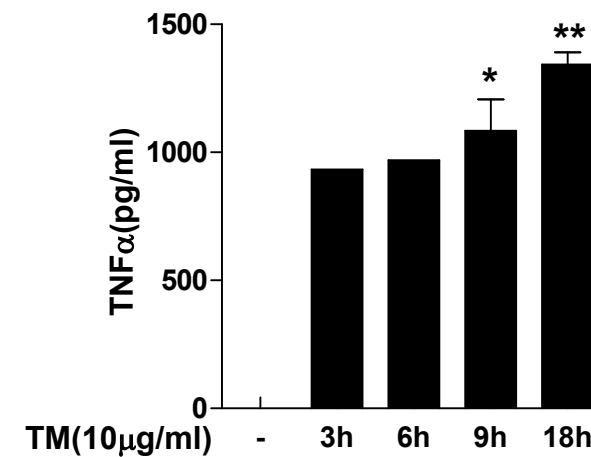
ERS induces IL-1 β through UPR



I. U937



J. Peritoneal macrophage

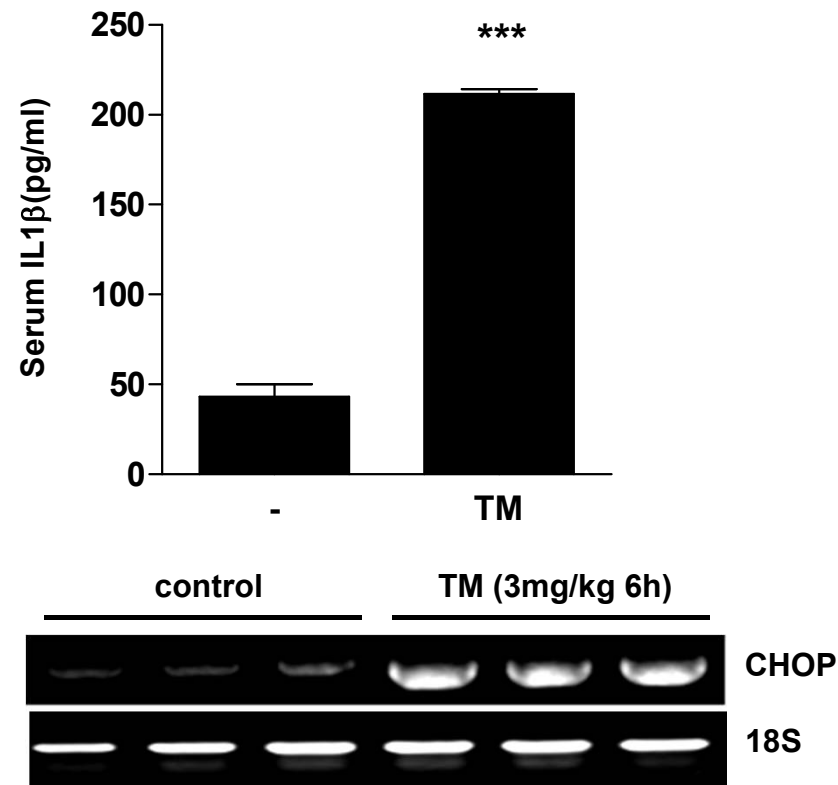


ERS · UPR induces Inflammasome induces IL-1 β

ERS induces IL-1 β through UPR



K. C57BL/6 Mouse

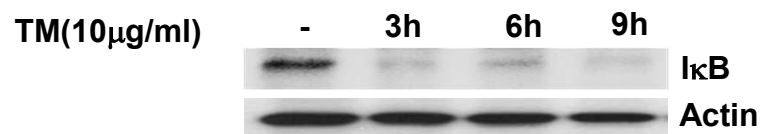


ERS · UPR induces Inflammasome induces IL-1 β

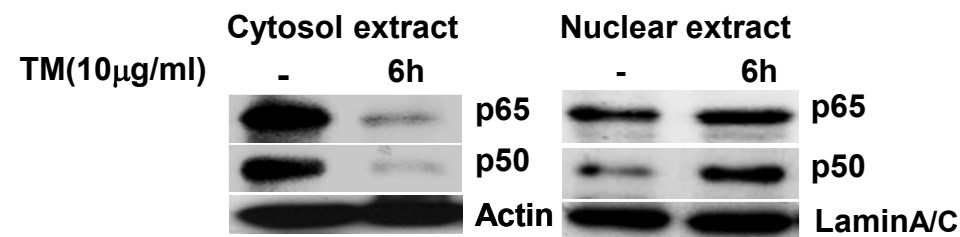
Priming of inflammasome assembly via NF- κ B activation



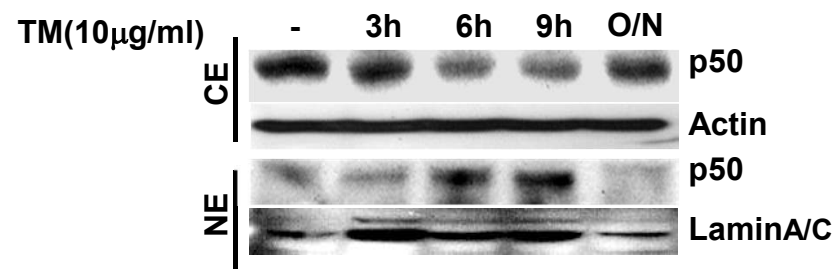
A. U937



B. Peritoneal macrophage



C. U937

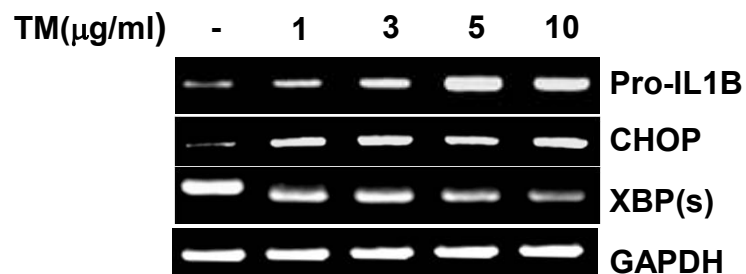


ERS · UPR induces Inflammation induces IL-1 β

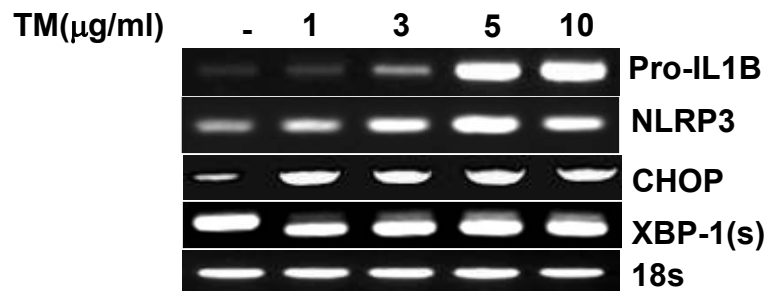
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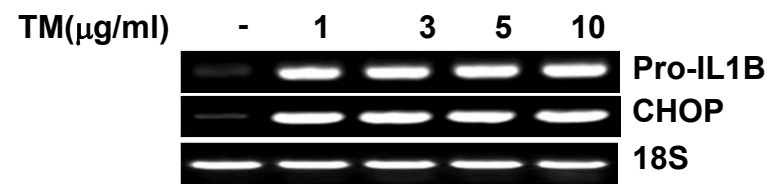
D. U937



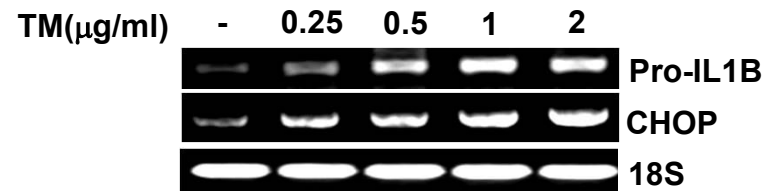
E. Peritoneal macrophage



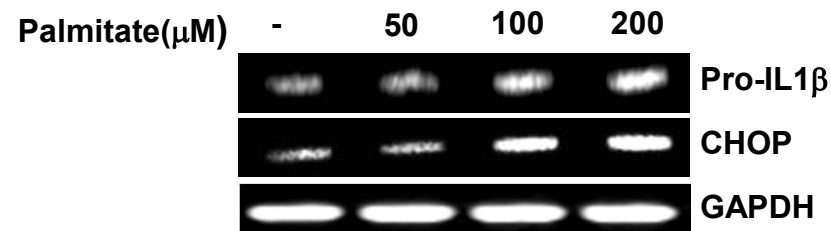
F. BMDM



G. Adipocyte



H. U937

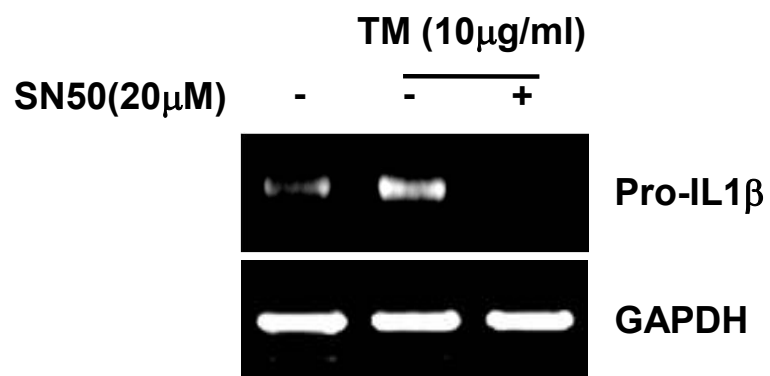


ERS · UPR induces Inflammasome induces IL-1 β

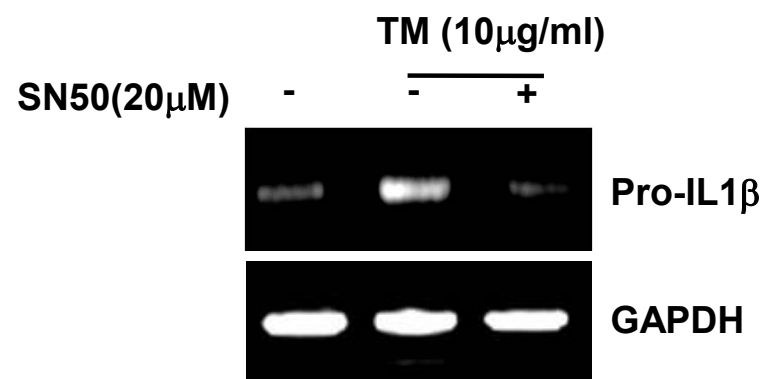
Priming of inflammasome assembly via NF- κ B activation



I. U937



J. THP-1

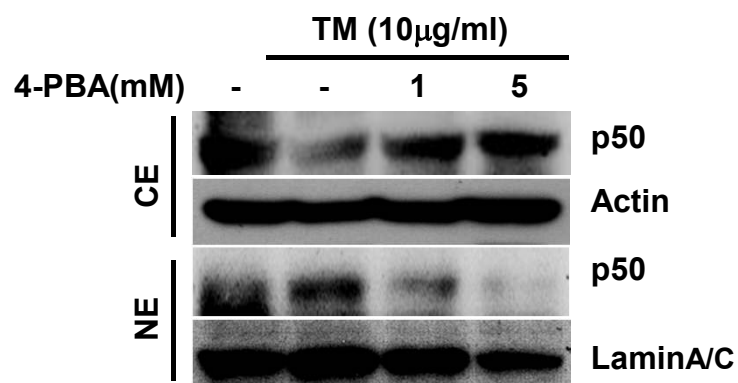


ERS · UPR induces Inflammasome induces IL-1 β

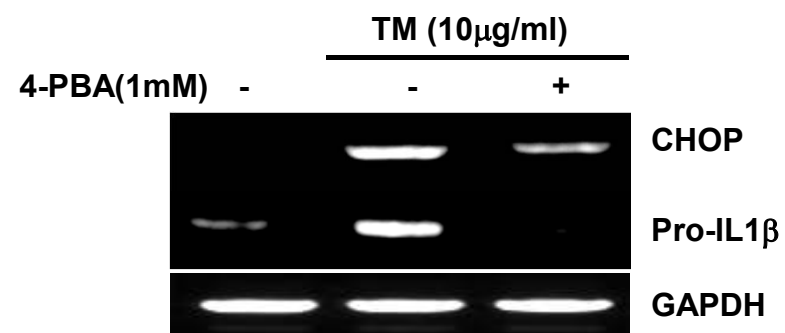
Chemical chaperones inhibit IL-1 β production



A. U937



B. U937

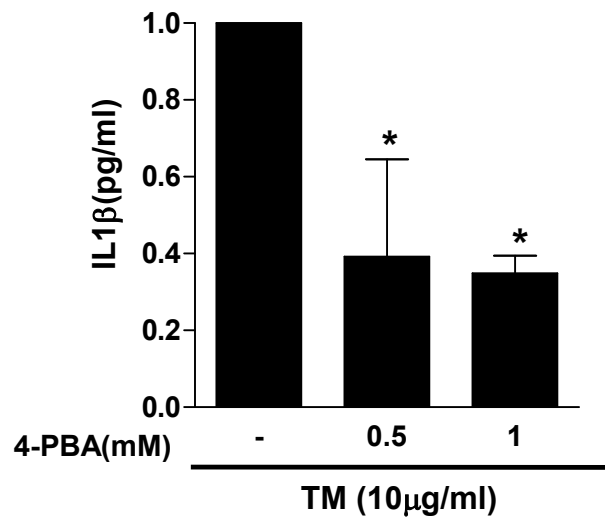


ERS · UPR induces Inflammasome induces IL-1 β

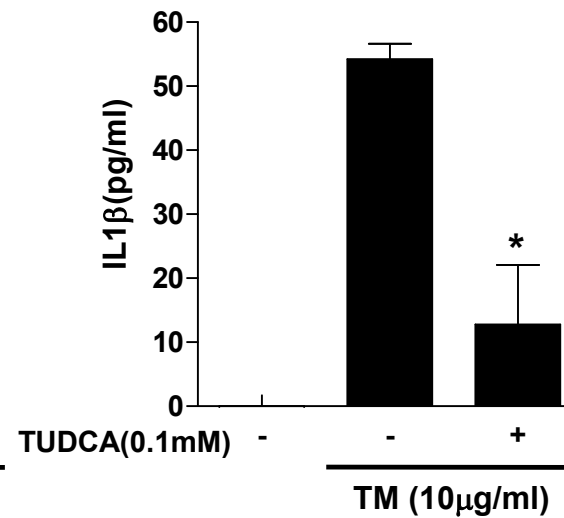
Chemical chaperones inhibit IL-1 β production



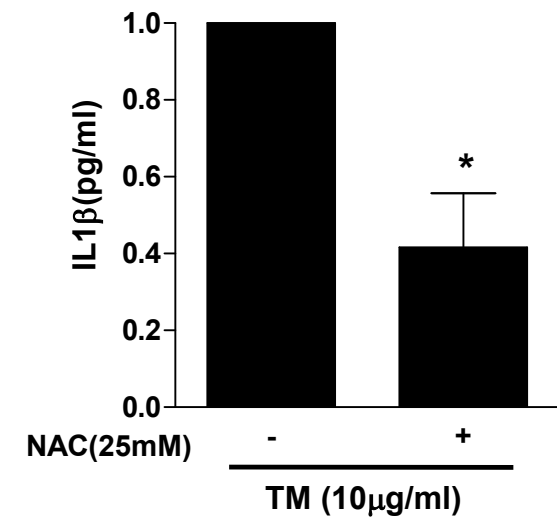
C. U937



D. U937



E. U937

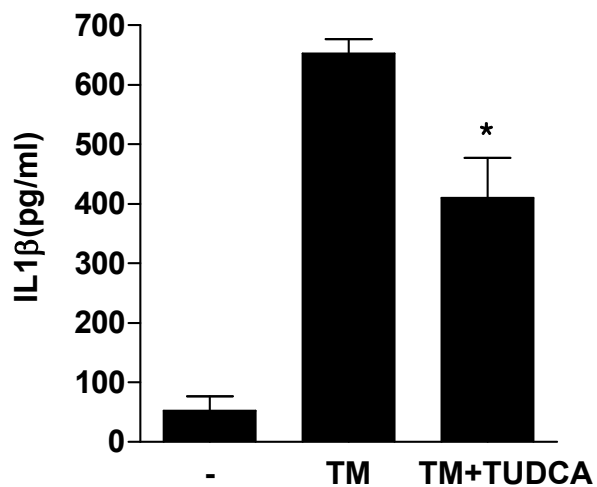


ERS · UPR induces Inflammasome induces IL-1 β

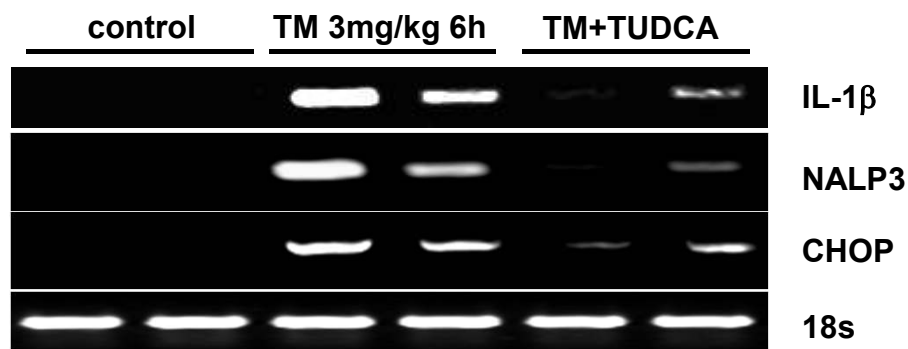
Chemical chaperones inhibit IL-1 β production



F. In vivo



G. In vivo

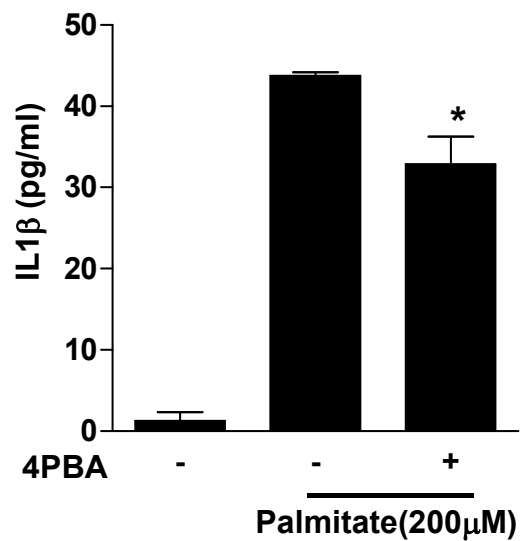


ERS · UPR induces Inflammasome induces IL-1 β

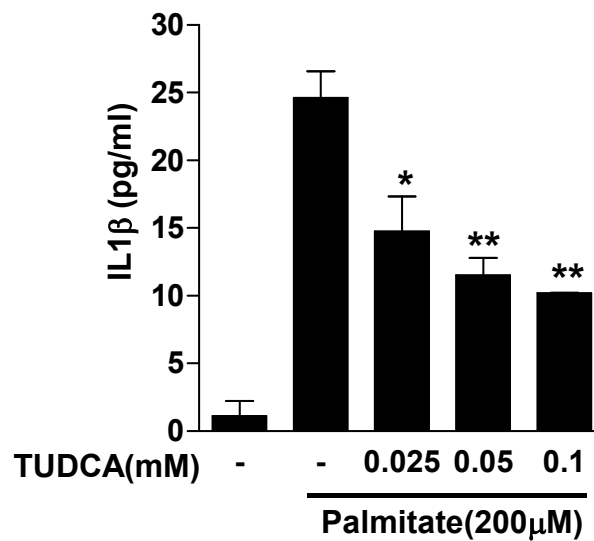
Chemical chaperones inhibit IL-1 β production



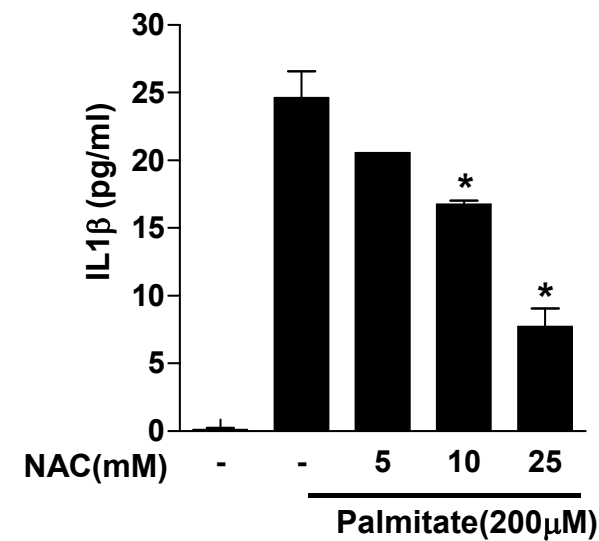
H. U937



I. U937



J. U937

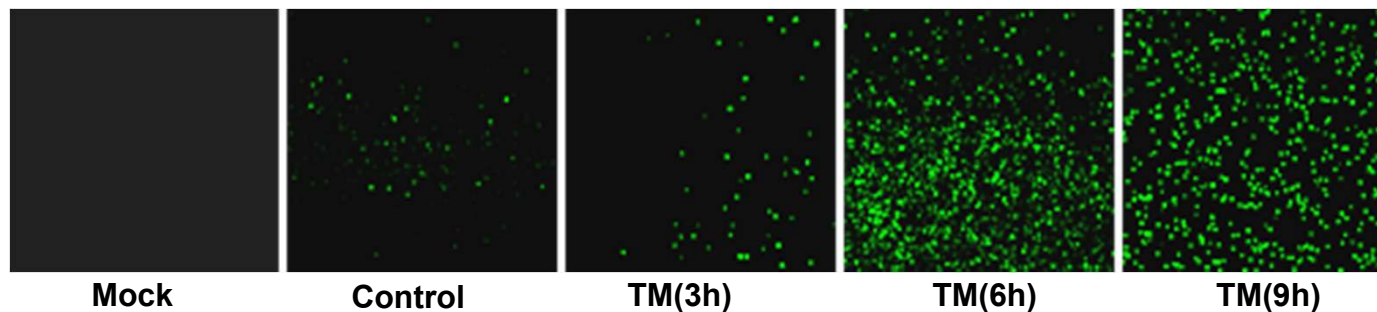


ERS · UPR induces Inflammasome induces IL-1 β

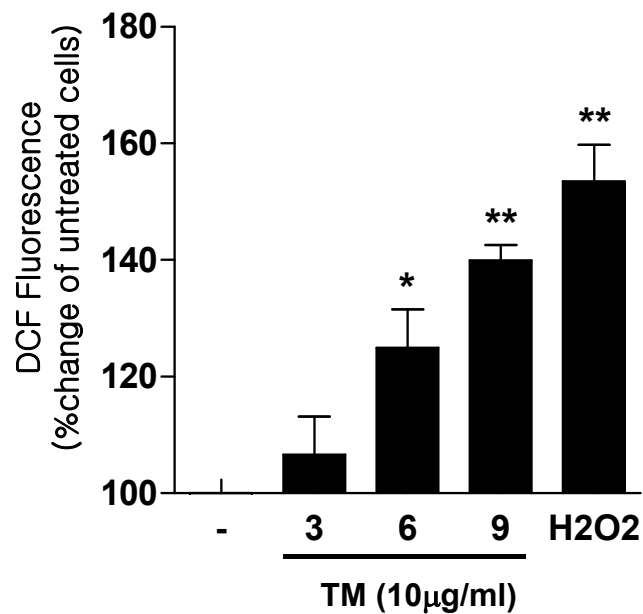
ERS-induced NLRP3 activation via ROS production



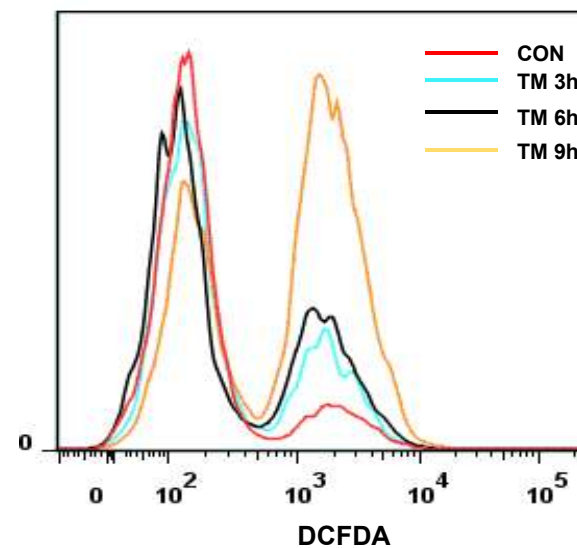
A. U937



B.



C.

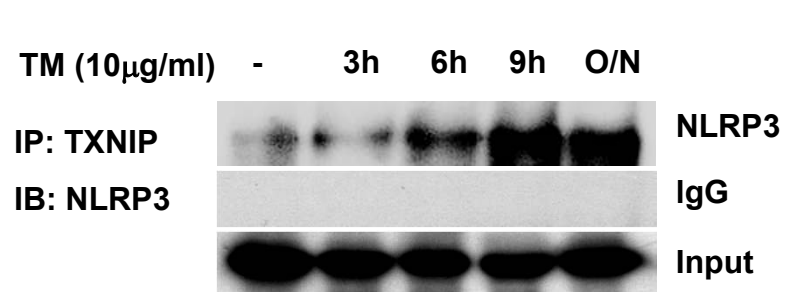


ERS · UPR induces Inflammasome induces IL-1 β

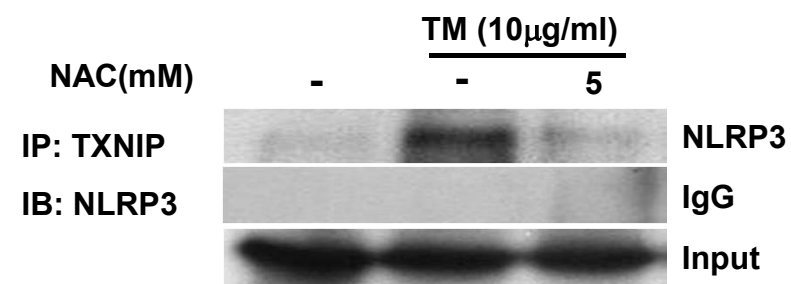
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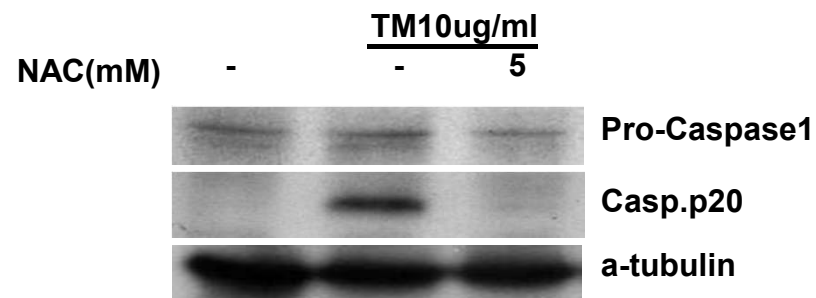
D. U937



E. U937

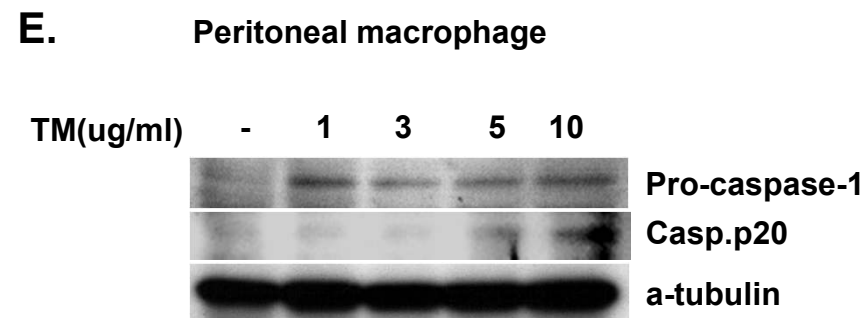
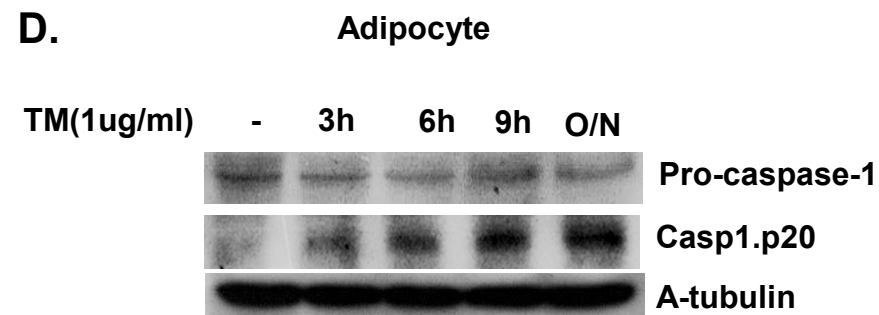
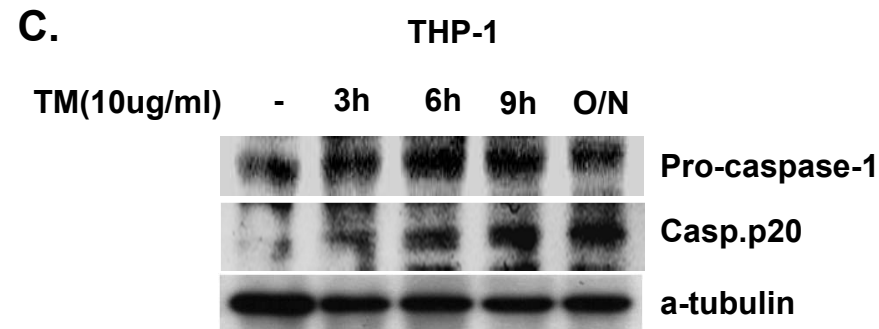
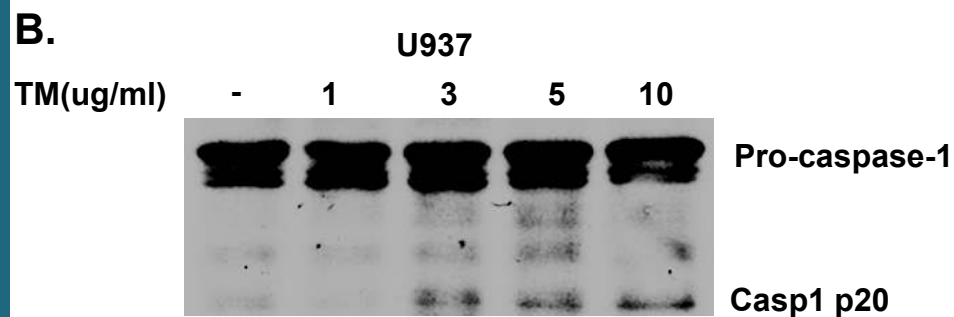
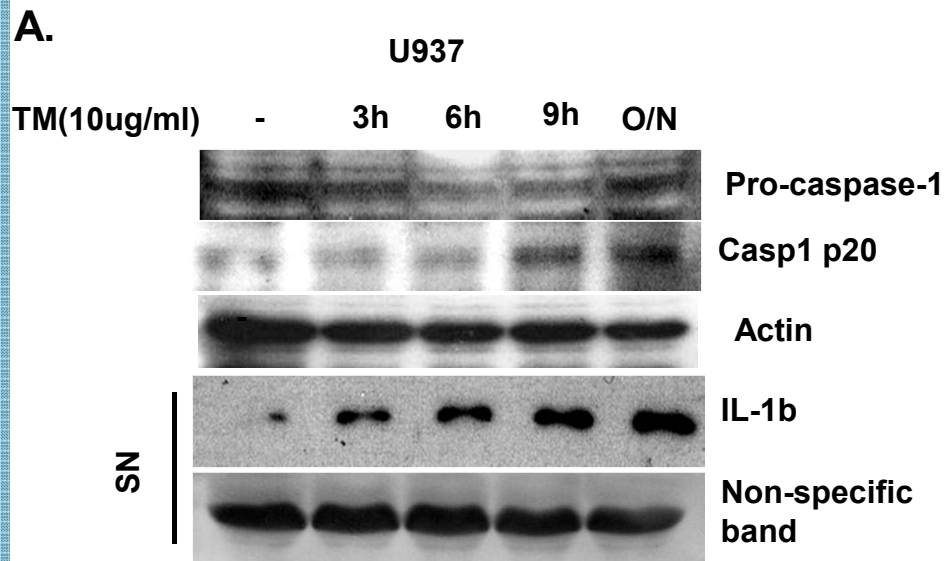


F. U937



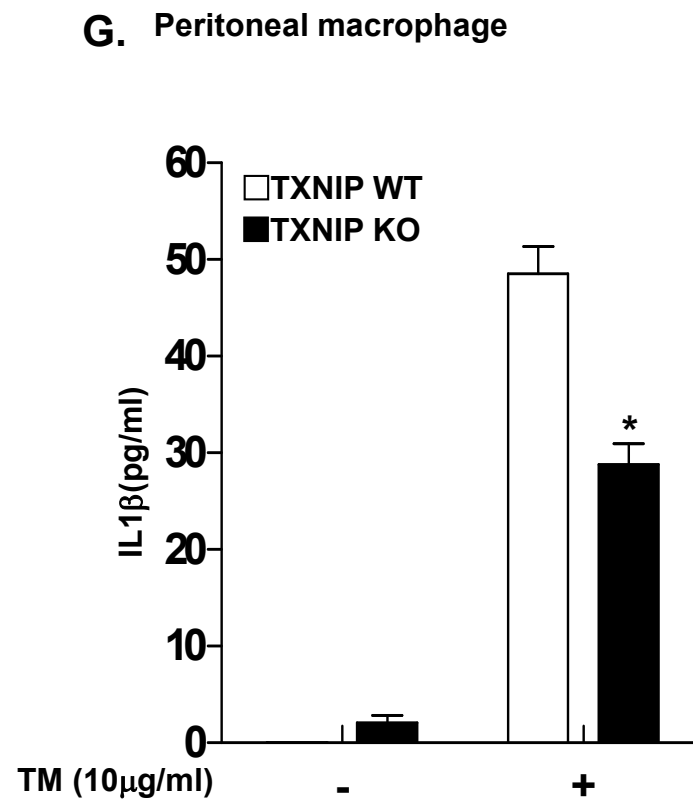
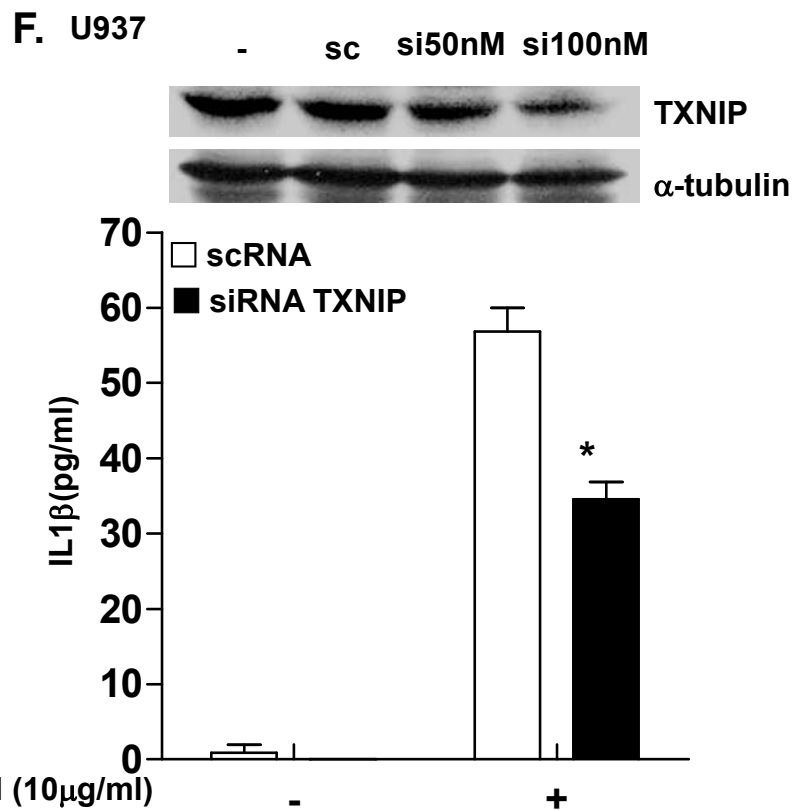
ERS · UPR induces Inflammasome induces IL-1 β

ERS-induced NLRP3 activation via ROS production



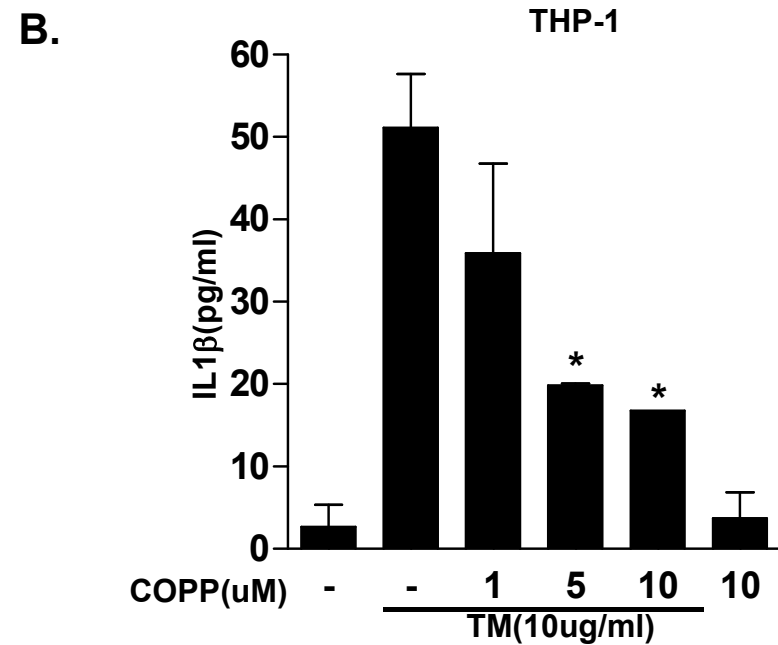
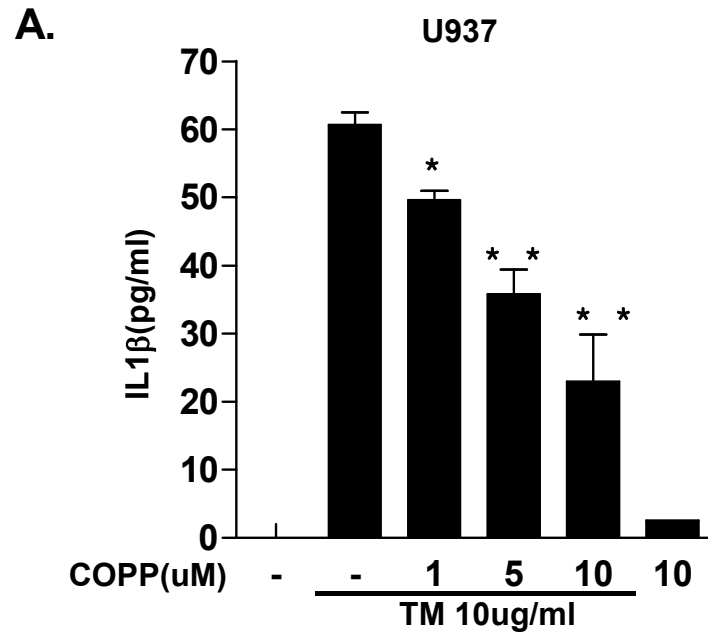
ERS · UPR induces Inflammasome induces IL-1 β

ERS-induced NALP3 activation via ROS production

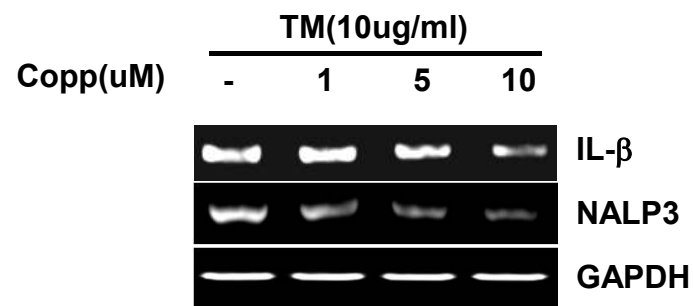


ERS · UPR induces Inflammasome induces IL-1 β

HO-1/CO system inhibits IL-1 β secretion



C.

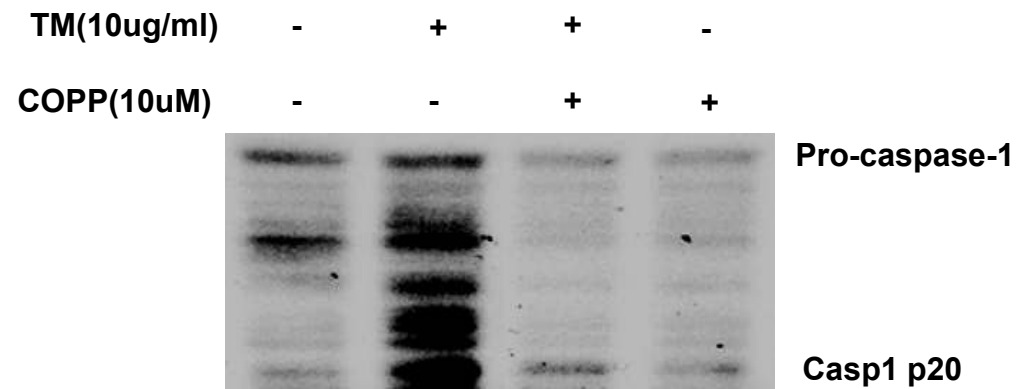


ERS · UPR induces Inflammasome induces IL-1 β

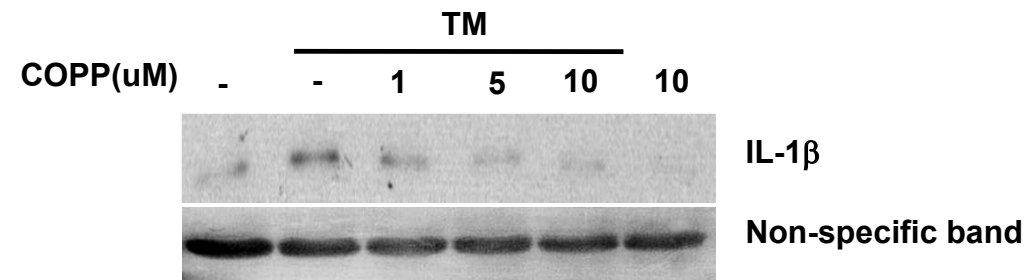
HO-1/CO system inhibits IL-1 β secretion



D. U937



E. U937

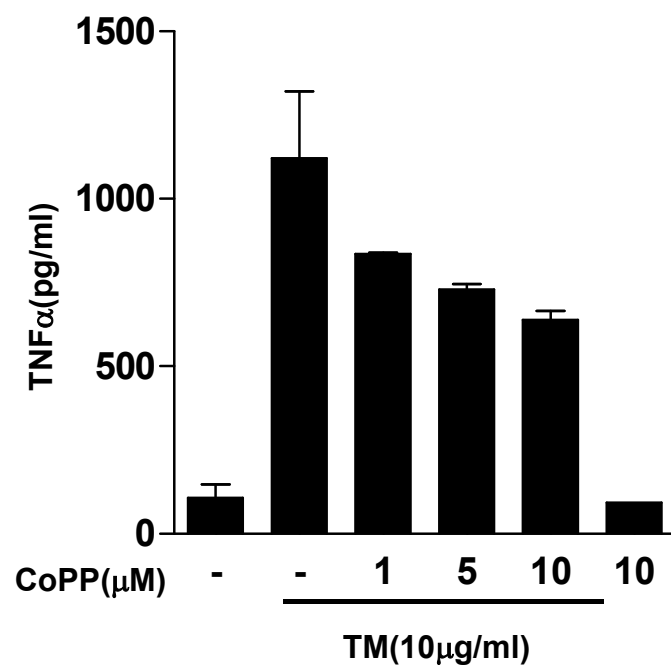


ERS · UPR induces Inflammasome induces IL-1 β

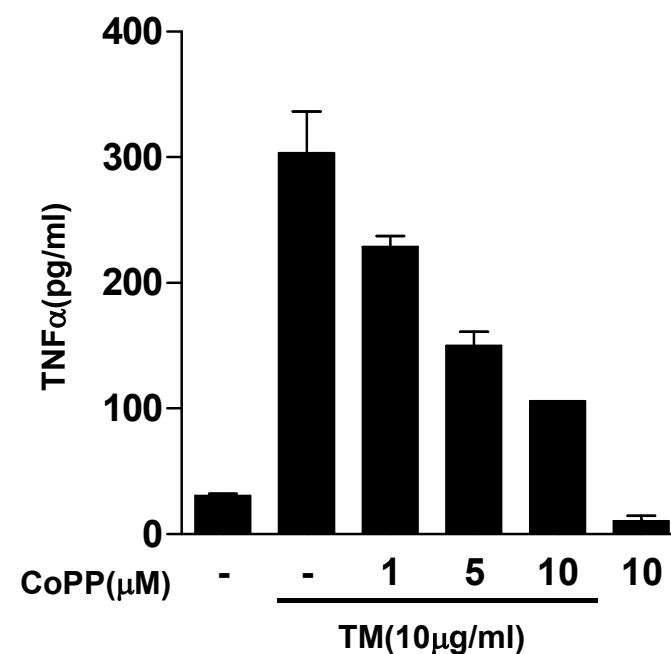
HO-1/CO system inhibits IL-1 β secretion



F. U937



G. THP-1

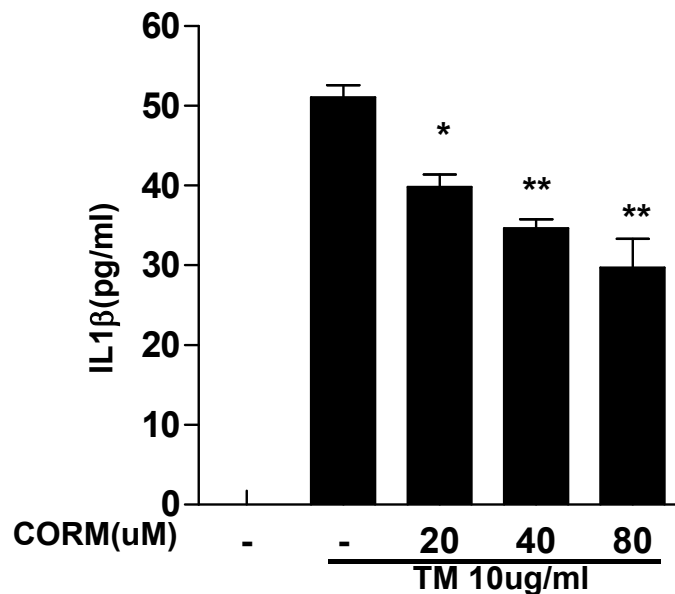


ERS · UPR induces Inflammasome induces IL-1 β

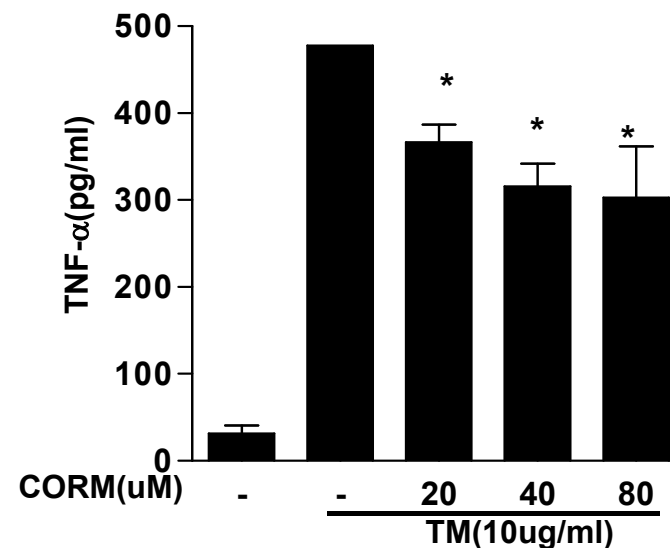
HO-1/CO system inhibits IL-1 β secretion



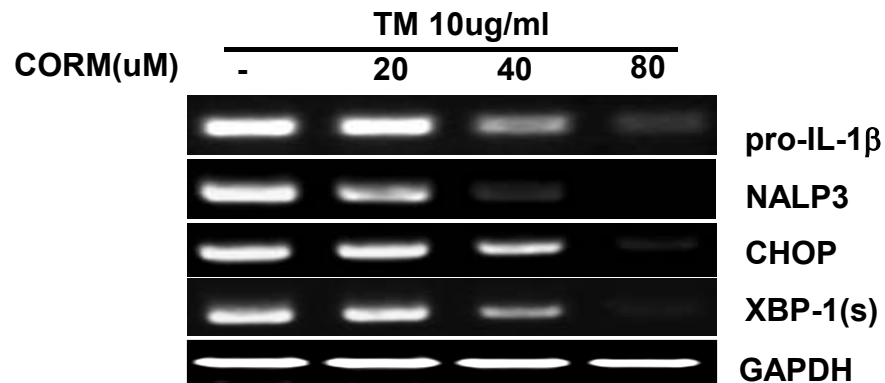
H. U937



I. U937



J. U937



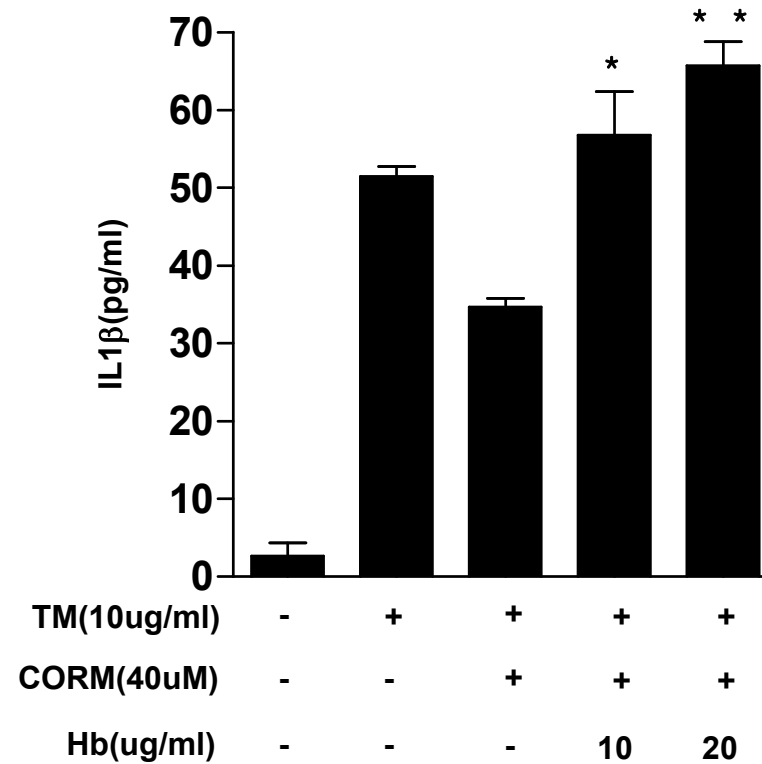
ERS · UPR induces Inflammasome induces IL-1 β

HO-1/CO system inhibits IL-1 β secretion



K.

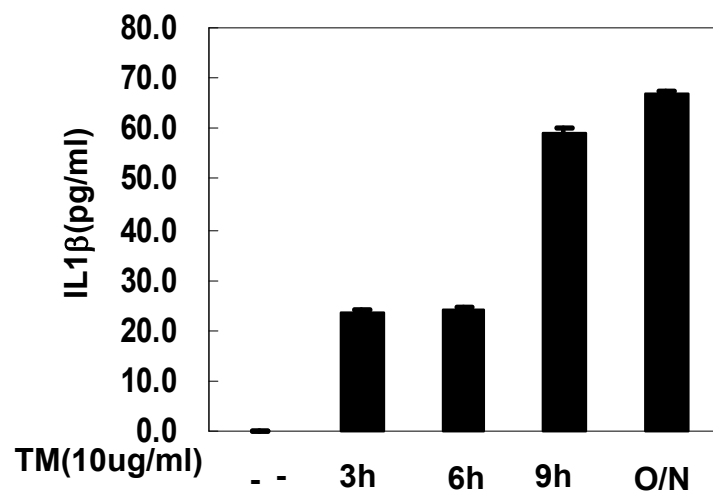
U937



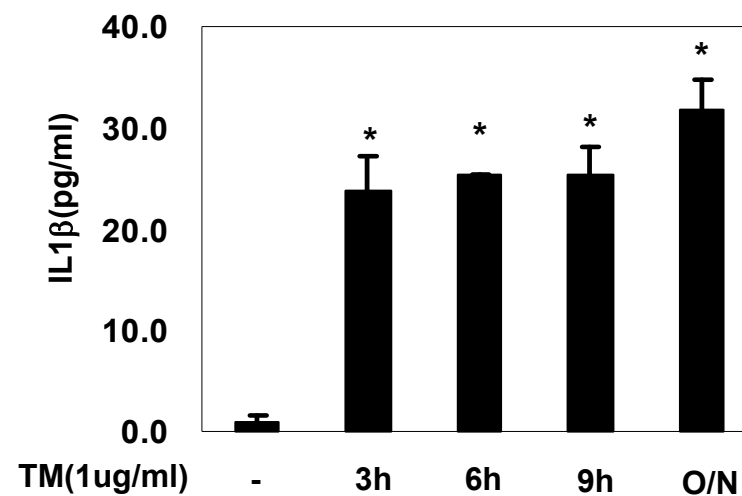
Supplementary1 ER stress induces IL1 β production in both in vitro and in vivo



A. Peritoneal macrophage

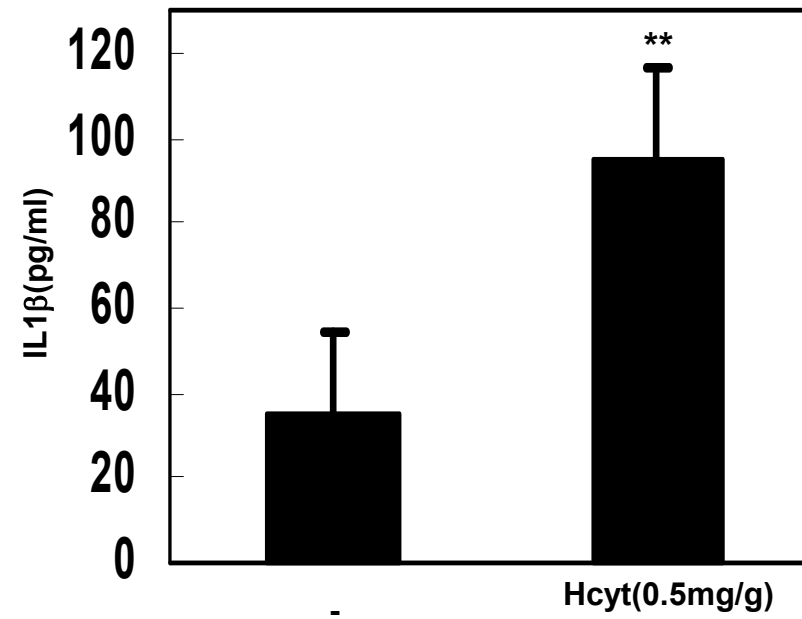


B. Adipocyte_ELISA





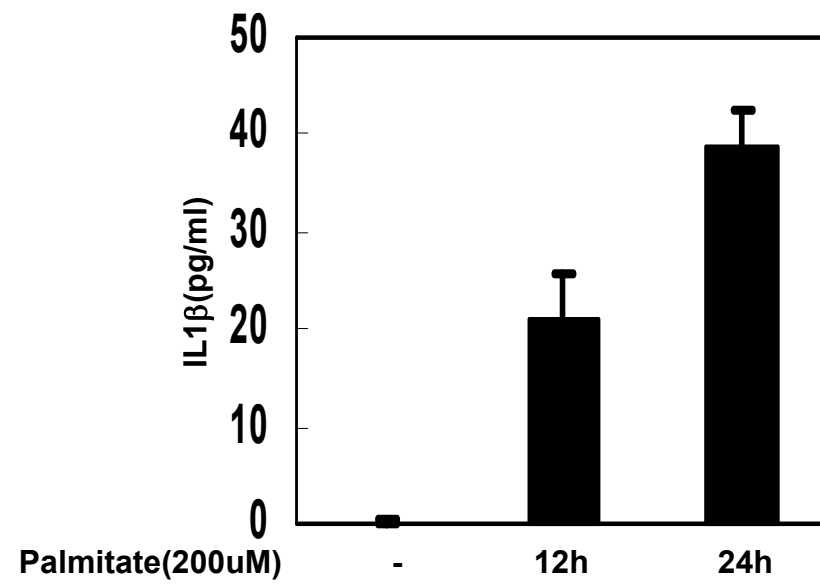
C. In vivo



Hcyt 0.5mg/g 1h C57B

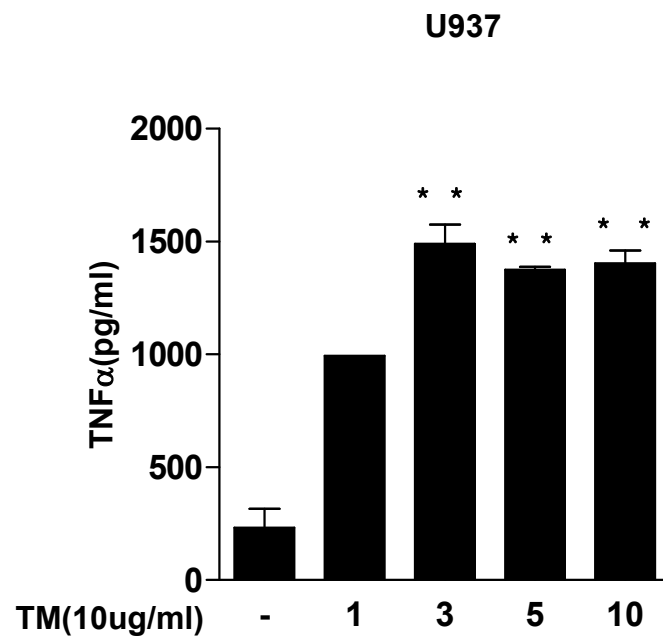


D. U937

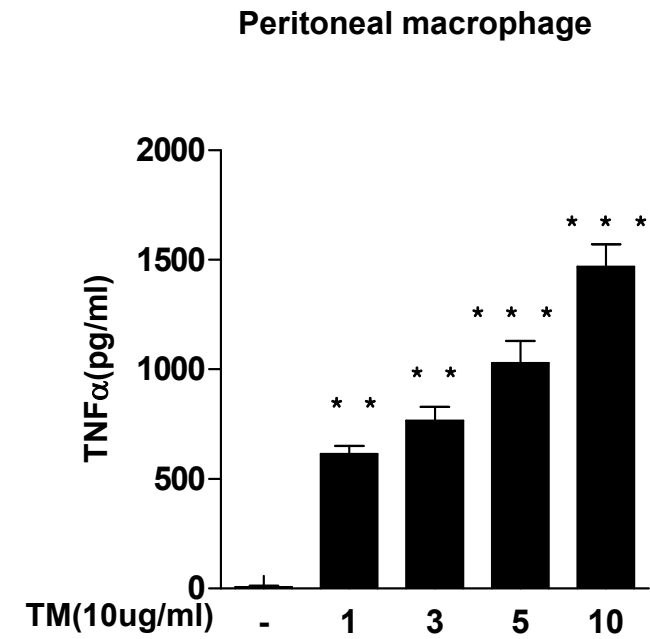




E.



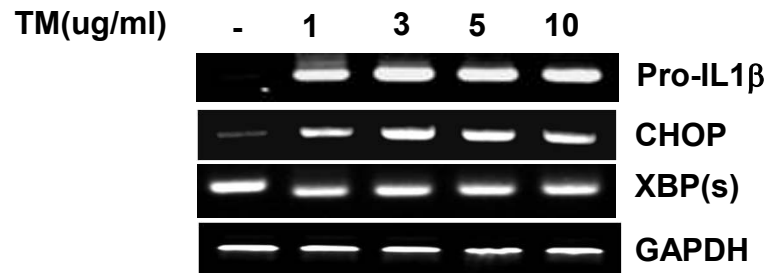
F.



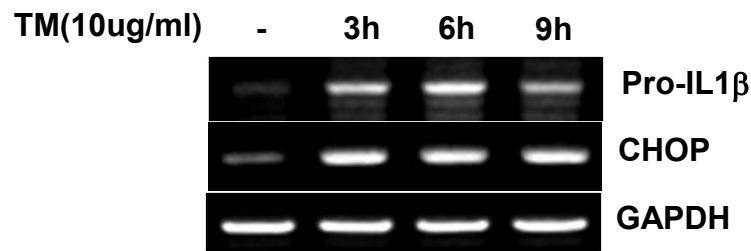
Supplementary2. ER stress induces expression of pro-IL-1 β mRNA



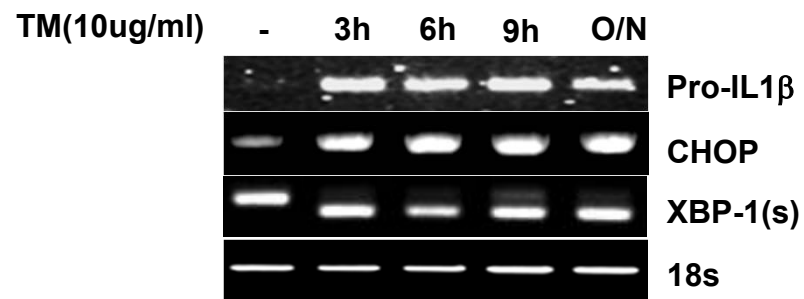
A. THP-1



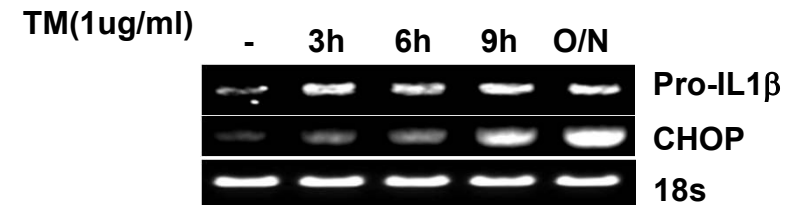
B. U937



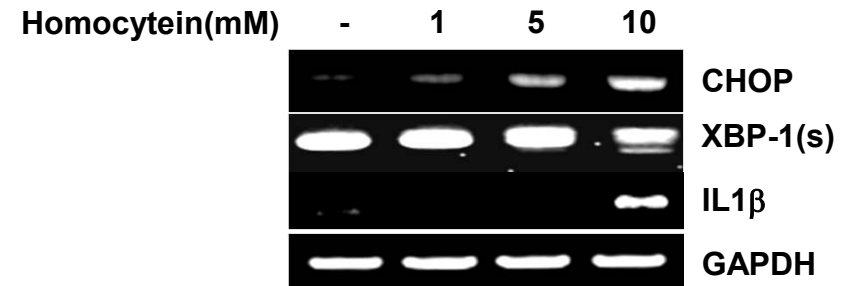
C. Peritoneal macrophage



D. Adipocyte

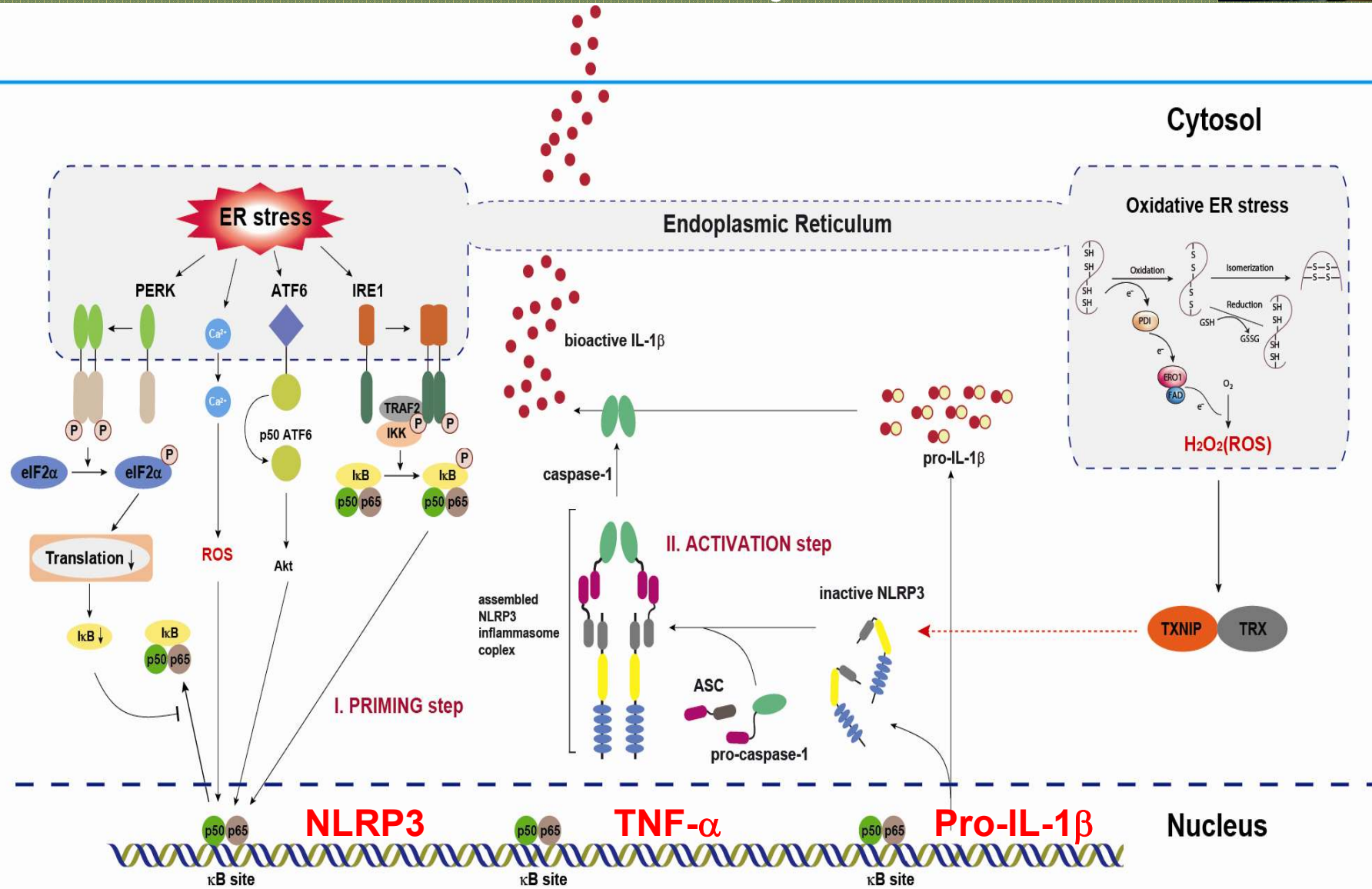


E. U937



ERS · UPR induces Inflammasome induces IL-1 β

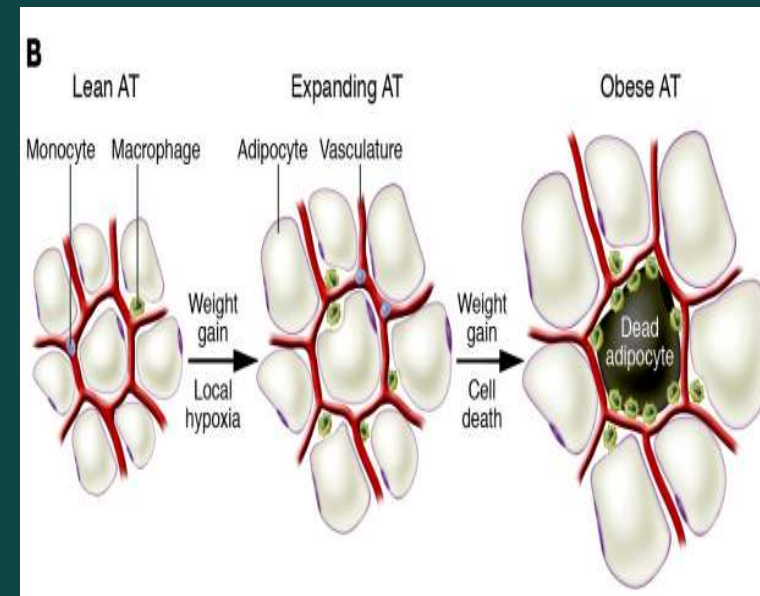
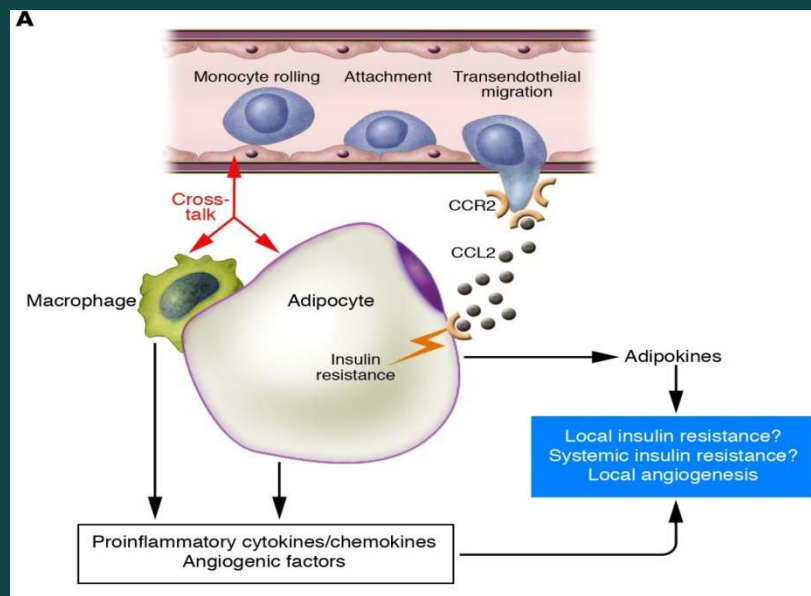
Summary



OUR QUESTION



Inflamed fat: what starts the fire?



[J Clin Invest.](#) 2006 Jan;116(1):33-5 [Neels JG,](#) [Olefsky JM.](#)

OUR ANSWER



HFD, Obesity
(caloric imbalance)



ERS-UPR, Mt Dysfunction
Autophagy Deficiency



m-Inflammation, **Inflammasome Formation**



CardioMet & Autoimmune Diseases

Flow Chart

from **HFD** to **CardioMet** & **Autoimmune Diseases**



HFD, Obesity
(caloric imbalance)



ERS-UPR, Mt Dysfunction
Autophagy Deficiency

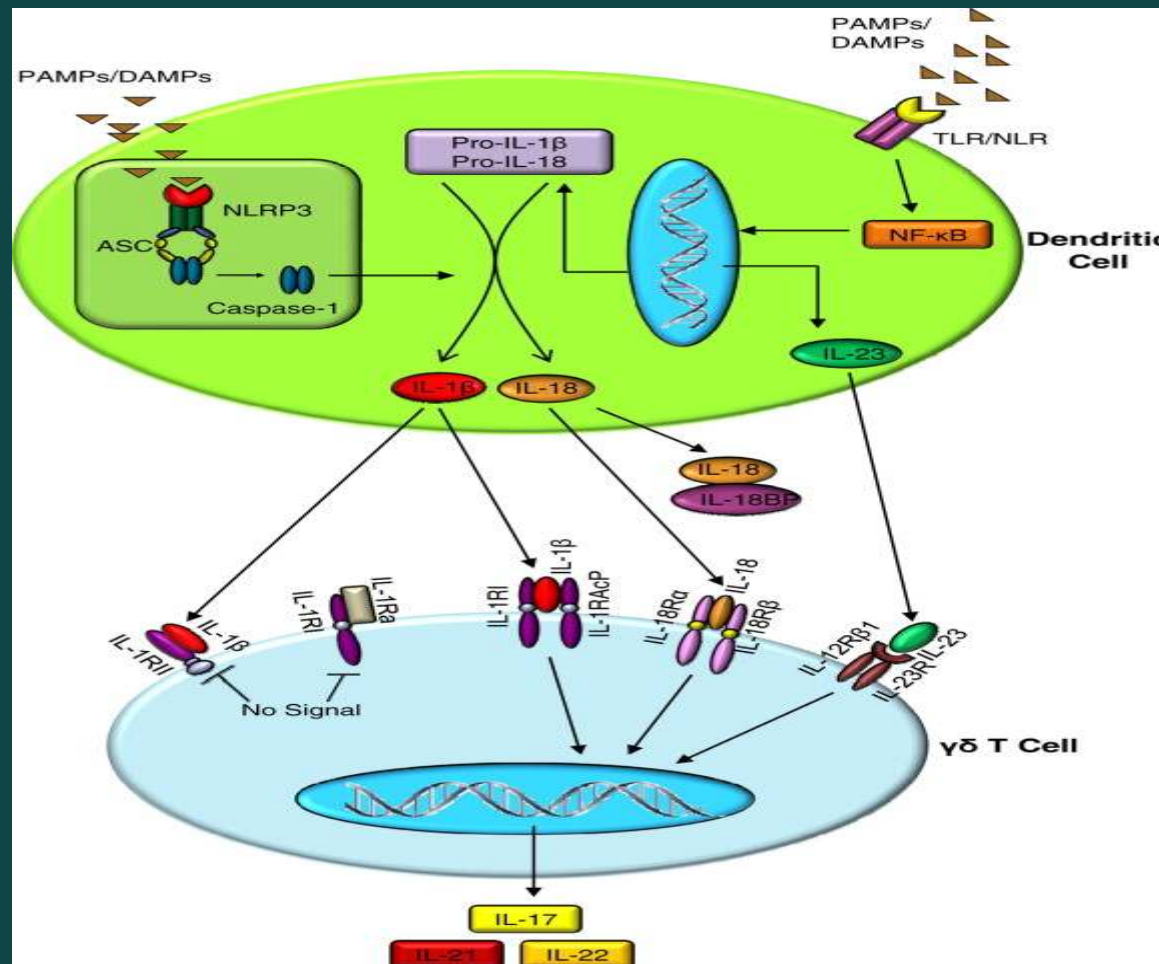


m-Inflammation, Inflammasome Formation



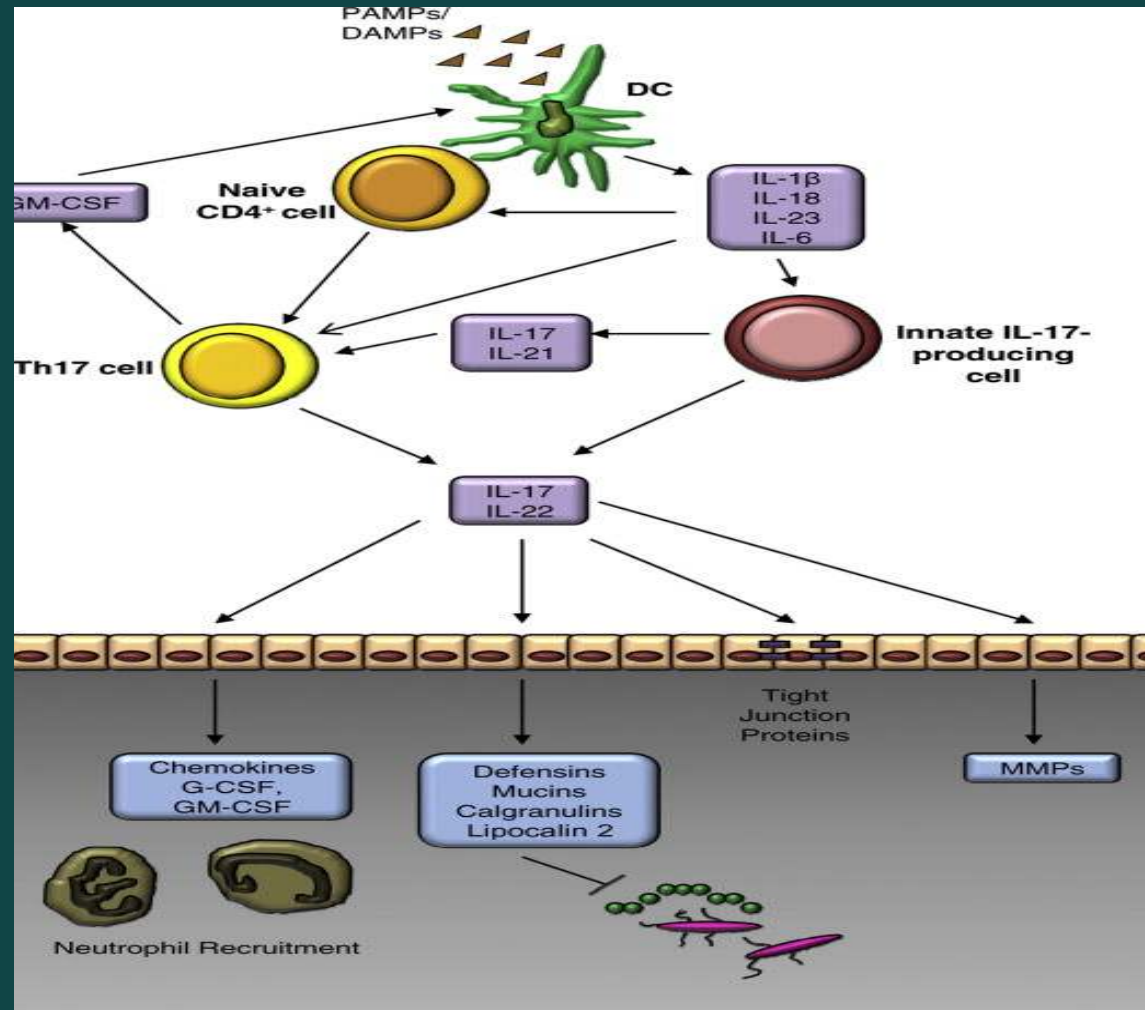
CardioMet & Autoimmune Diseases

Caspase-1-Processed Cytokines Induces IL-17 by Innate T cells That Mediate Autoimmunity (1)



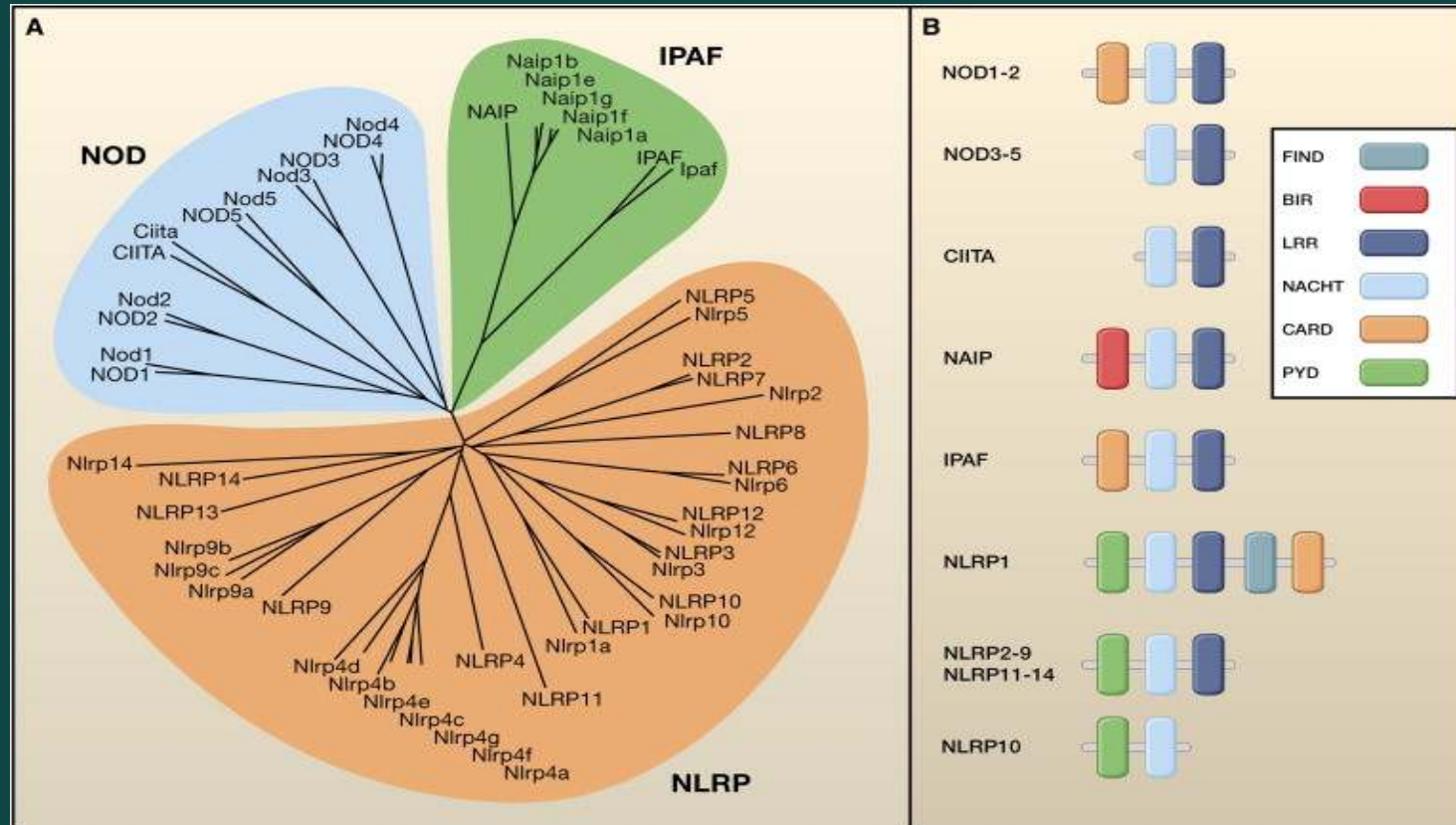
Cytokine. 2011 Oct;56(1):126-32.

Caspase-1-Processed Cytokines Induces IL-17 by Innate T cells That Mediate Autoimmunity (2)



[Cytokine](#). 2011 Oct;56(1):126-32.

NLR Function beyond the Inflammasome (1)



Human and Mouse NLR Family Members

[Cell. 2010 Mar 19;140\(6\):821-32](#)

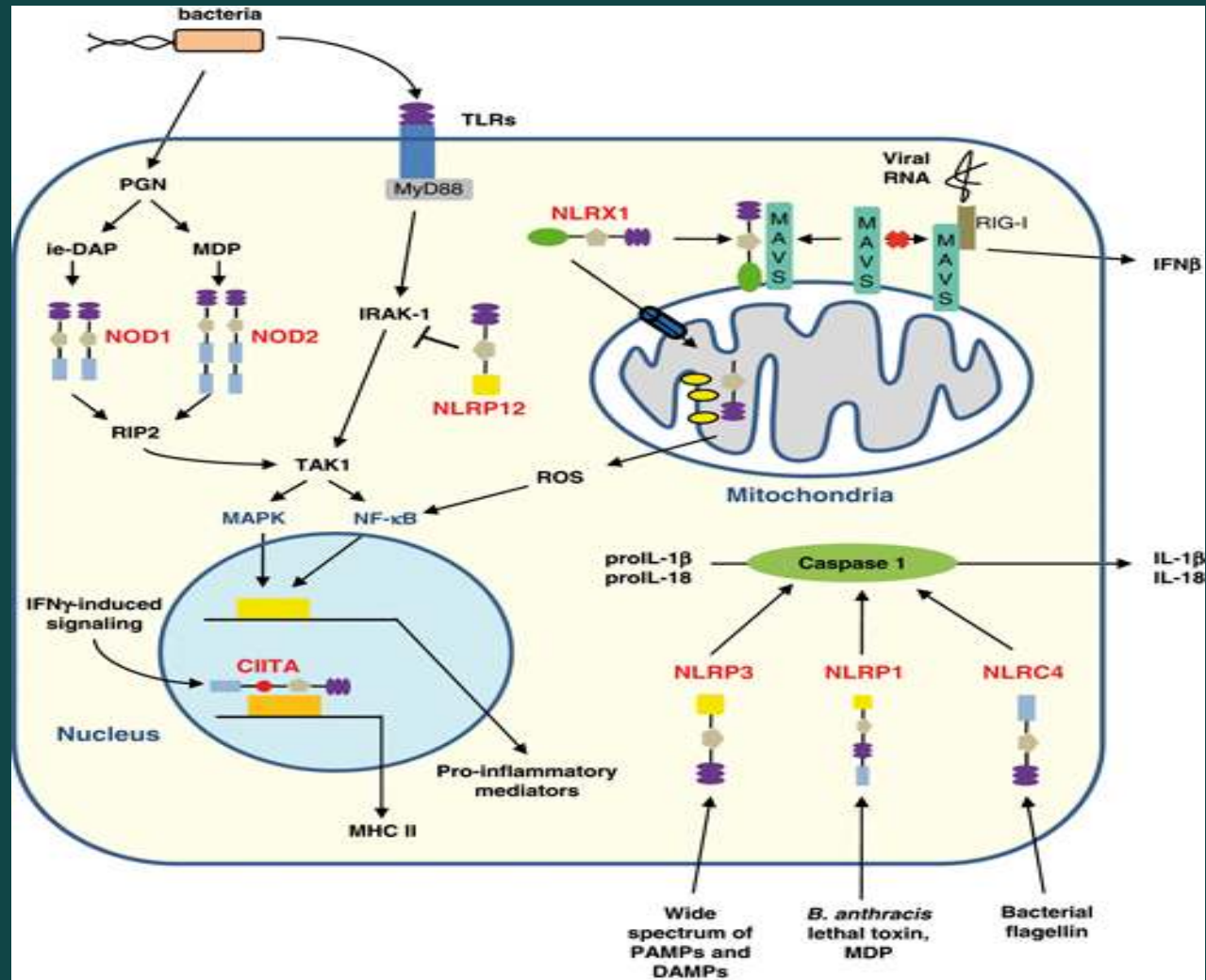
NLR Signaling beyond the Inflammasome (2)



NLR	Structure	Function(s)
CIITA		Master regulator of <u>MHC II expression</u>
NLRP12		Regulation of inflammatory pathways via <u>NF-κB inhibition</u>
NLRX1		Inhibition of viral defense via interaction with MAVS OR Generation of <u>ROS</u> to amplify <u>NF-κB activation</u>
NOD1		Recognition of bacterial PGN fragments inducing <u>NF-κB activation</u>
NOD2		
NLRP3		Activation by a wide spectrum of PAMPs and DAMPs resulting in caspase-1 activation
NLRP1		Recognition of MDP and <i>Bacillus anthracis</i> lethal toxin inducing caspase-1 activation
NLRC4		Recognition of bacterial flagellin to induce caspase-1 activation
	CARD domain Pyrin domain Mitochondrial localization sequence	
	Leucine-rich repeat NACHT domain Acid transactivation domain	

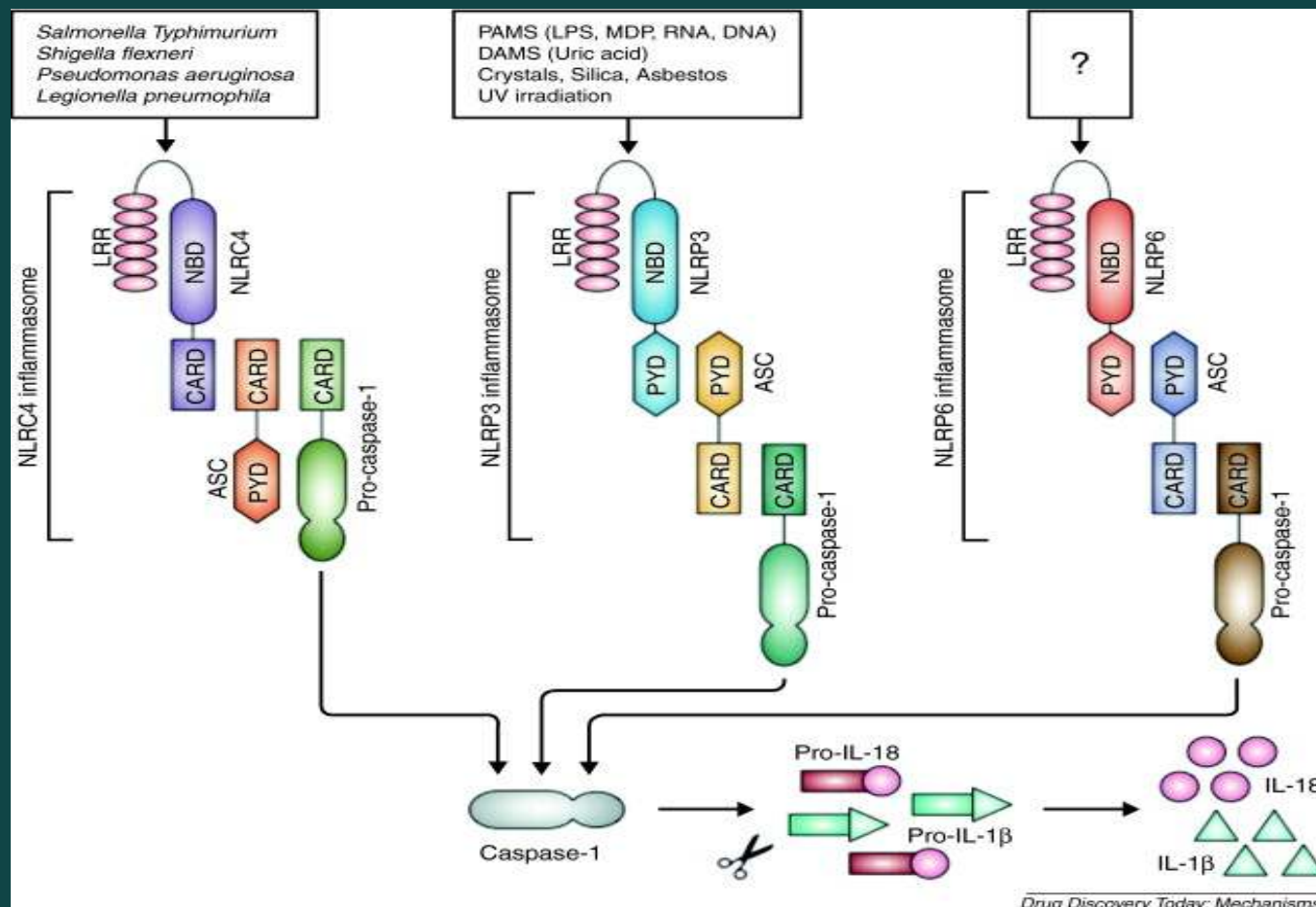
Eur. J. Immunol. 2010. 40: 595–653

NLR Signaling beyond the Inflammasome (3)



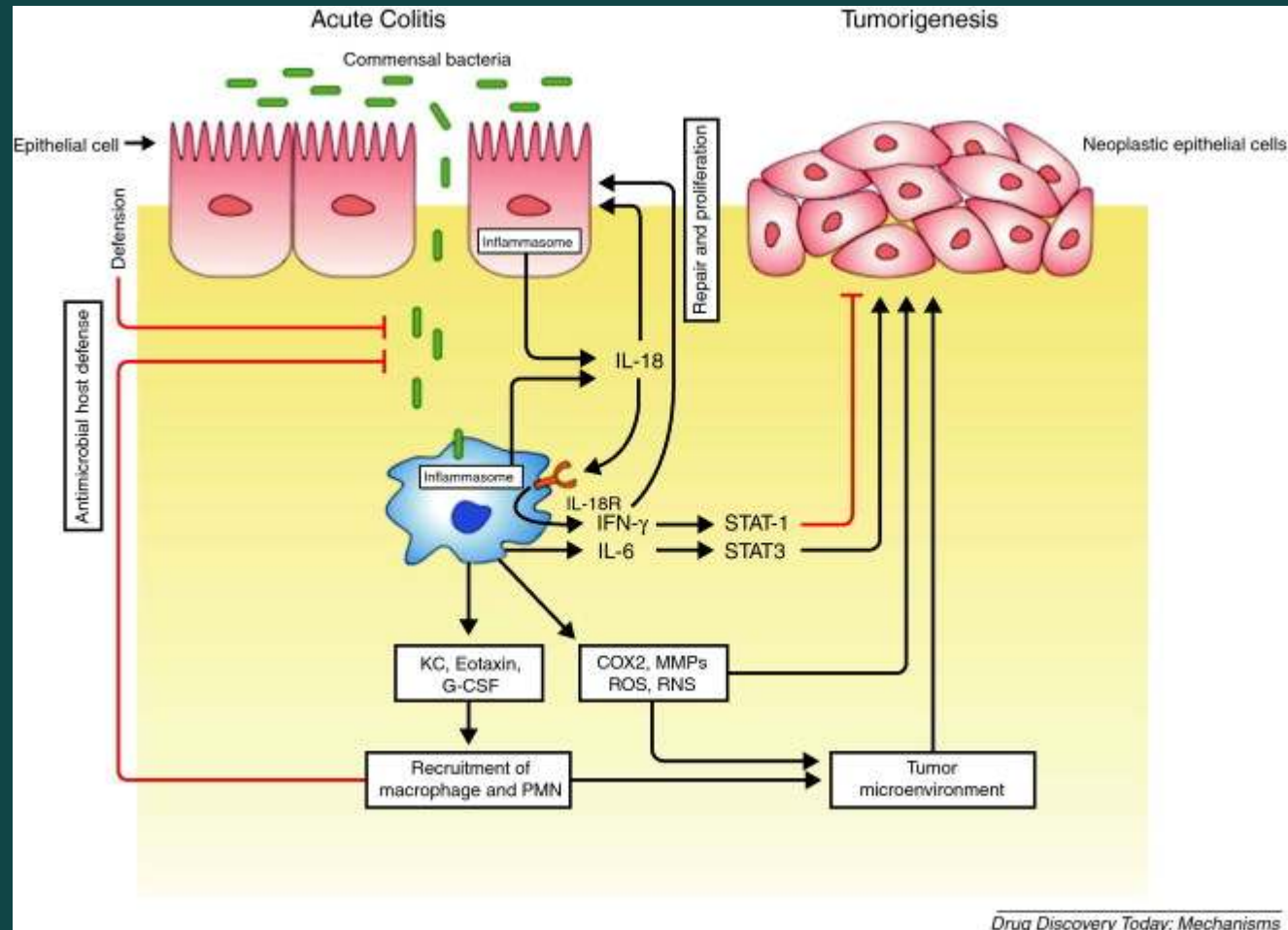
Eur. J. Immunol. 2010. 40: 595–653

Inflammasome protects against Colorectal Tumorigenesis(4)



[Drug Discovery Today: Disease Mechanisms](#)
Volume 8, Issues 3–4, Winter 2011, Pages e71–e78

Inflammasome protects against Colorectal Tumorigenesis(5)

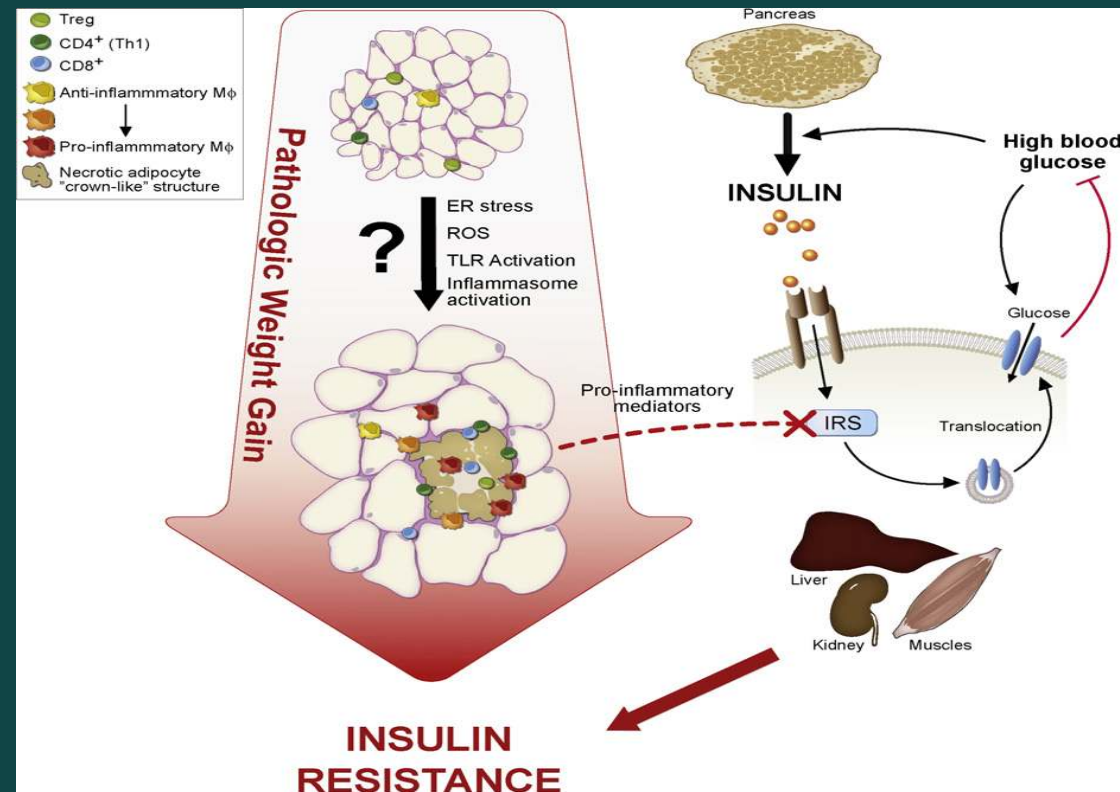


[Drug Discovery Today: Disease Mechanisms](#)
Volume 8, Issues 3–4, Winter 2011, Pages e71–e78

IMMUNOMETABOLISM(1)



Multi-level Interaction between the Metabolic & Immune System



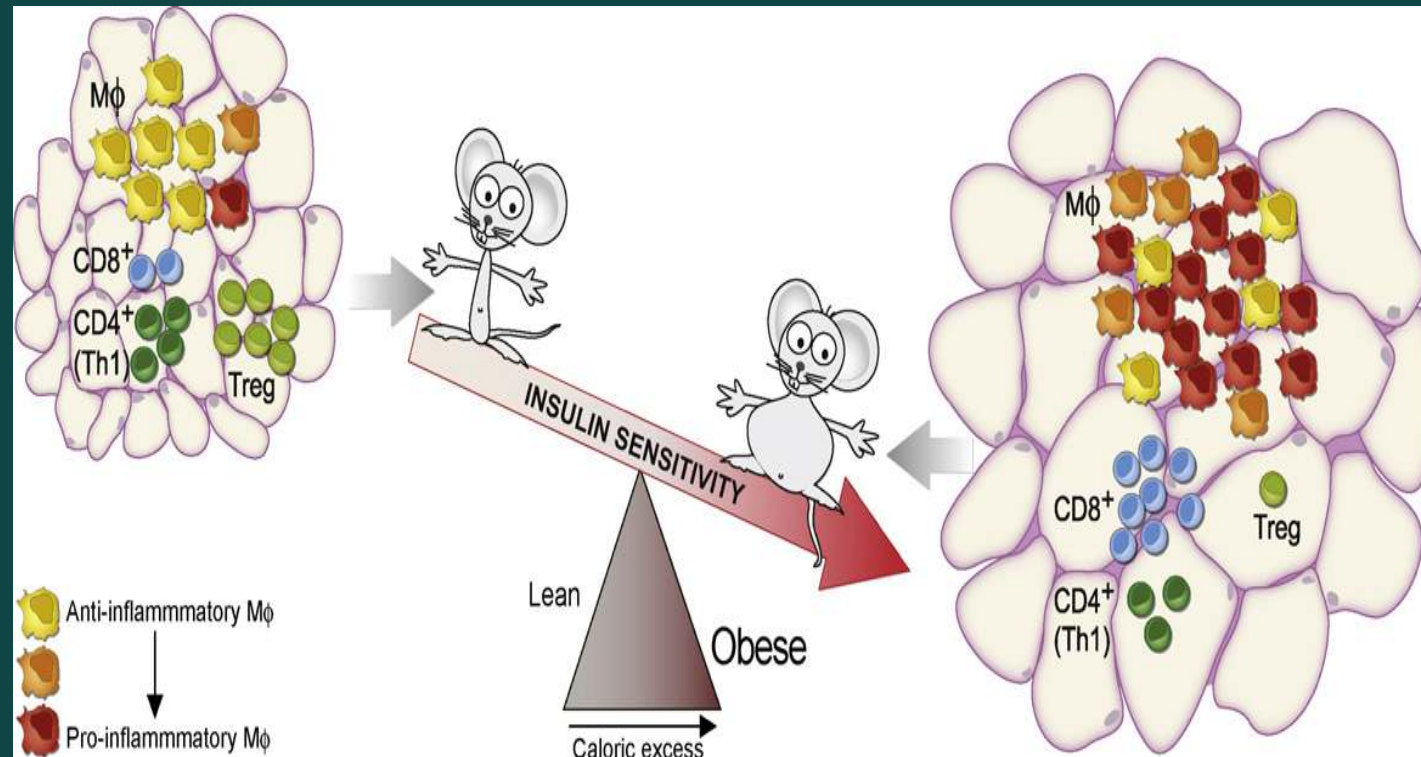
Obesity results in systemics, chronic low-grade inflammation and insulin resistance

Seminars in Immunology 23 (2011) 431– 437

IMMUNOMETABOLISM(2)



Multi-level Interaction between the Metabolic & Immune System



Cellular and metabolic alternations in adipose tissue during obesity

Seminars in Immunology 23 (2011) 431– 437

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Meta-Inflammation Research Institute

Thank you



Meta-Inflammation Research Institute