The Protective Role of NOD2 in Arteriosclerotic Vascular Diseases

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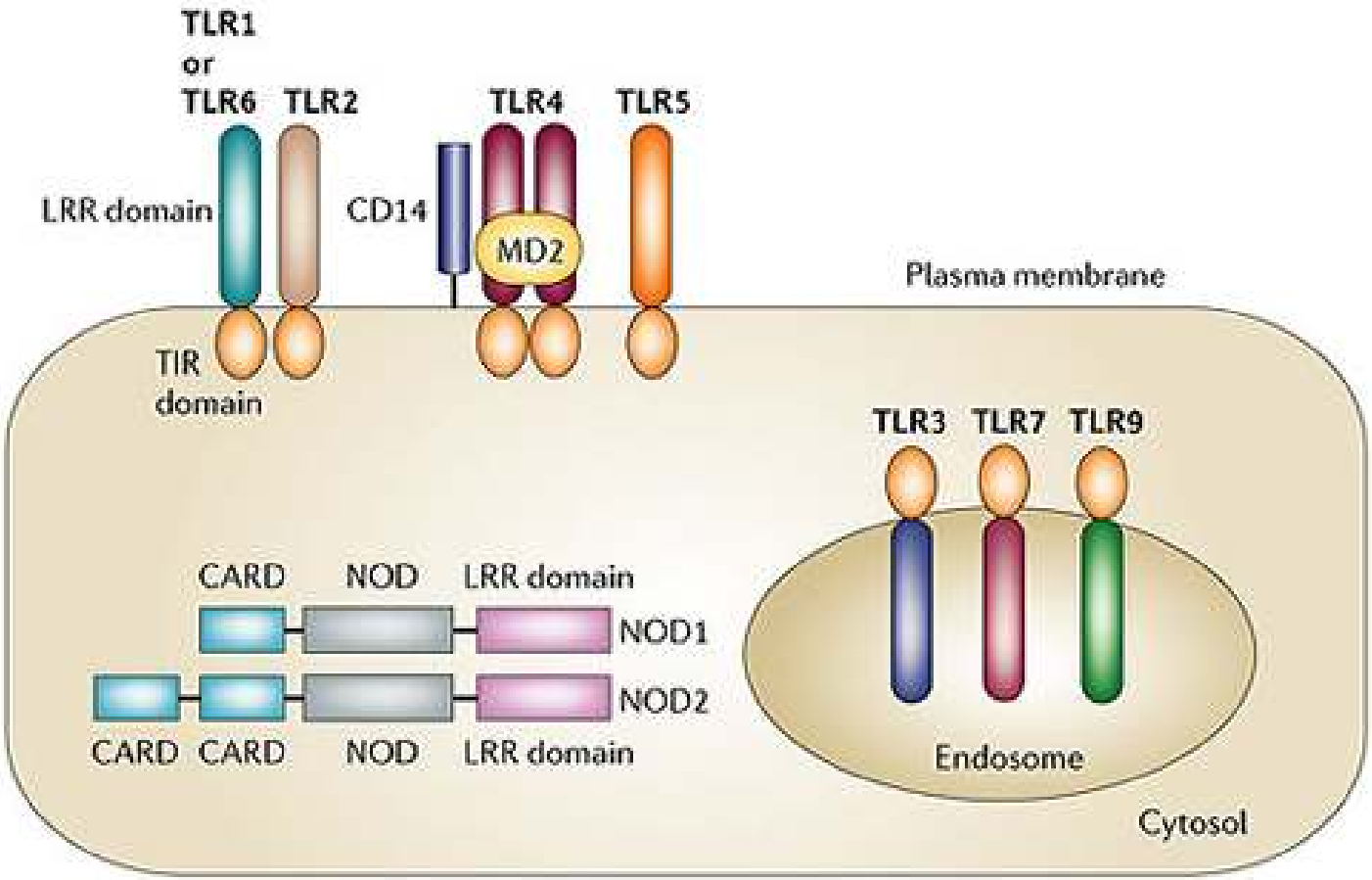
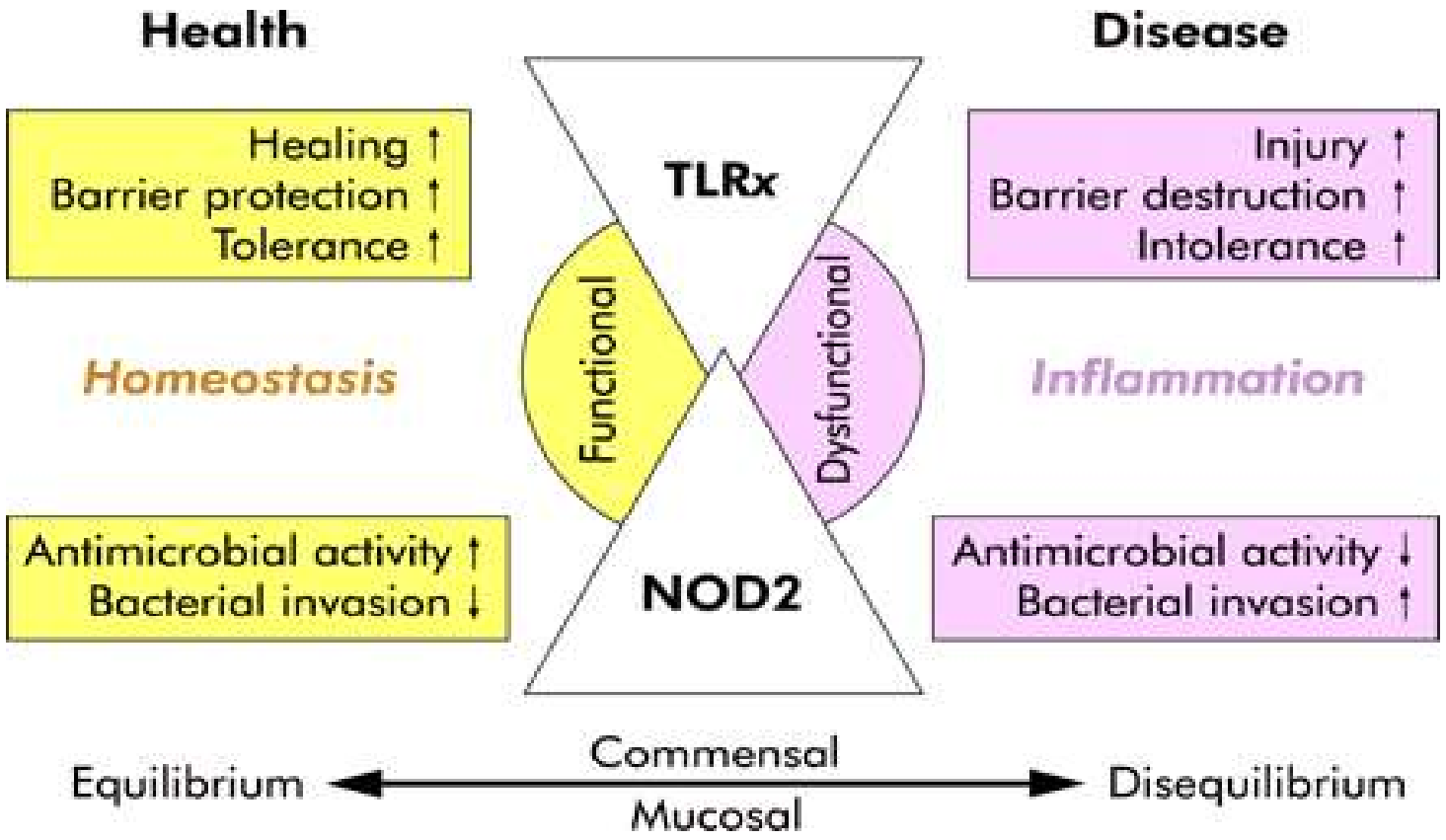
Structure and Cellular Location of TLRs, NOD1, and NOD2



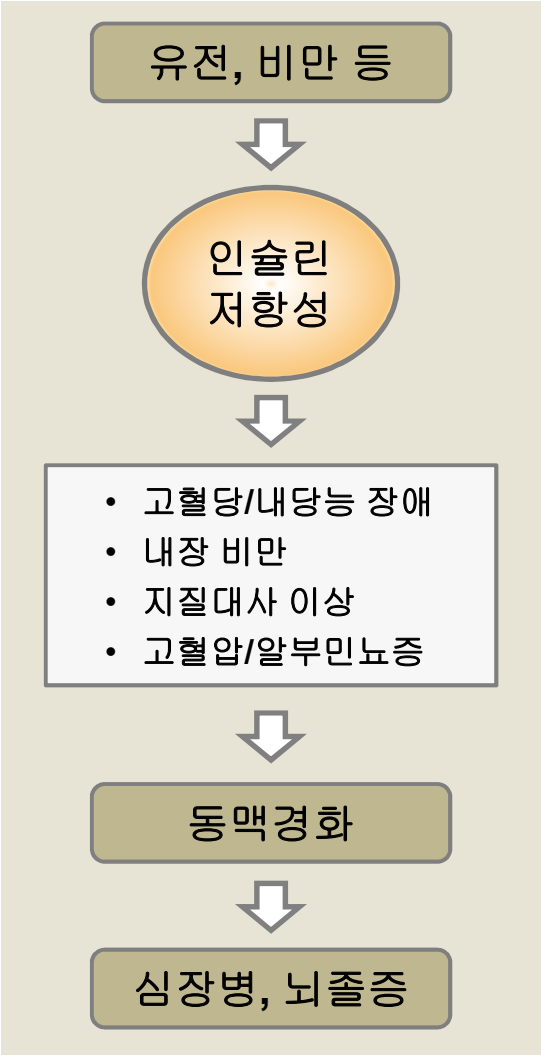
W Strober, *Nature Reviews Immunology* 2006;6:9-20

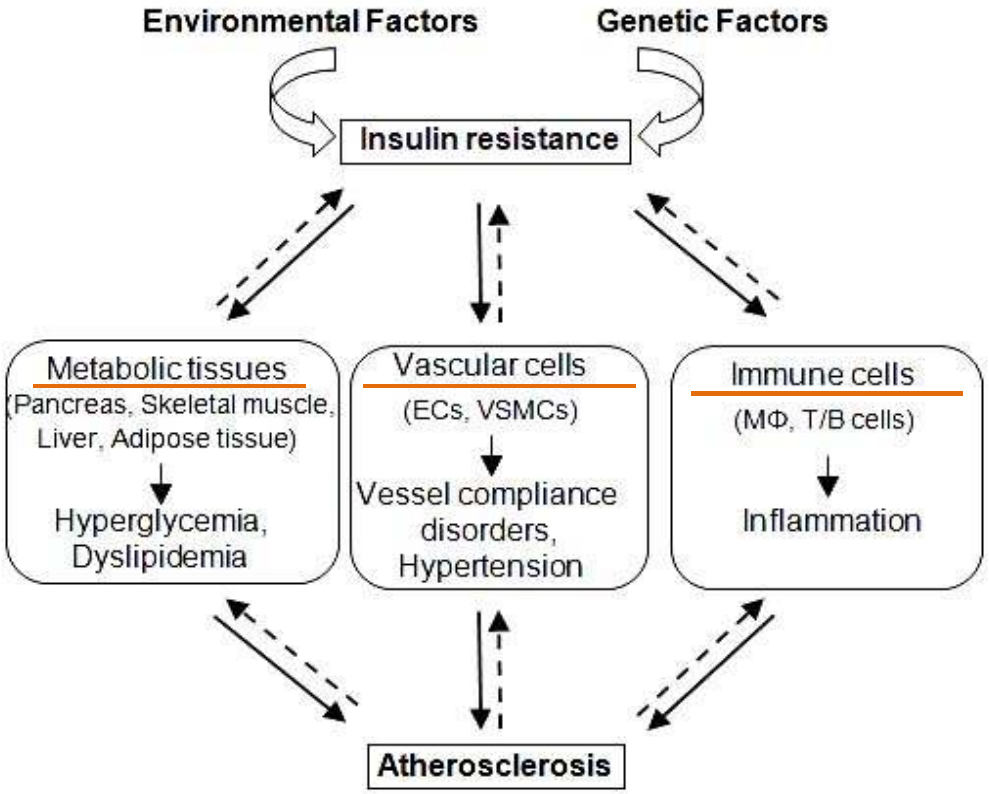
TLRx/NOD2 Physiology and Pathophysiology



E Cario, *Gut* 2005;54:1182-1193

Mechanism of Metabolic Syndrome

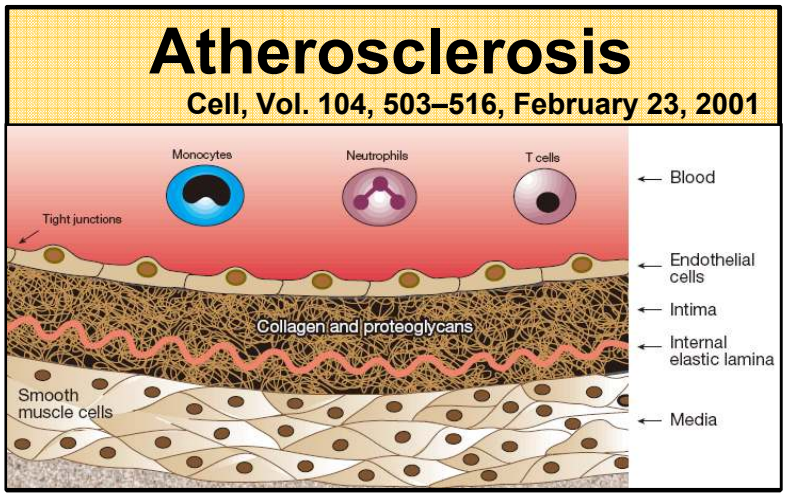




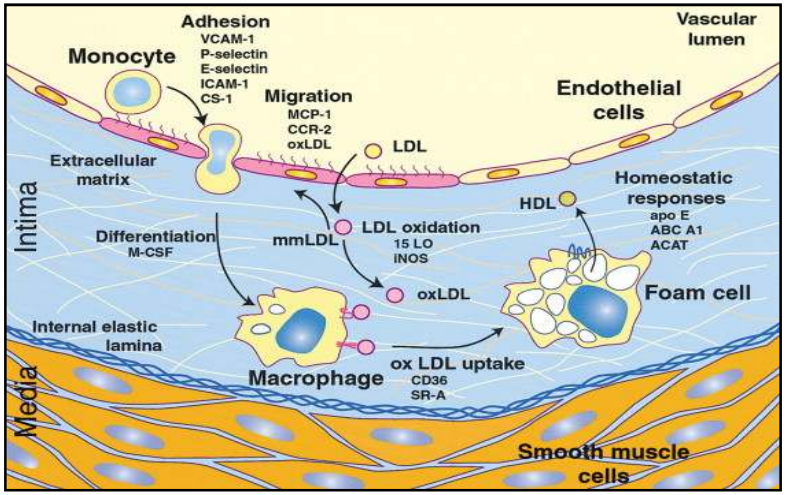
Frontiers in Bioscience S4, 916-931, January 1, 2012

Progression of Atherosclerosis

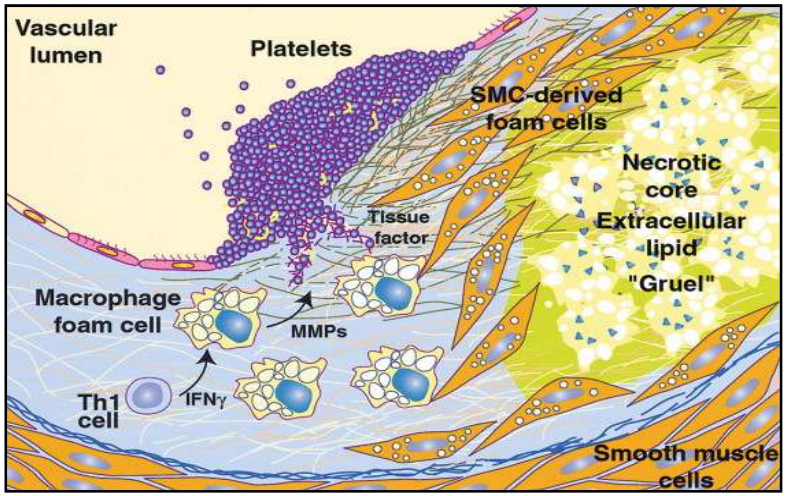
❖ Normal Artery



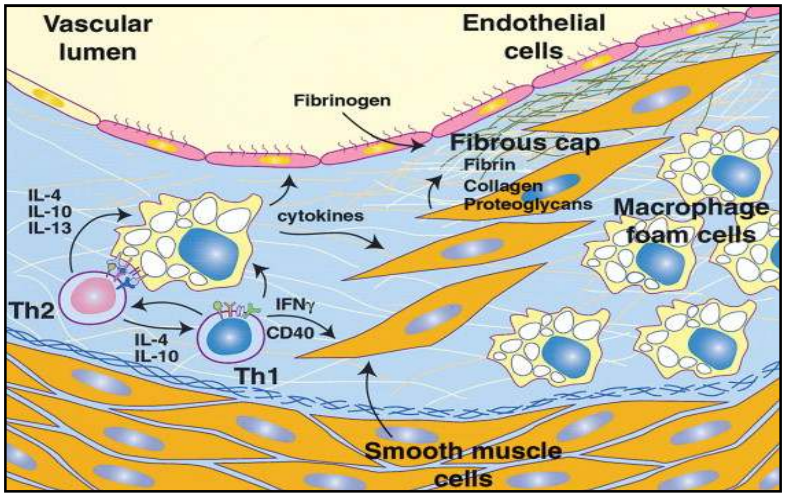
❖ Initiating Events



❖ Plaque Rupture & Thrombosis

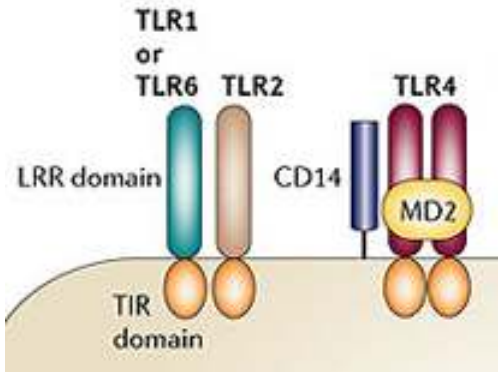


❖ Lesion Progression



Role of TLRs in Extent of Aortic Atherosclerosis and Vascular Injury

Stimulation of TLR4 by Adventitial Application of LPS-augmented Neointima Formation



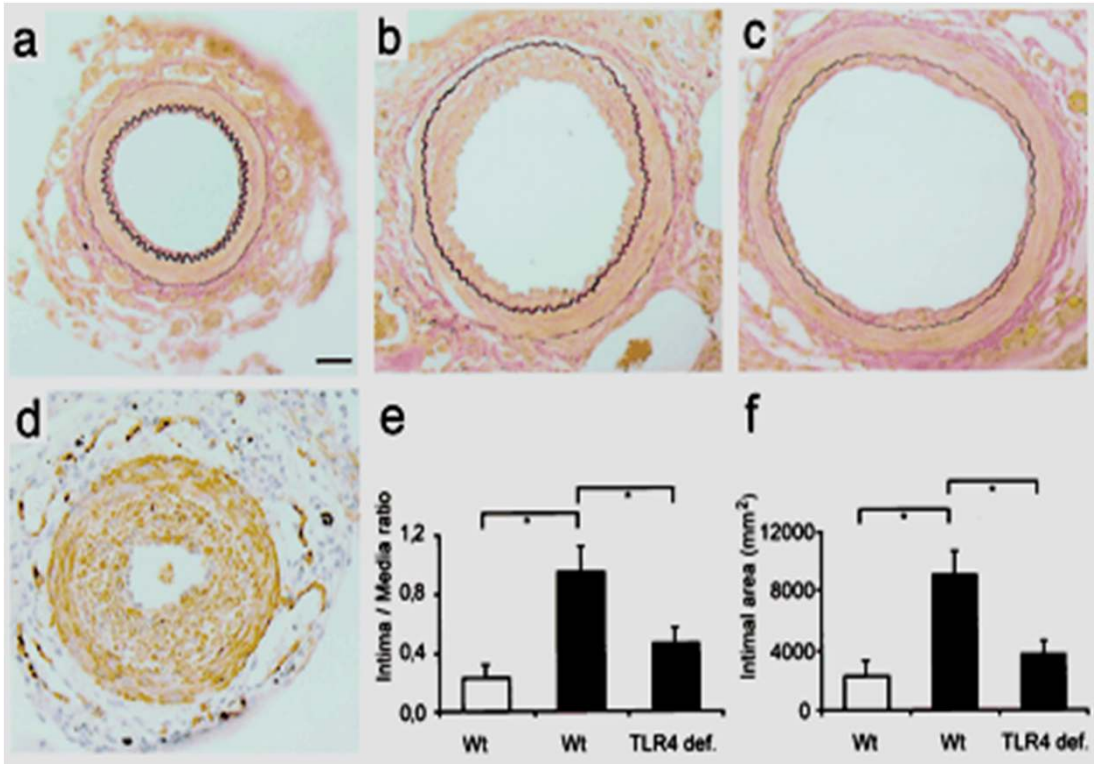
LPS/HFD

↓

TLR4$^{+/+}$ & TLR4$^{-/-}$

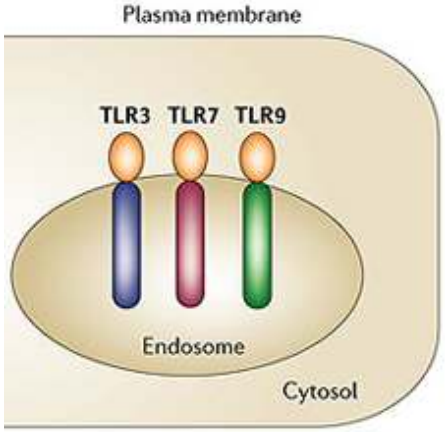
↓

Neointima Formation



Vink A, *Circulation*. 2002. 106:1985-1990

TLR3 Deficiency Accelerates early Atherosclerotic Lesion Development in the Aortic Root



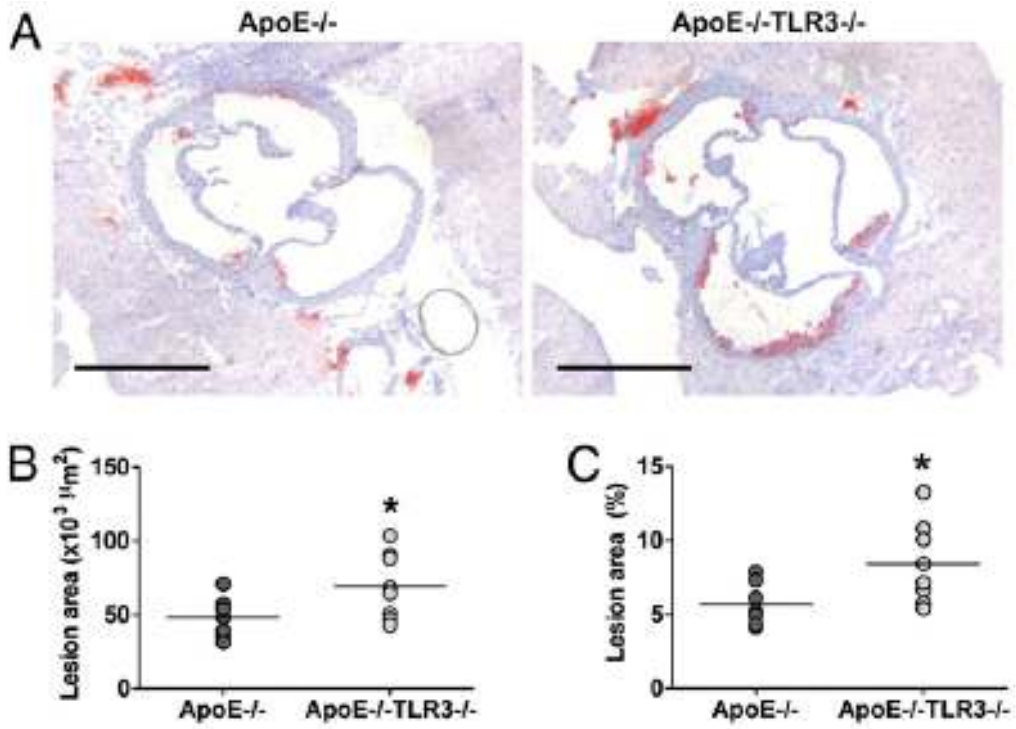
Normal Diet

↓

TLR3$^{+/+}$ & TLR3$^{-/-}$

↓

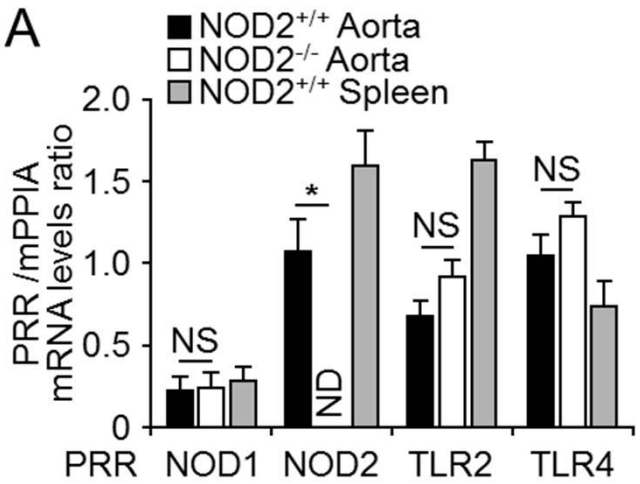
Atherosclerotic Lesion

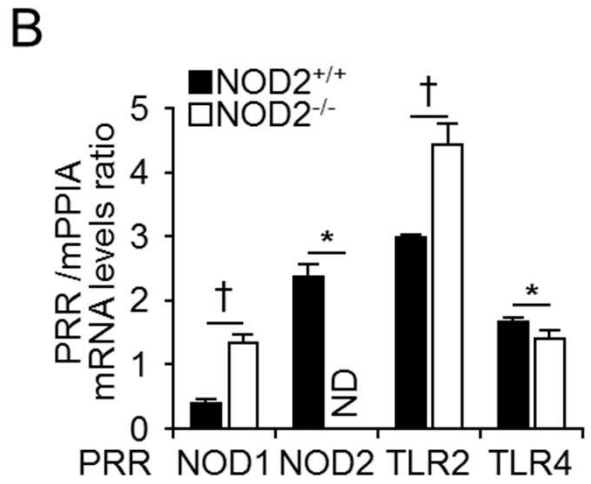


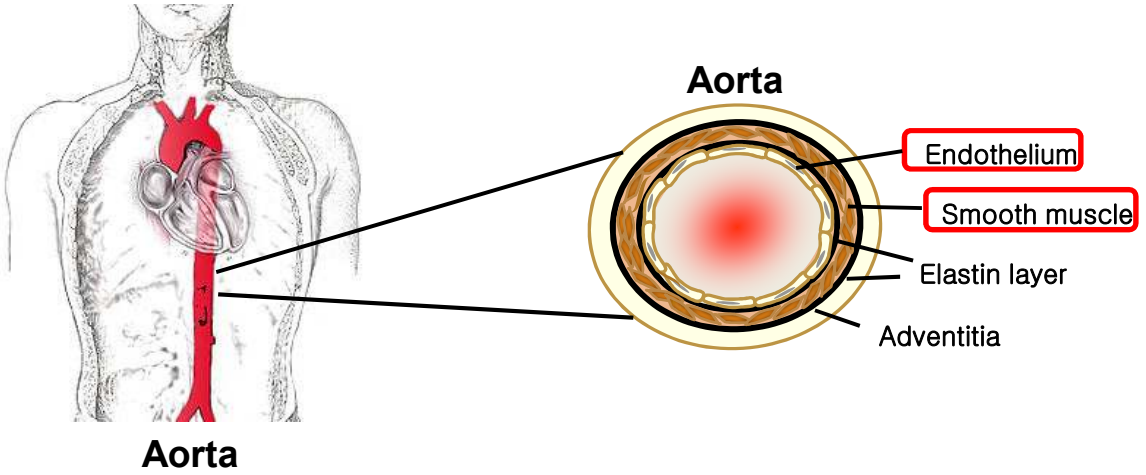
Cole JE, *Proc Natl Acad Sci U S A*. 2011;108(6):2372-7

What is the Role of NOD2 in Arteriosclerotic Vascular Diseases?

NOD2 mRNA Is Expressed in VSMCs

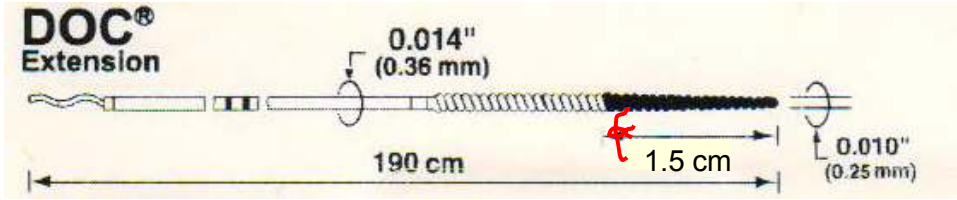


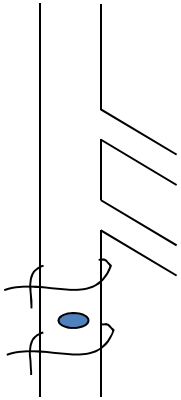


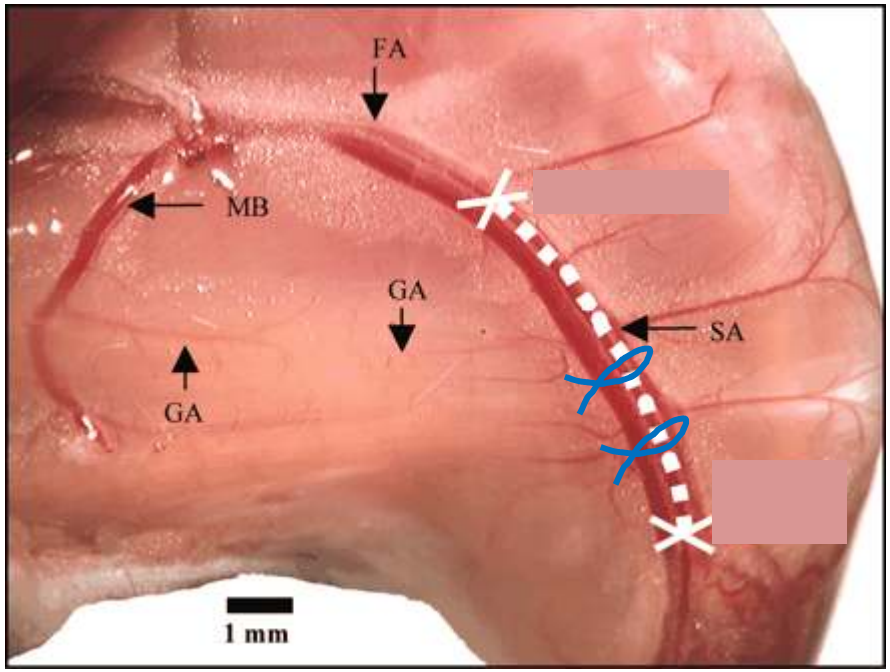


Arterioscler Thromb Vasc Biol. 2011 Nov;31(11):2441-7

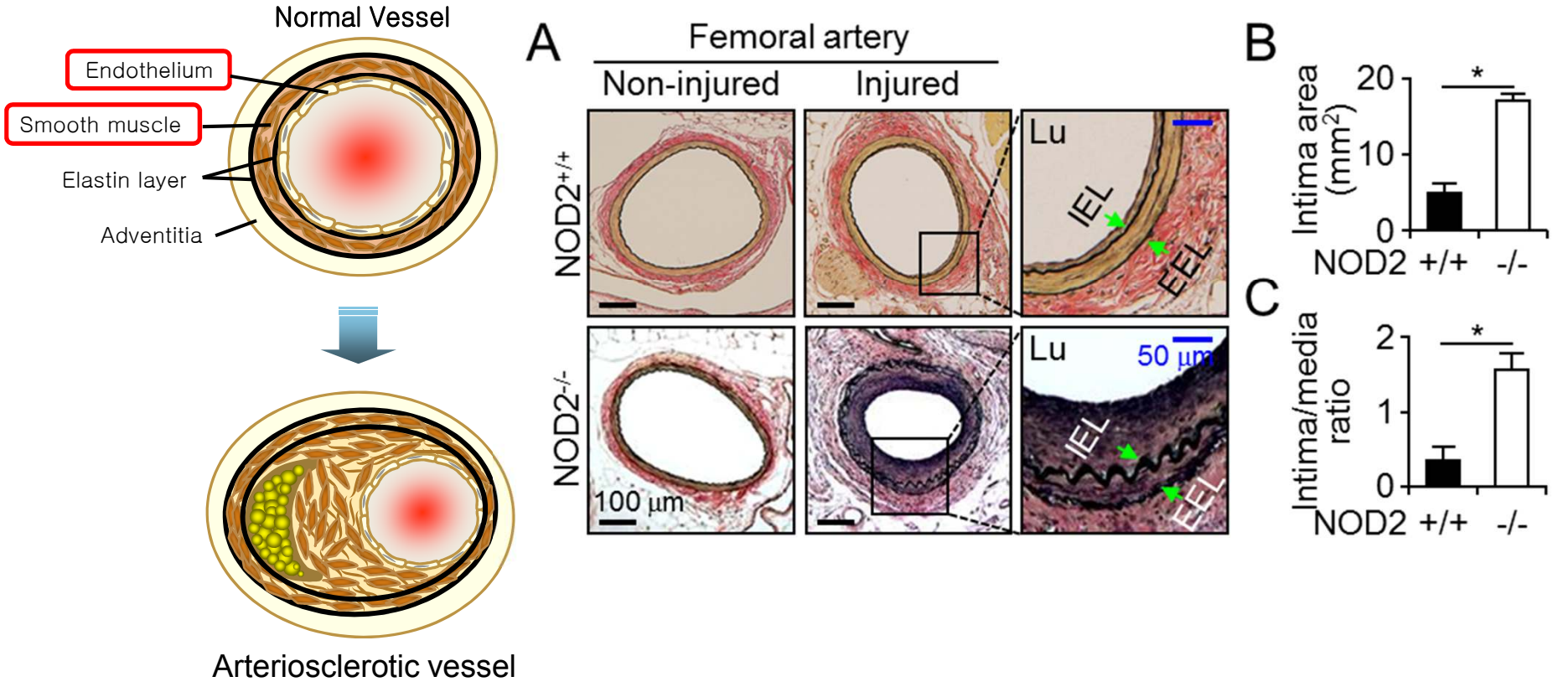
Femoral Artery Injury Model







NOD2 Deficiency Accelerates Neointima Formation after Vascular Injury in Mice



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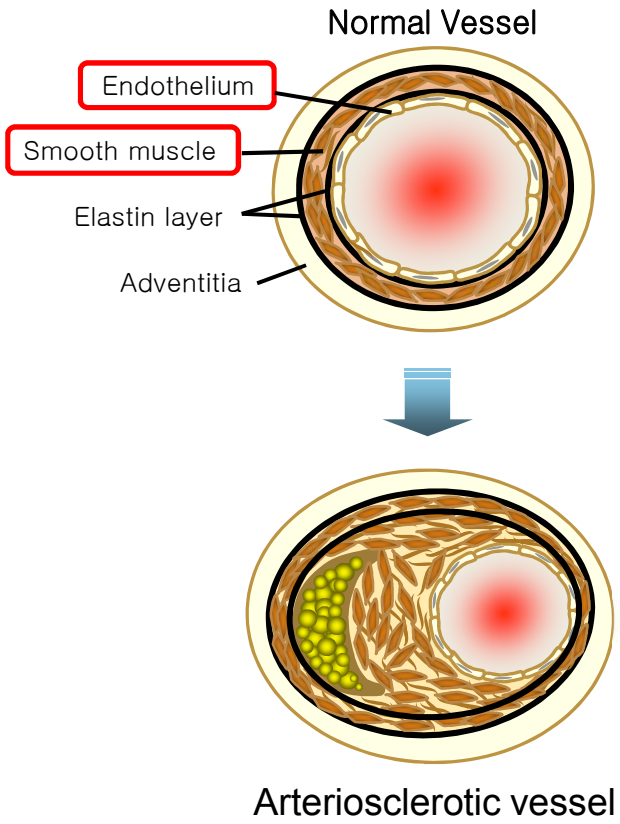
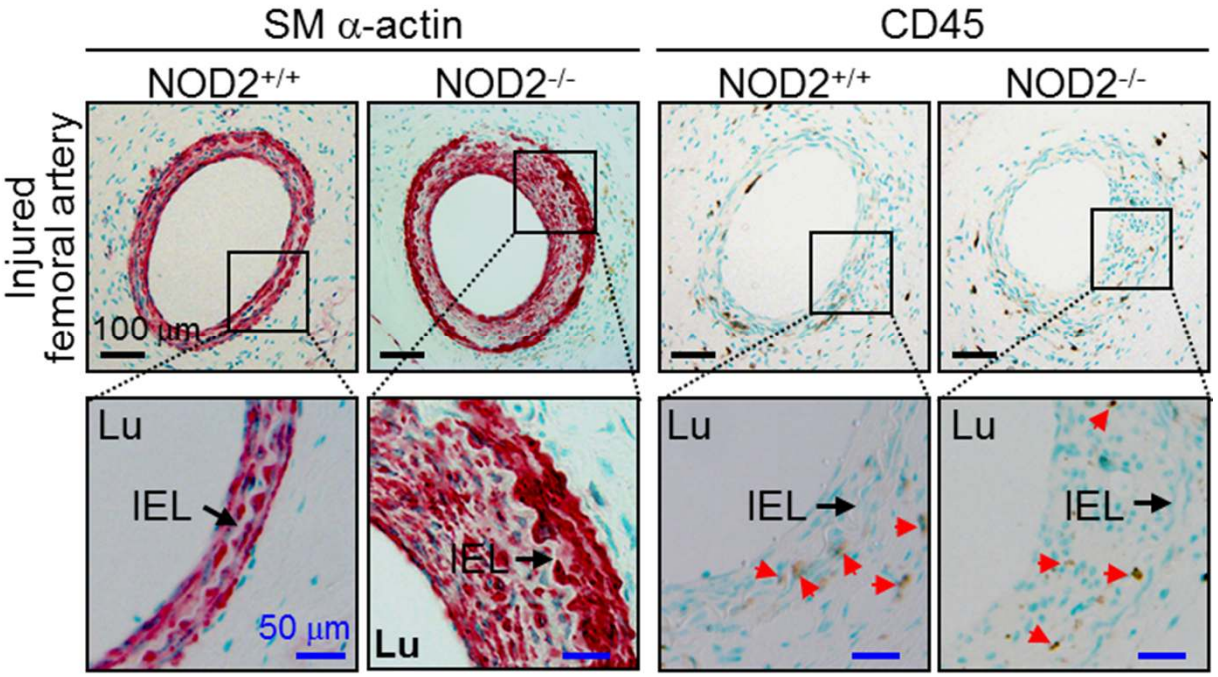
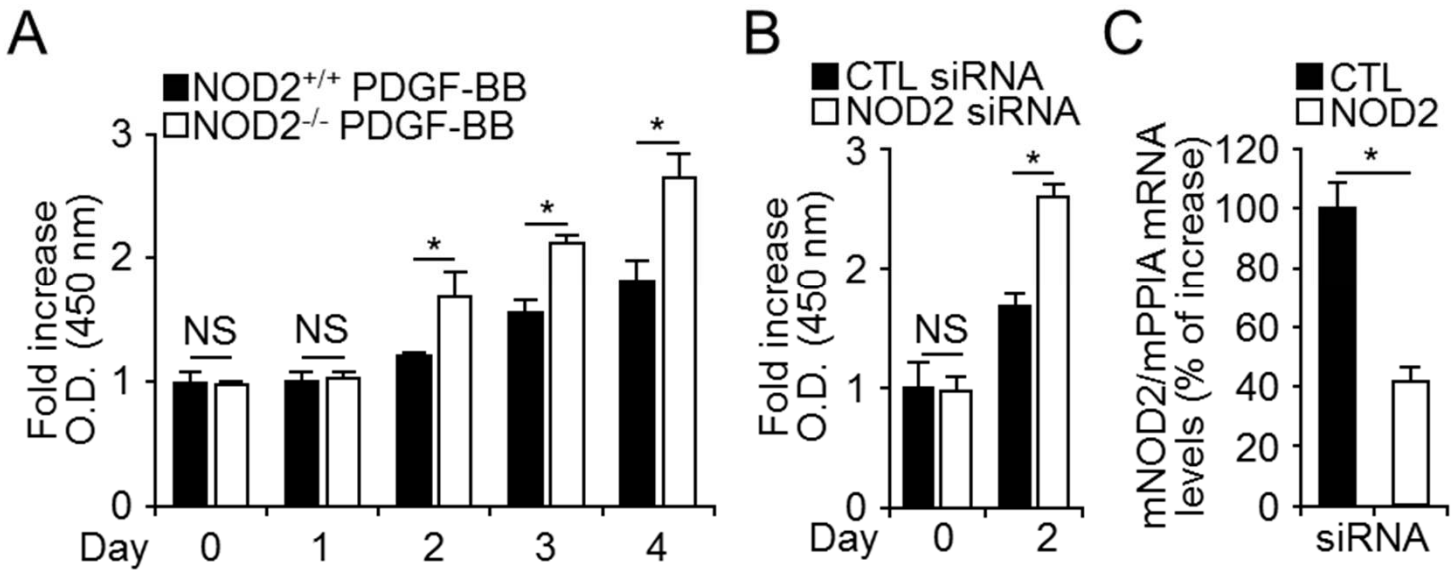




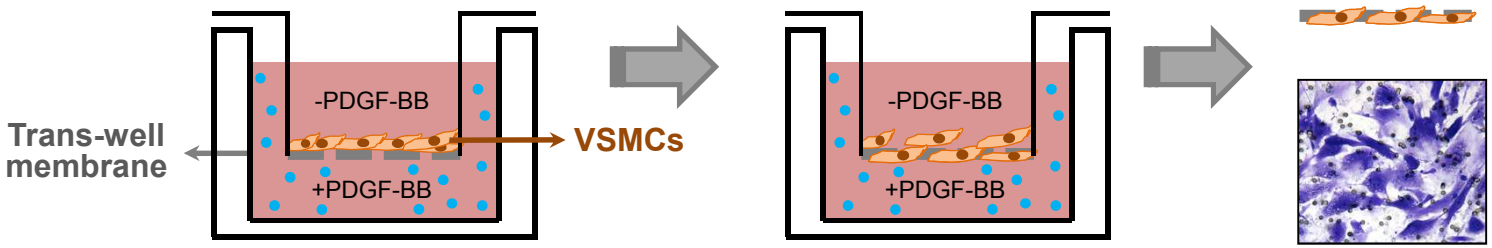
Arterioscler Thromb Vasc Biol. 2011 Nov;31(11):2441-7

NOD2 Deficiency Promotes Proliferation of Mouse VSMCs

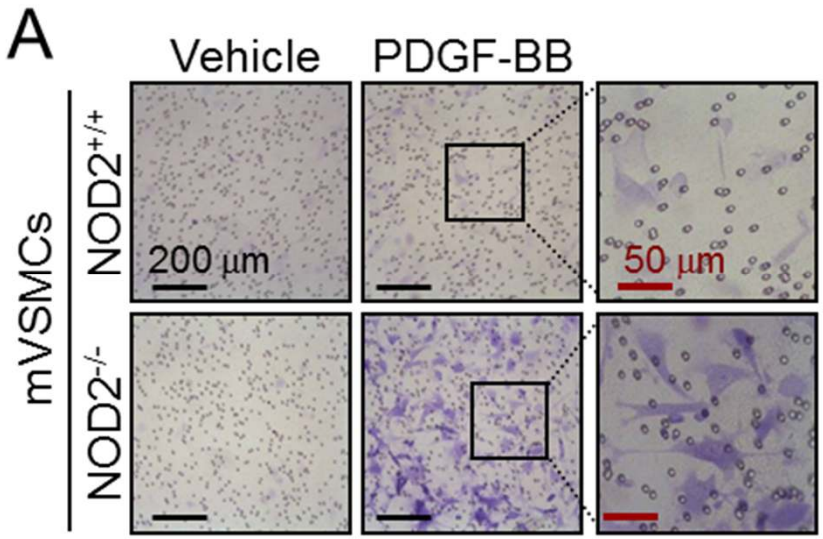


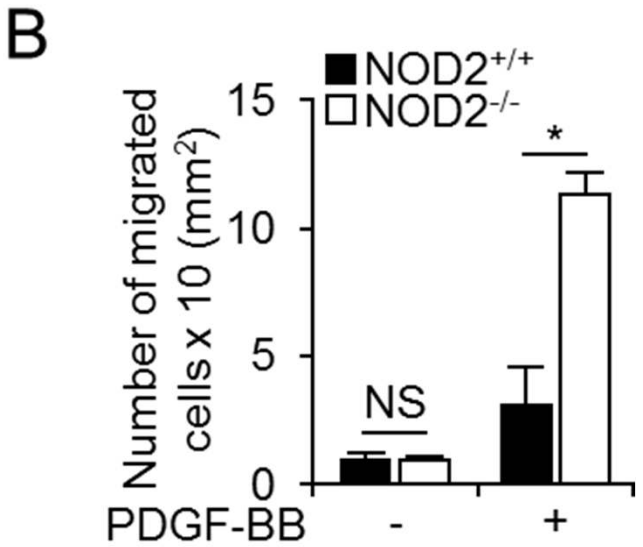
Arterioscler Thromb Vasc Biol. 2011 Nov;31(11):2441-7

NOD2 Deficiency Increases Migration of VSMCs in Response to PDGF-BB



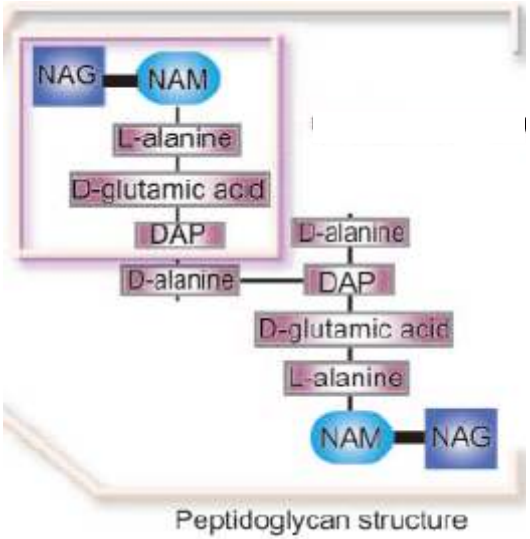
Trans-well Migration Assay



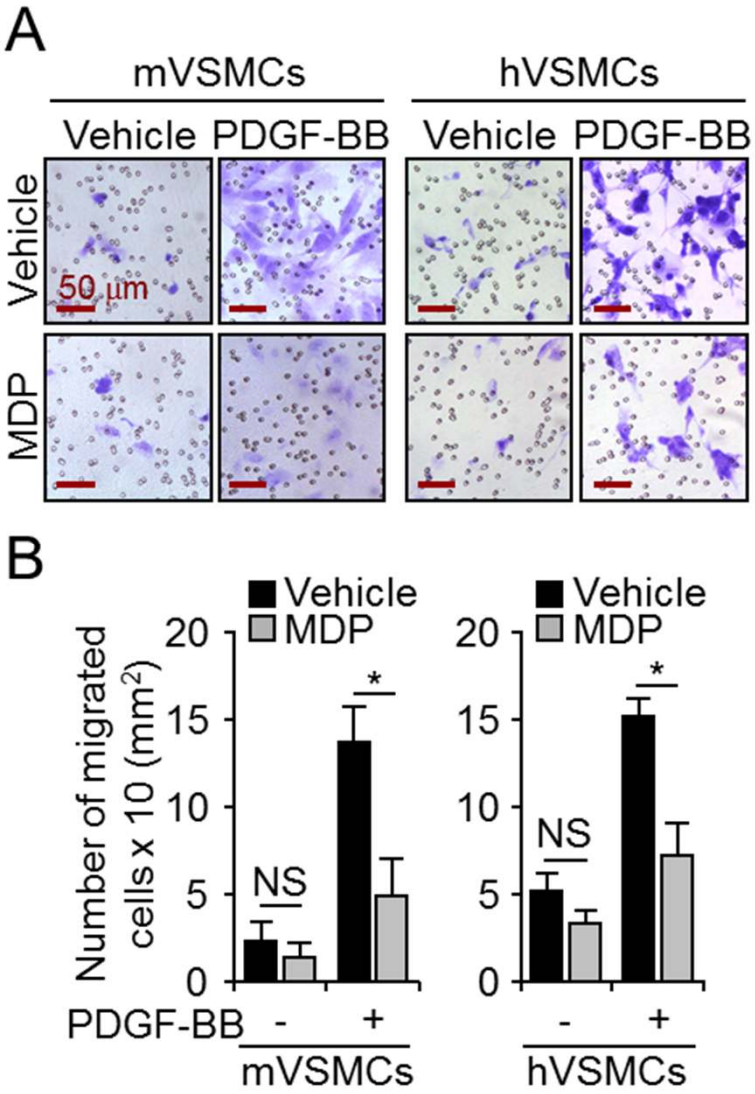


Arterioscler Thromb Vasc Biol. 2011 Nov;31(11):2441-7

Activation of NOD2 Inhibits Migration of VSMCs in Response to PDGF-BB



Peptidoglycan structure



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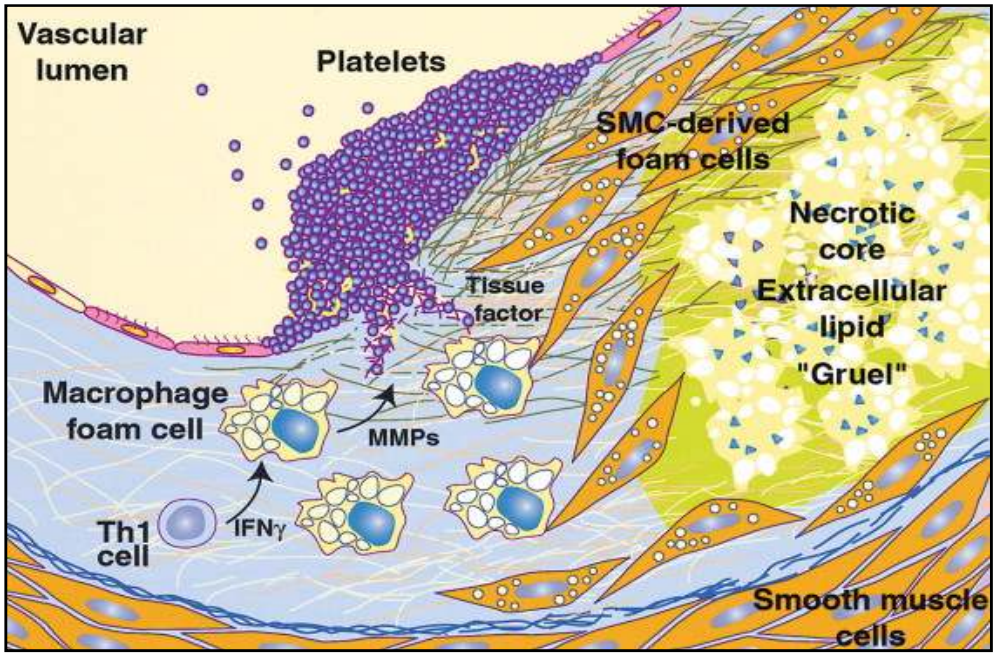
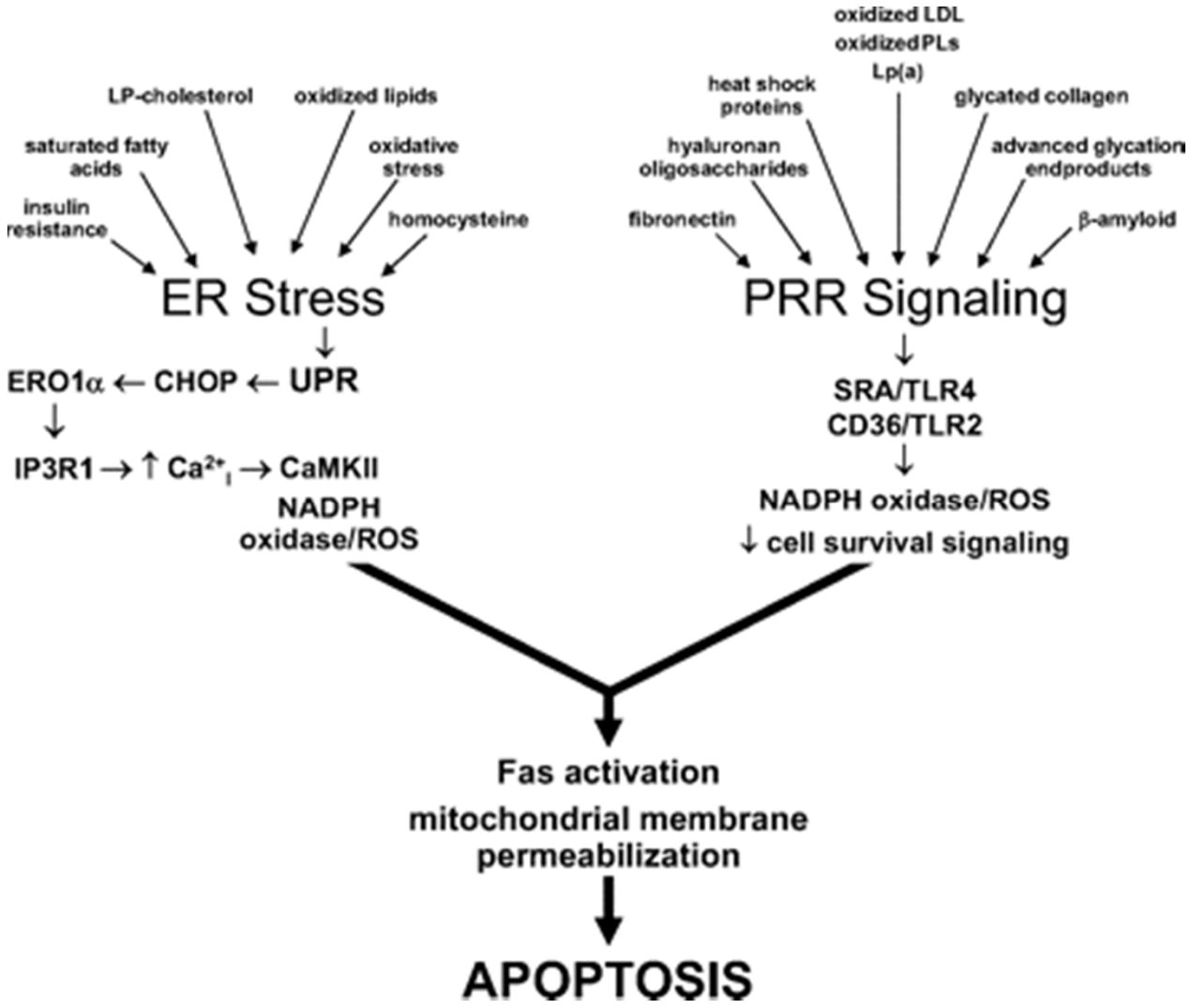
The Most Important Phenomena in Plaque Rupture and Thrombosis During Atherogenesis

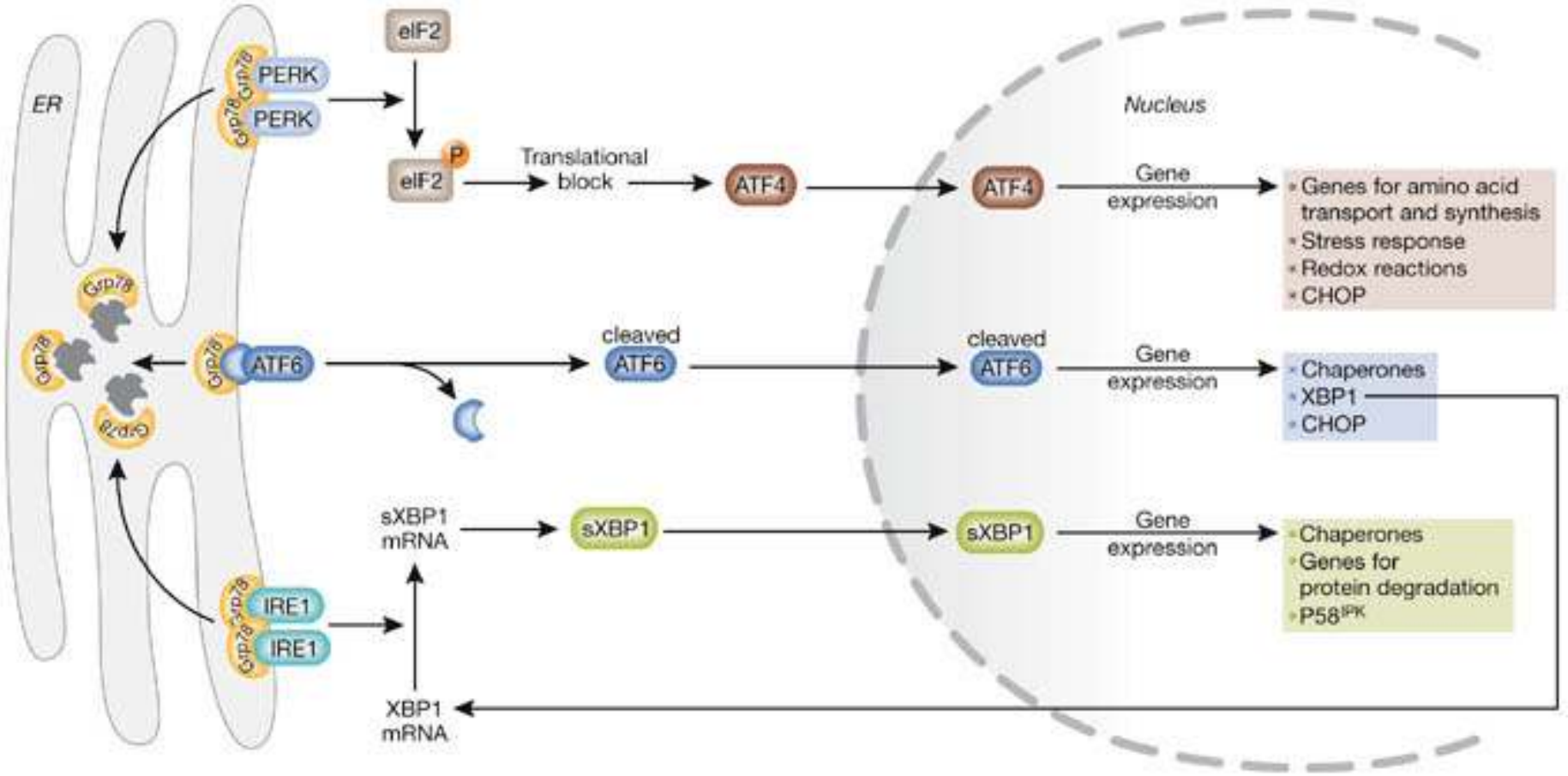


- Cell death
  - Macrophagy
  - VSMC

Model of ER Stress–Induced Apoptosis in Advanced Lesional Macrophages

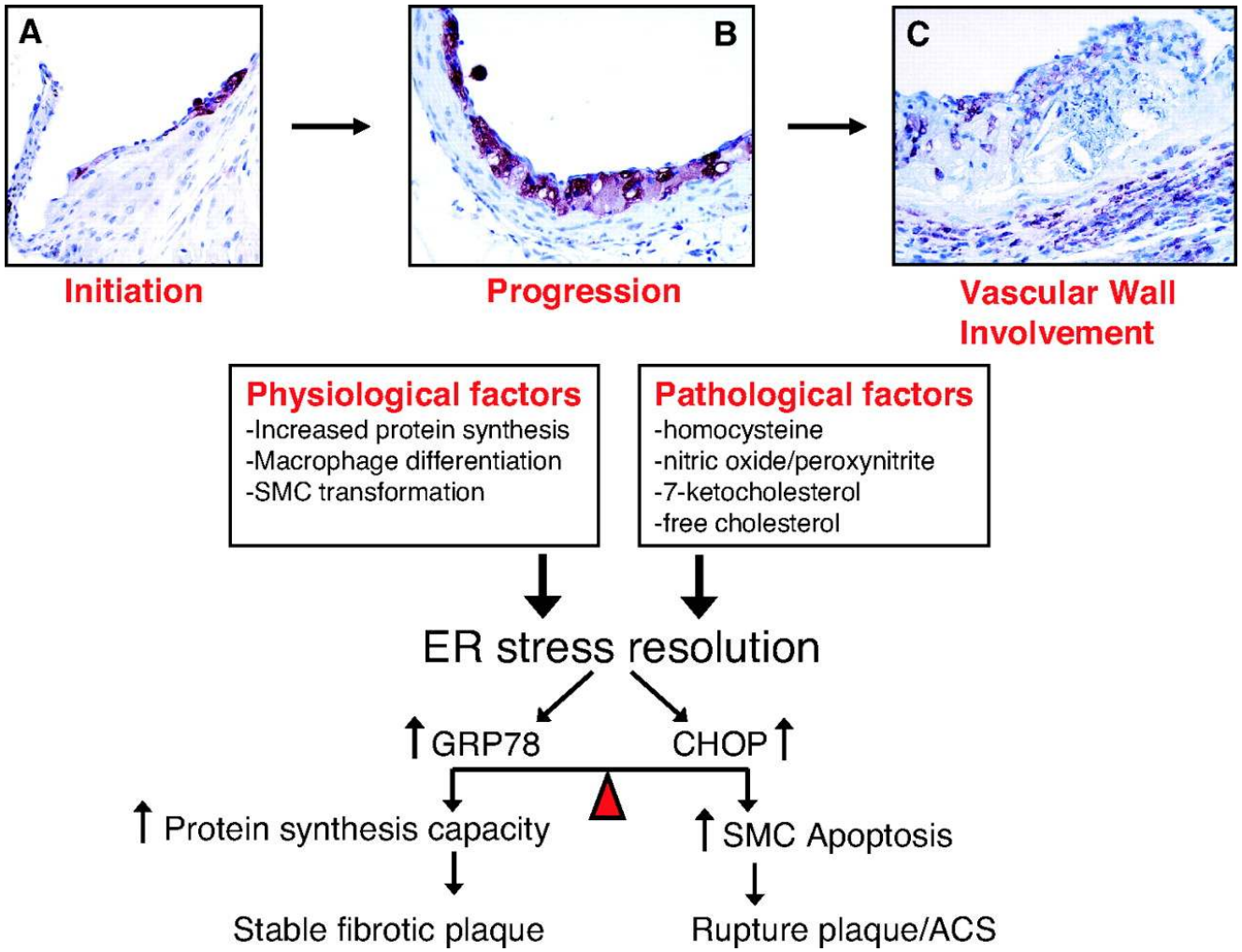


The Mechanisms of ER Stress Response



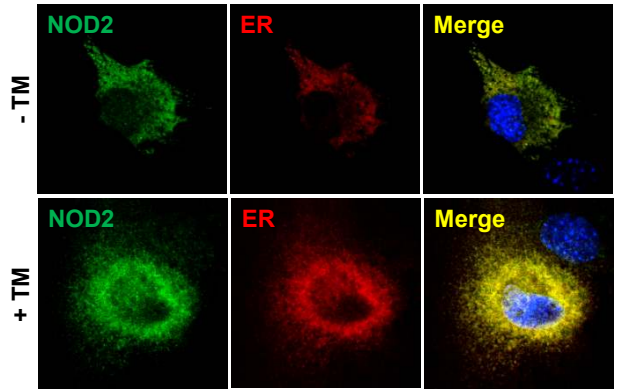
EMBO reports (2006) 7, 880 – 885 Eva Szegezdi

Model of ER Stress–Induced Apoptosis in Advanced Lesional VSMC

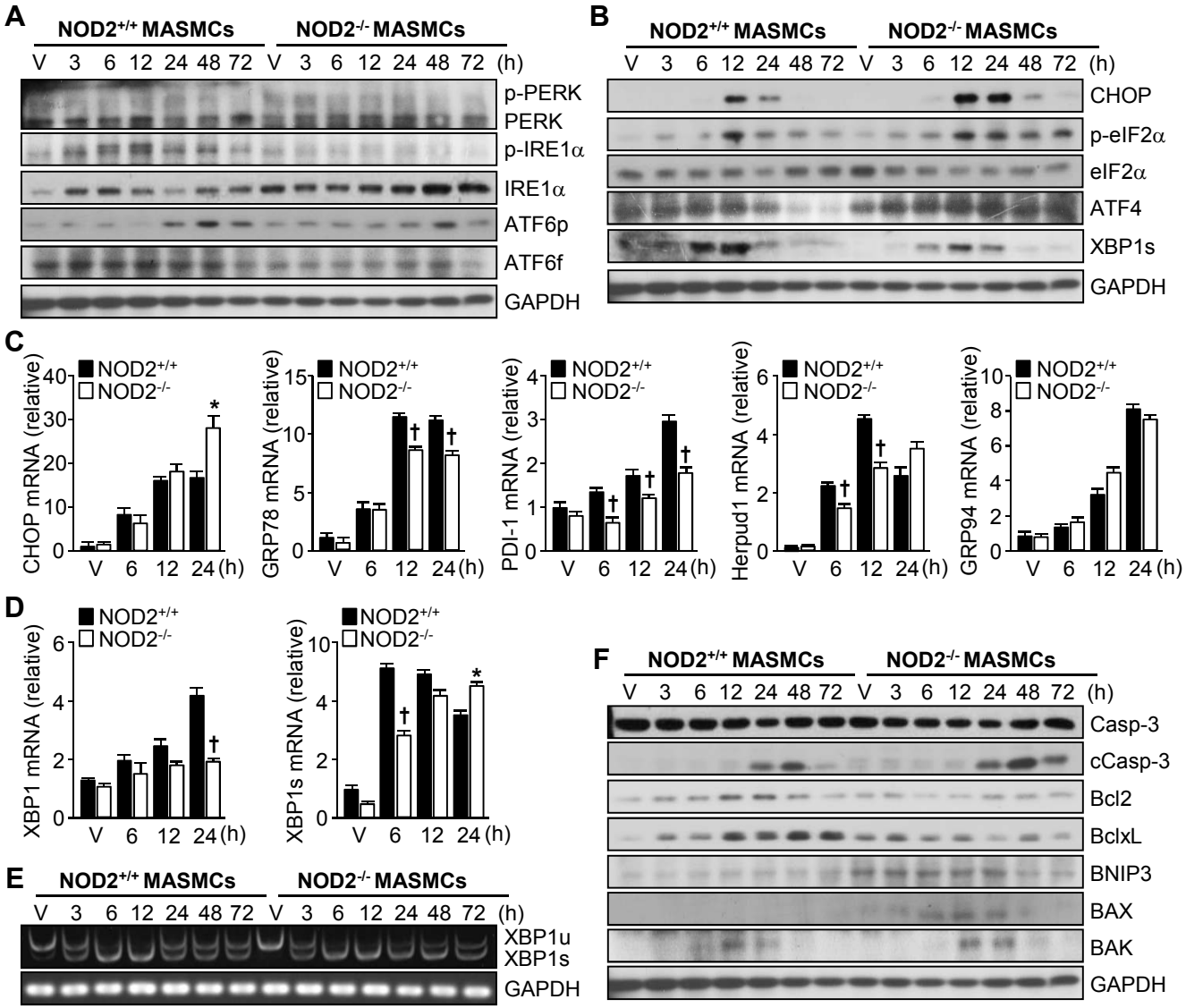


Circulation 2007; 116: 1214-1216

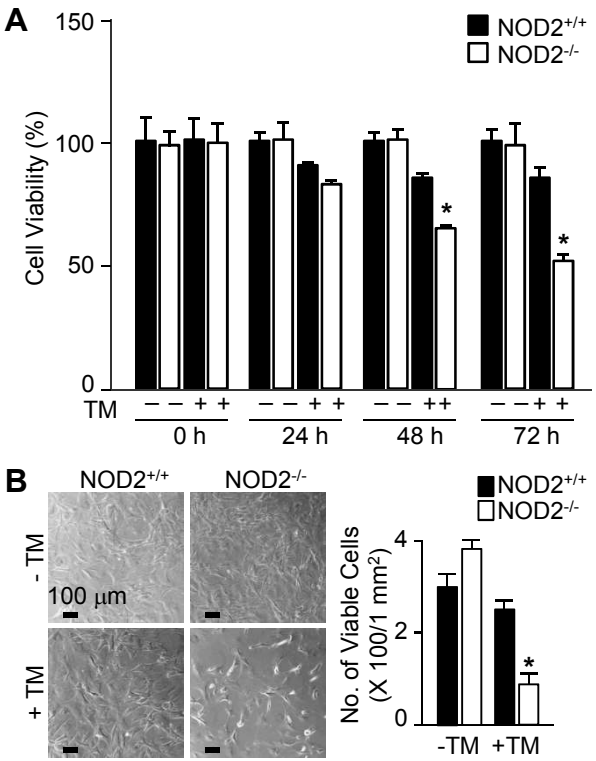
NOD2 locates in ER during ER stress



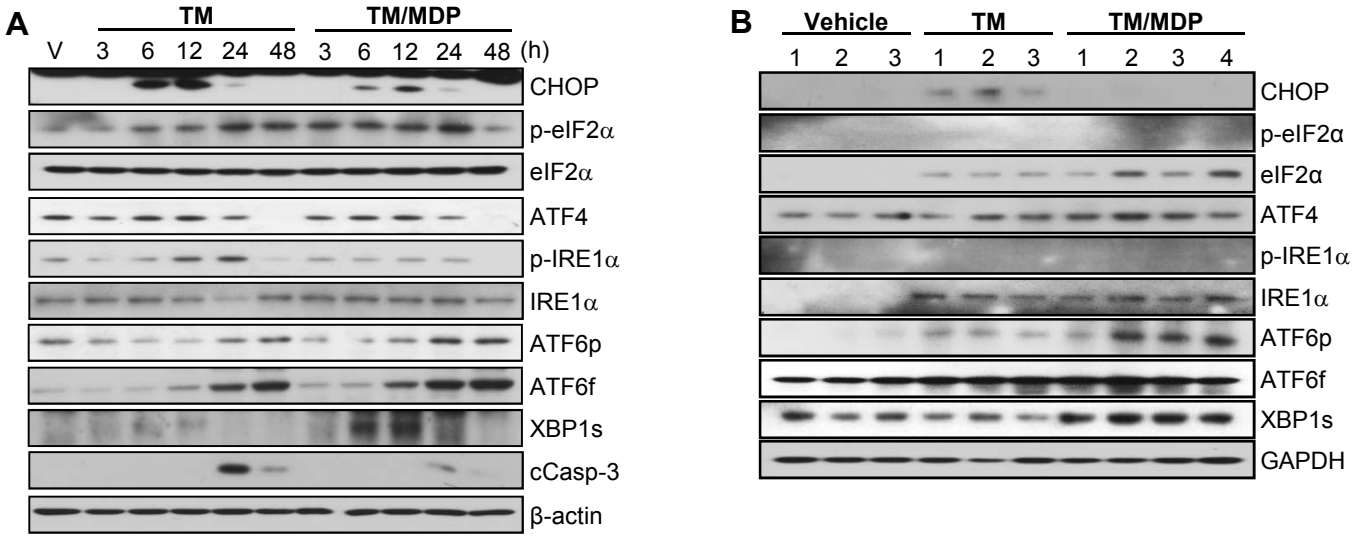
ER Stress-Induced Apoptosis Enhances in NOS2 Deficient Cells



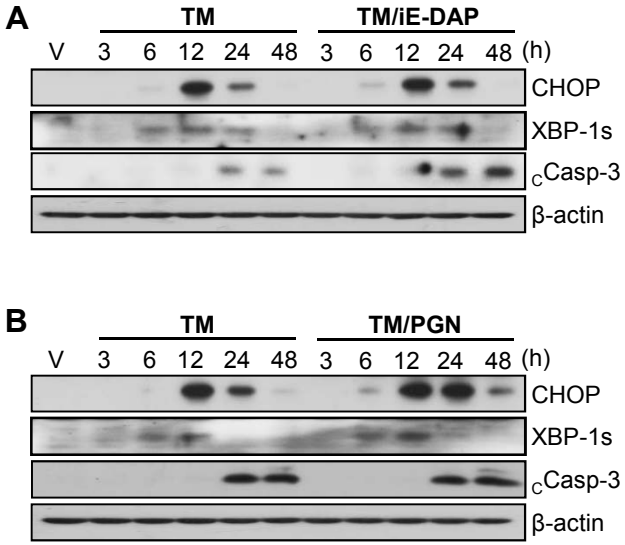
NOD2 Deficiency Accelerates ER Stress Induced Cell Death



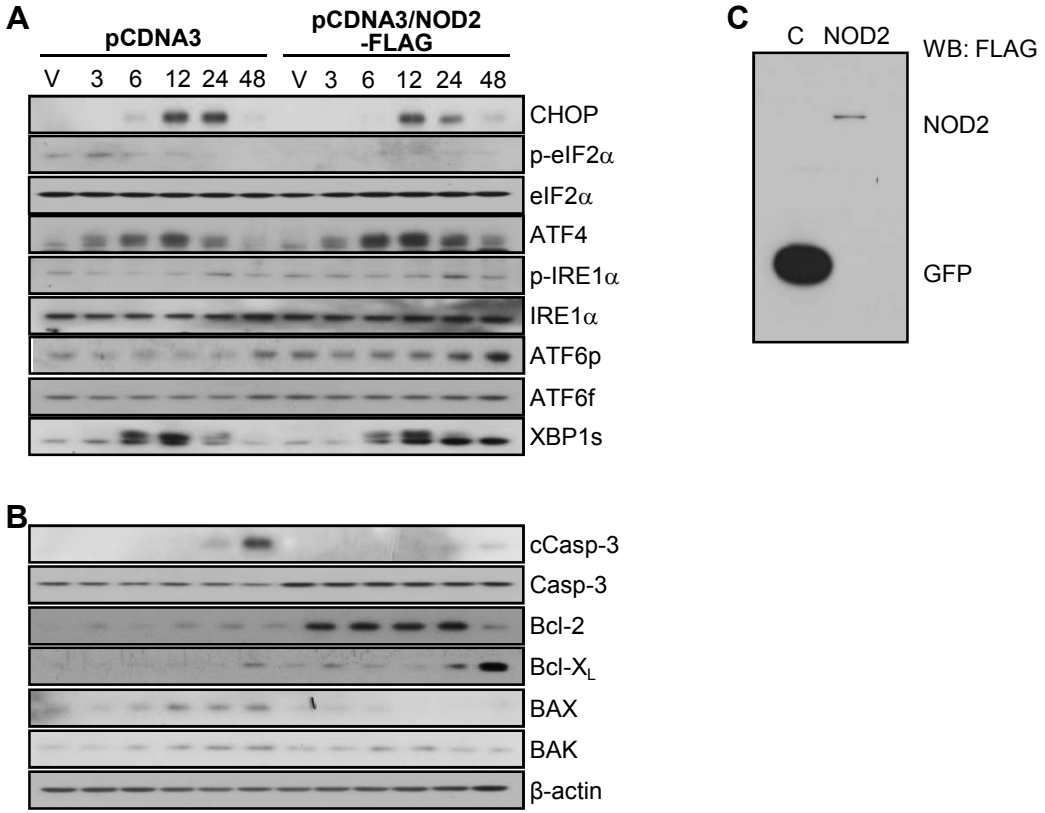
NOD2 Ligand Decreases CHOP Expression



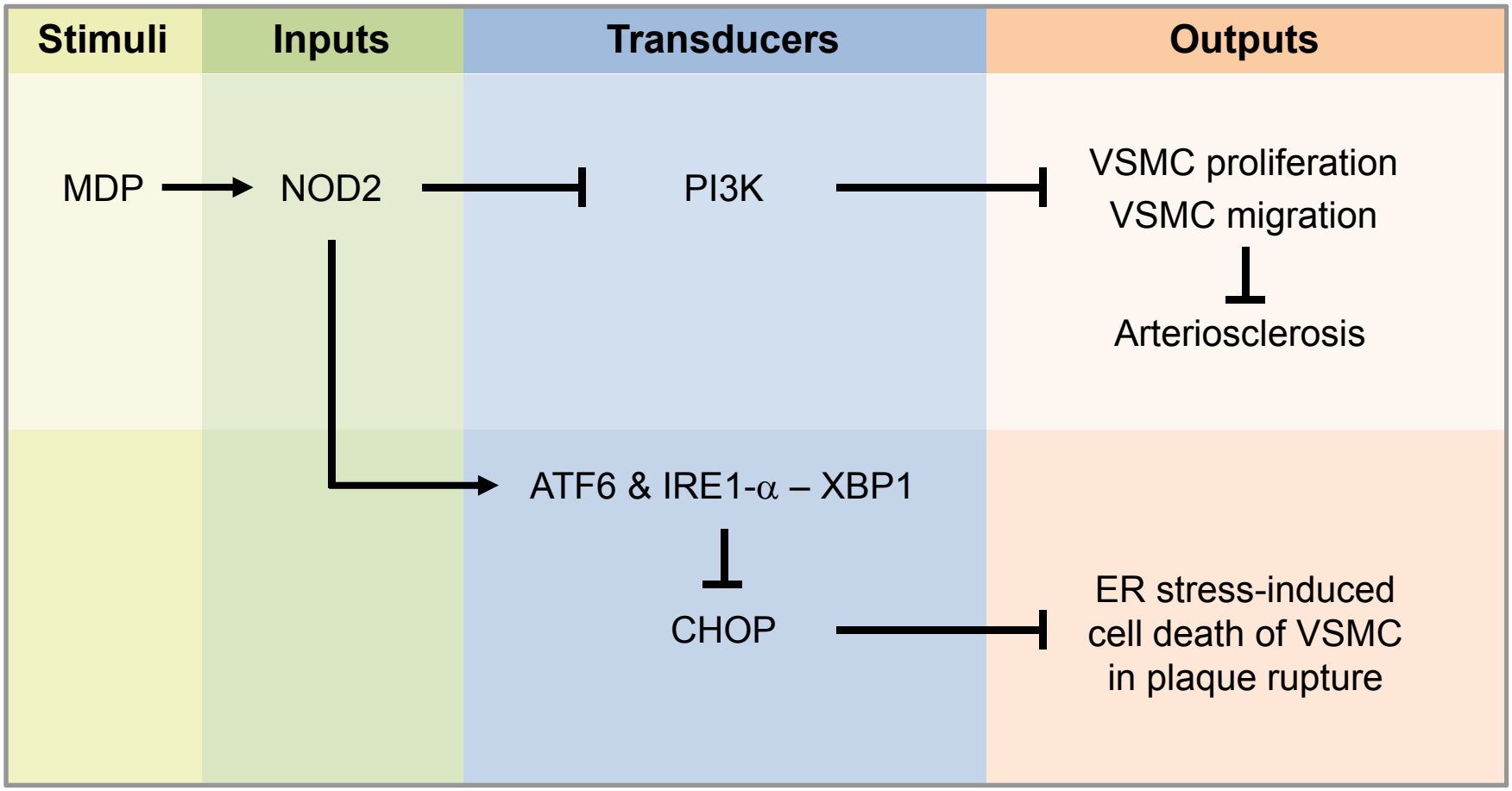
NOD1 and TLR2 Ligands Has No Effects on CHOP Expression



NOD2 Overexpression Attenuates ER Stress-Induced Apoptosis



CONCLUSION


Stimuli
Inputs
Transducers
Outputs
MDP
NOD2
PI3K
VSMC proliferation
VSMC migration
Arteriosclerosis
ATF6 & IRE1-α – XBP1
CHOP
ER stress-induced
cell death of VSMC
in plaque rupture

AKNOWLEGEMENTS

Lab Members

박사과정

Min-Young Kwon

졸업생

Young-Ho Kang

석사과정 & 학부생

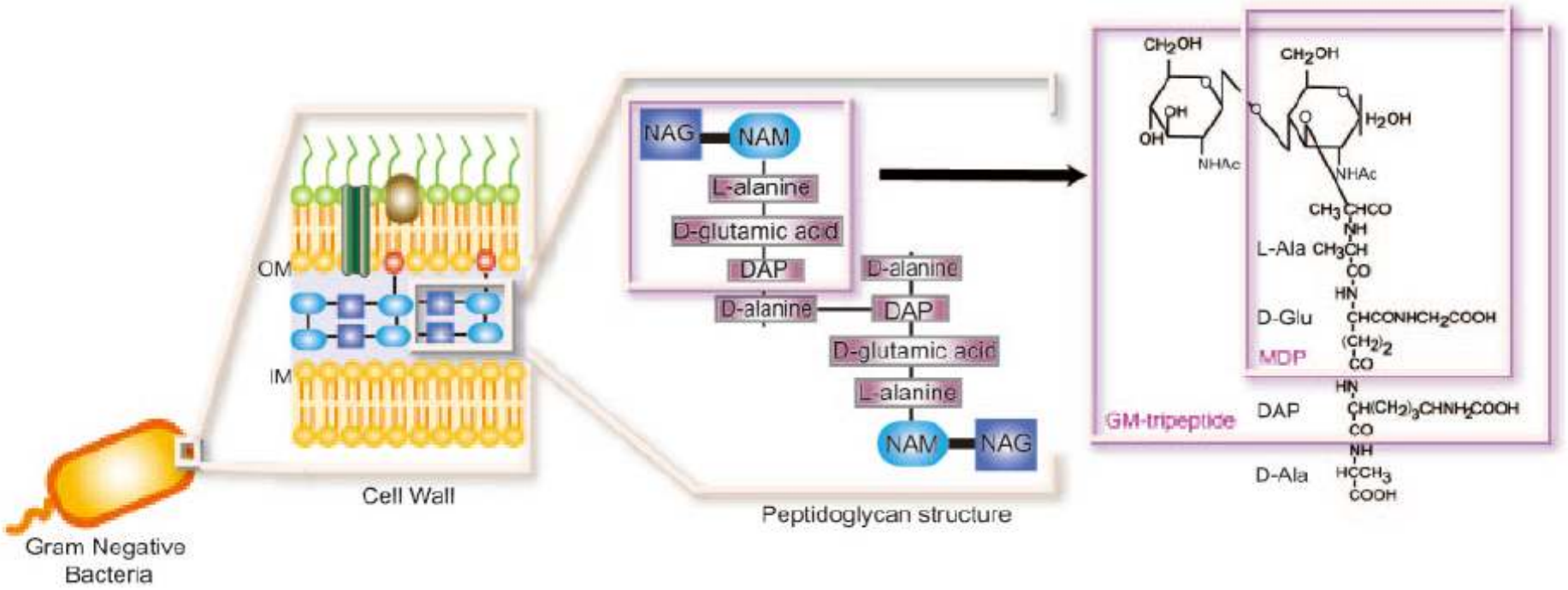
NaRae Hwang

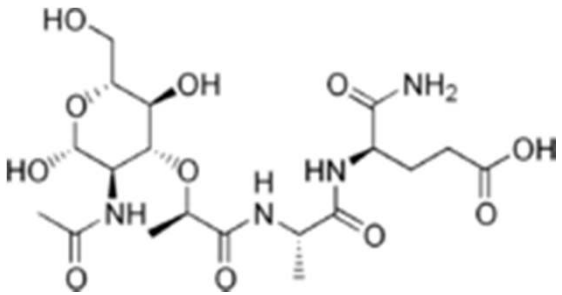
TaeJong Park

Collaborators

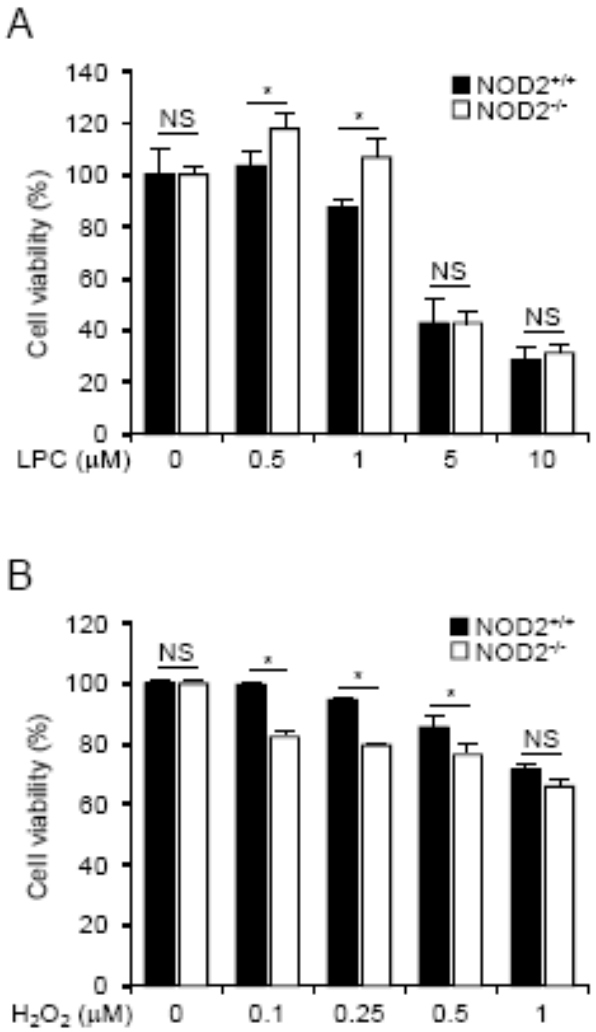
- **KRIBB**
  - Seon-Jin Lee, PhD
- **Harvard Medical School/BWH**
  - Mark A. Perrella, MD

NOD1/NOD2-Activating Peptidoglycan Moieties



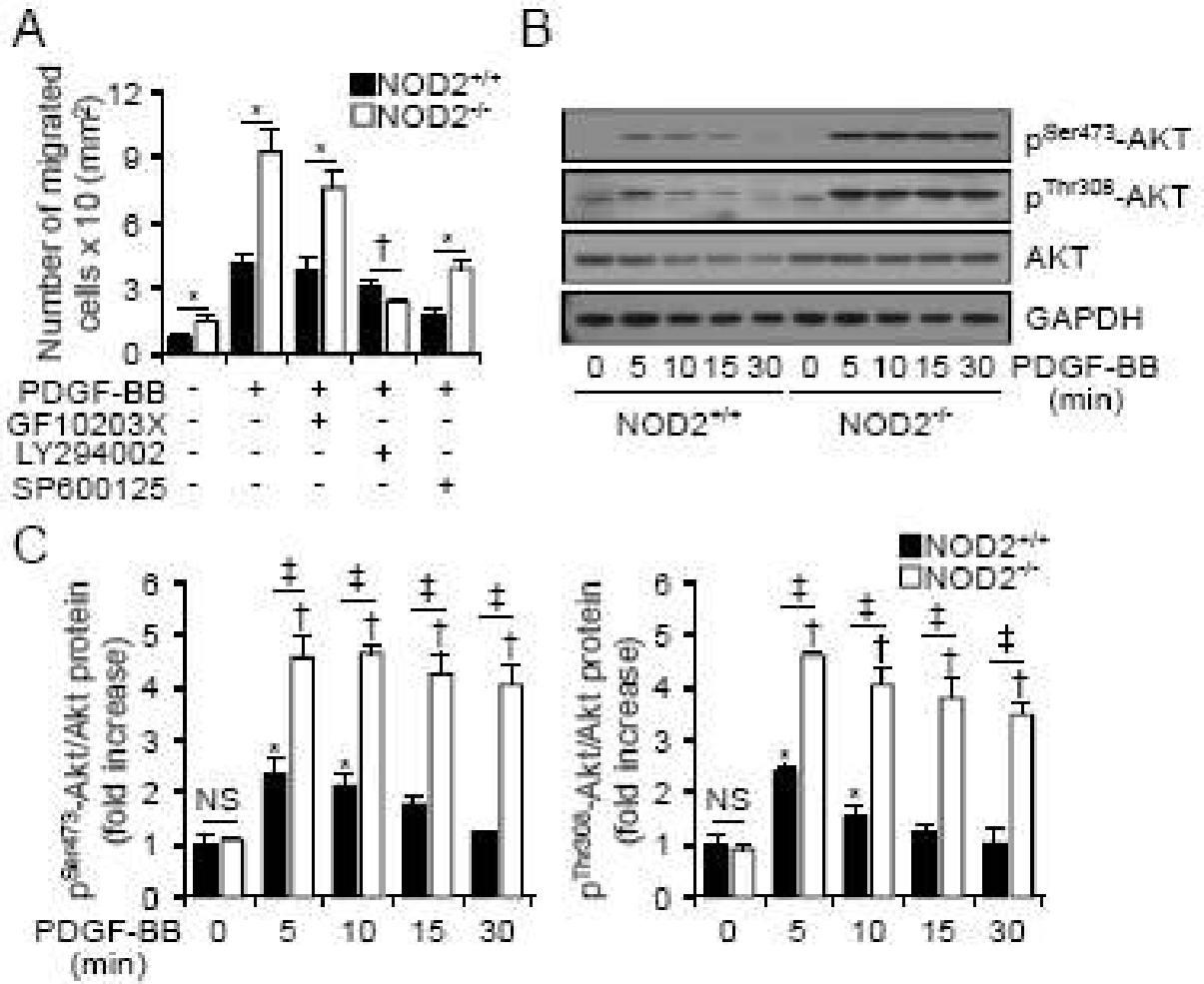


NOD2 Deficiency Has Minimal Effects on Cell Death in VSMCs.



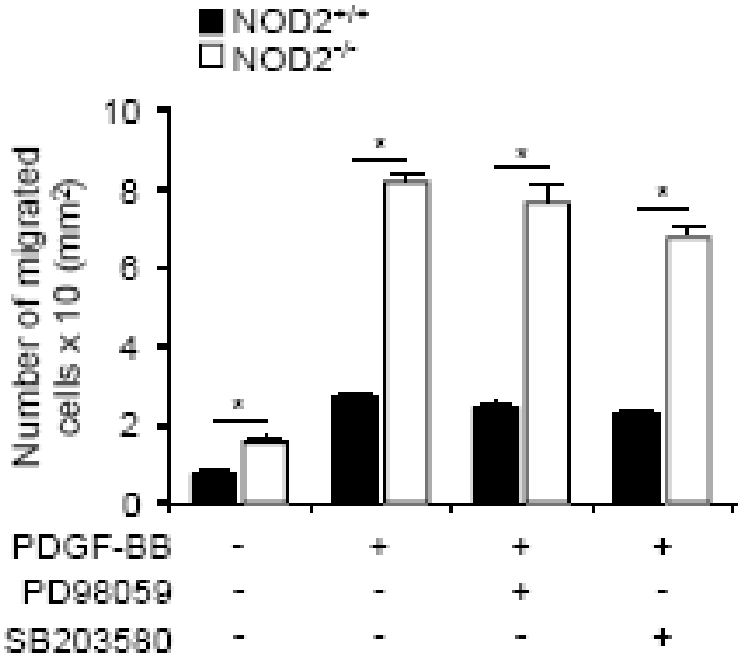
Arterioscler Thromb Vasc Biol. *In press*

Inhibition of the PI3 kinase Signaling Pathway Prevents Increased Migration in NOD2$^{-/-}$ VSMCs.



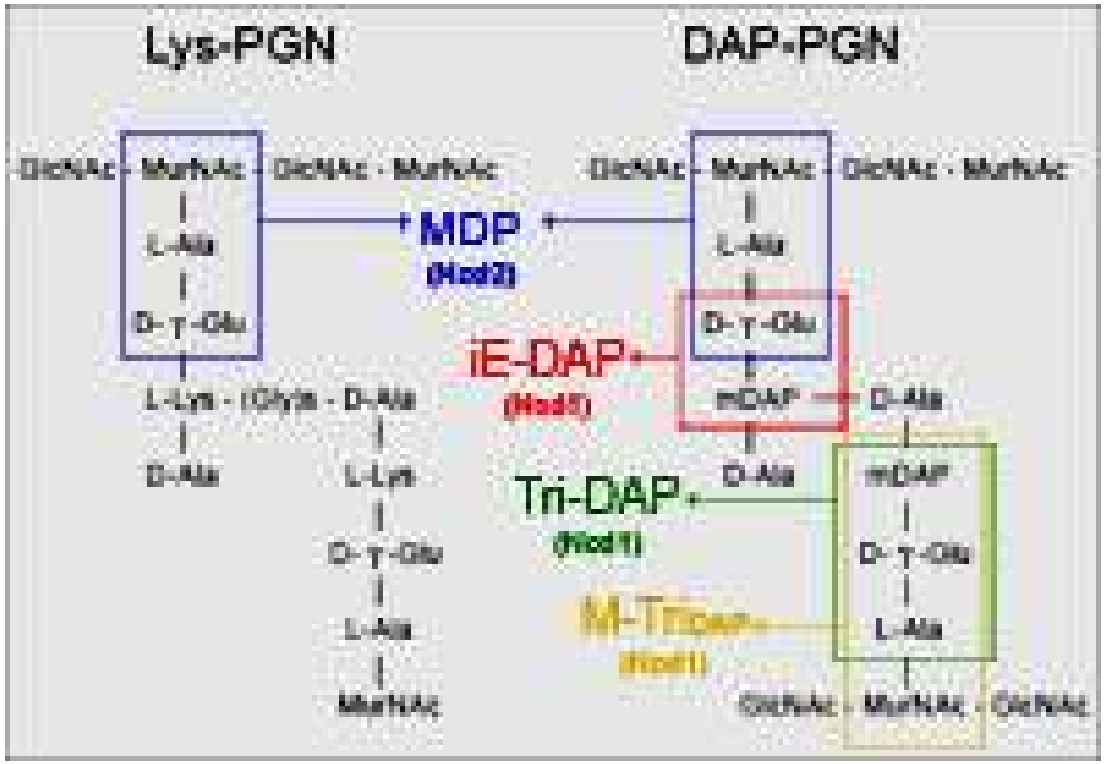
Arterioscler Thromb Vasc Biol. *In press*

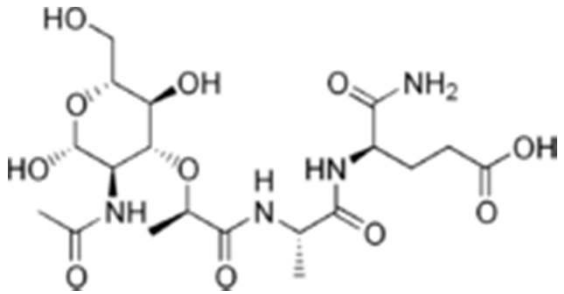
ERK and p38 Signaling Inhibitors Do not Alter Increased Migration in NOD2$^{-/-}$ VSMCs.



Arterioscler Thromb Vasc Biol. *In press*

The Chemical Structure of NOD2 Ligand





MDP