A Mitochondrial Perspective : Pathogenesis of Airway Disorders

Min-Jong Kang, M.D., Ph.D.

Associate Professor of Medicine,
Pulmonary, Critical Care & Sleep Medicine,
Yale University School of Medicine

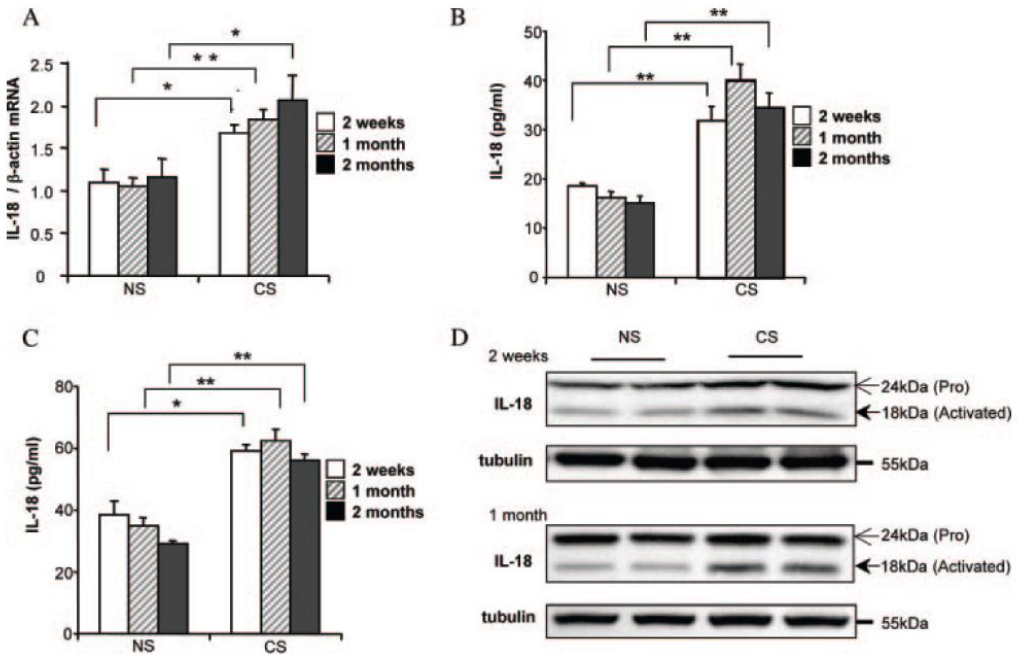
Overview

- ❑ Background: What led my lab into studying this theme?
- ❑ Mitochondrial function in cellular & organismal health
- ❑ Mitochondria-centric review of recent scientific advances in pulmonary medicine
  - ✓ Its implications in pulmonary diseases (Asthma, COPD)
  - ✓ Current researches in my laboratory
- ❑ Meaning of Mitochondria in Medicine/ Human Health

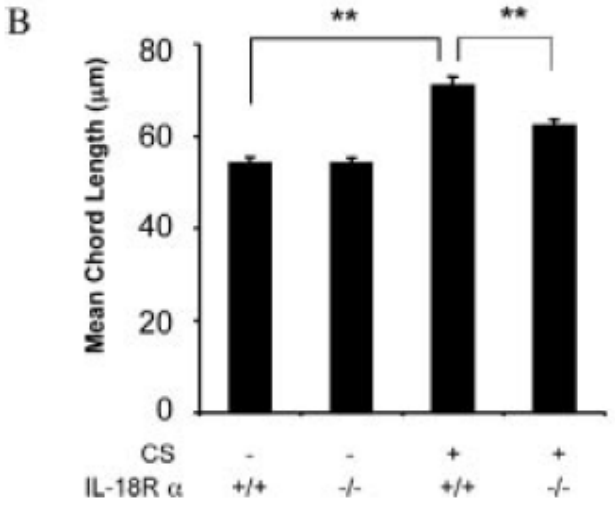
IL-18 Is Induced and IL-18 Receptor α Plays a Critical Role in the Pathogenesis of Cigarette Smoke-Induced Pulmonary Emphysema and Inflammation[1]

Min-Jong Kang,* Robert J. Homer,[†§] Amy Gallo,[‡] Chun Geun Lee,* Kristina A. Crothers,* Soo Jung Cho,* Carolyn Rochester,* Hilary Cain,* Geoffrey Chupp,* Ho Joo Yoon,[¶] and Jack A. Elias[2]*

CS induces & activates IL-18



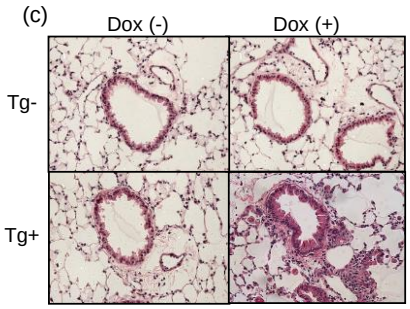
IL-18Rα Mediates CS-induced Emphysema

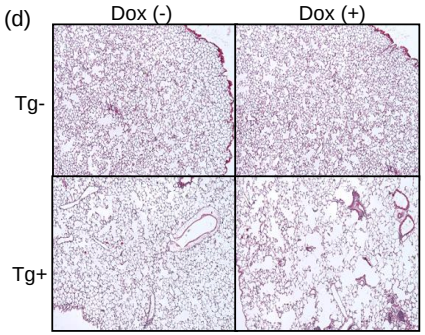


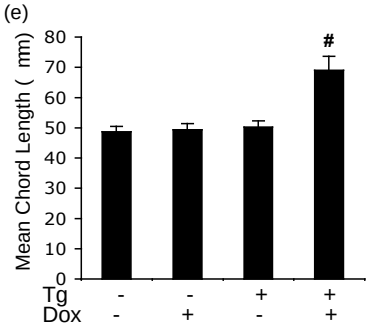
Kang MJ et al. J Immunol. 2007

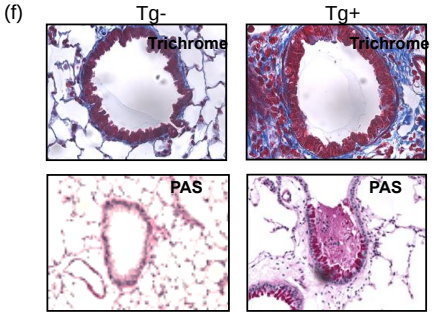
IL-18 Induces Emphysema and Airway and Vascular Remodeling via IFN-γ, IL-17A, and IL-13

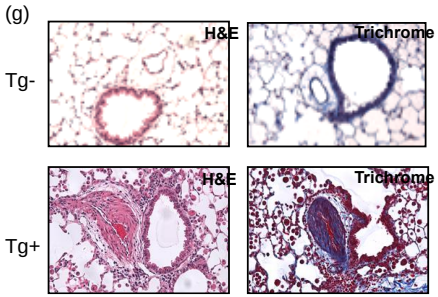
Min-Jong Kang[1*], Je-Min Choi[2,3*], Bo Hye Kim[1], Chang-Min Lee[1], Won-Kyung Cho[1], Gina Choe[1], Do-Hyun Kim[2,3], Chun Geun Lee[1], and Jack A. Elias[1]

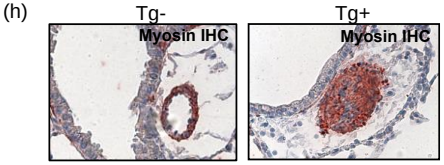


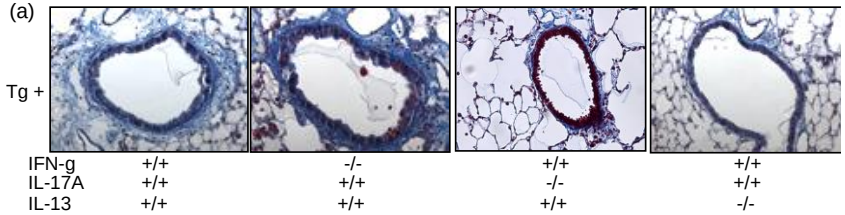








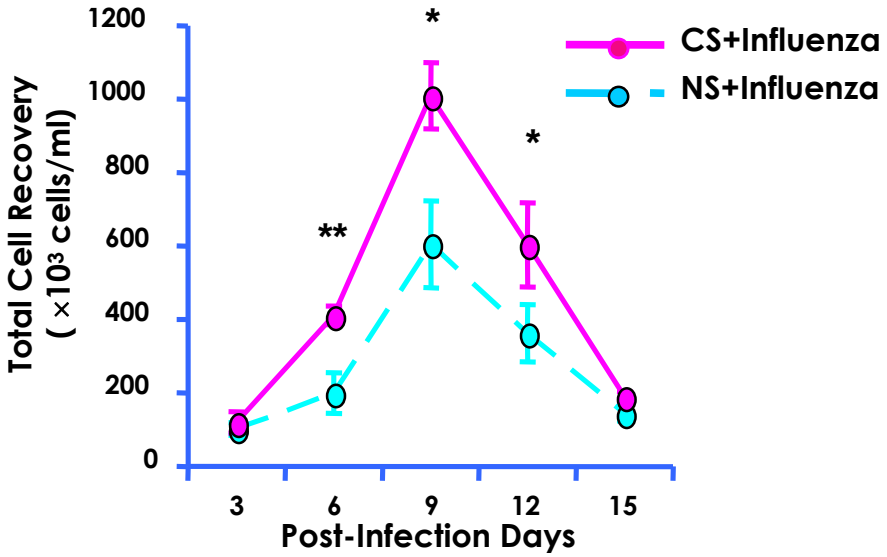


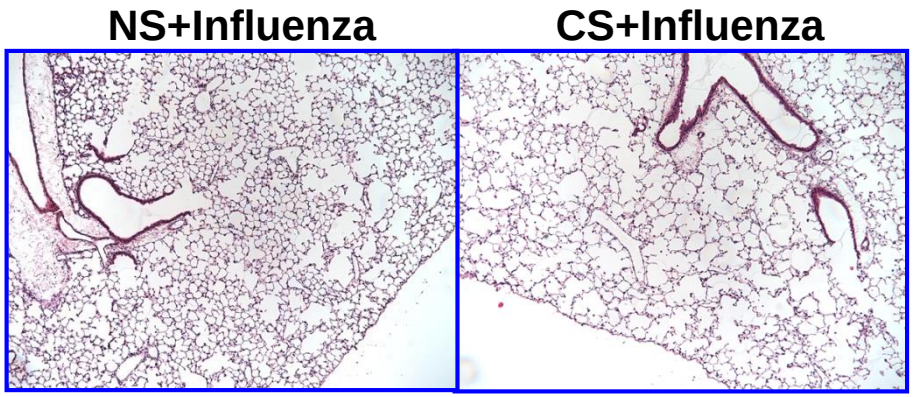


Kang MJ et al. AJRCCM. 2012

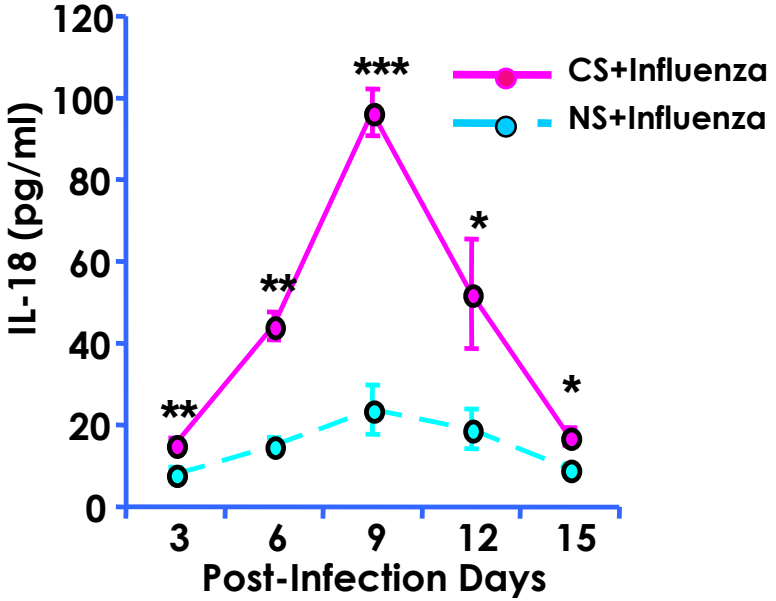
What led us to study mitochondria?

Murine Study of AECOPD : CS + Influenza virus



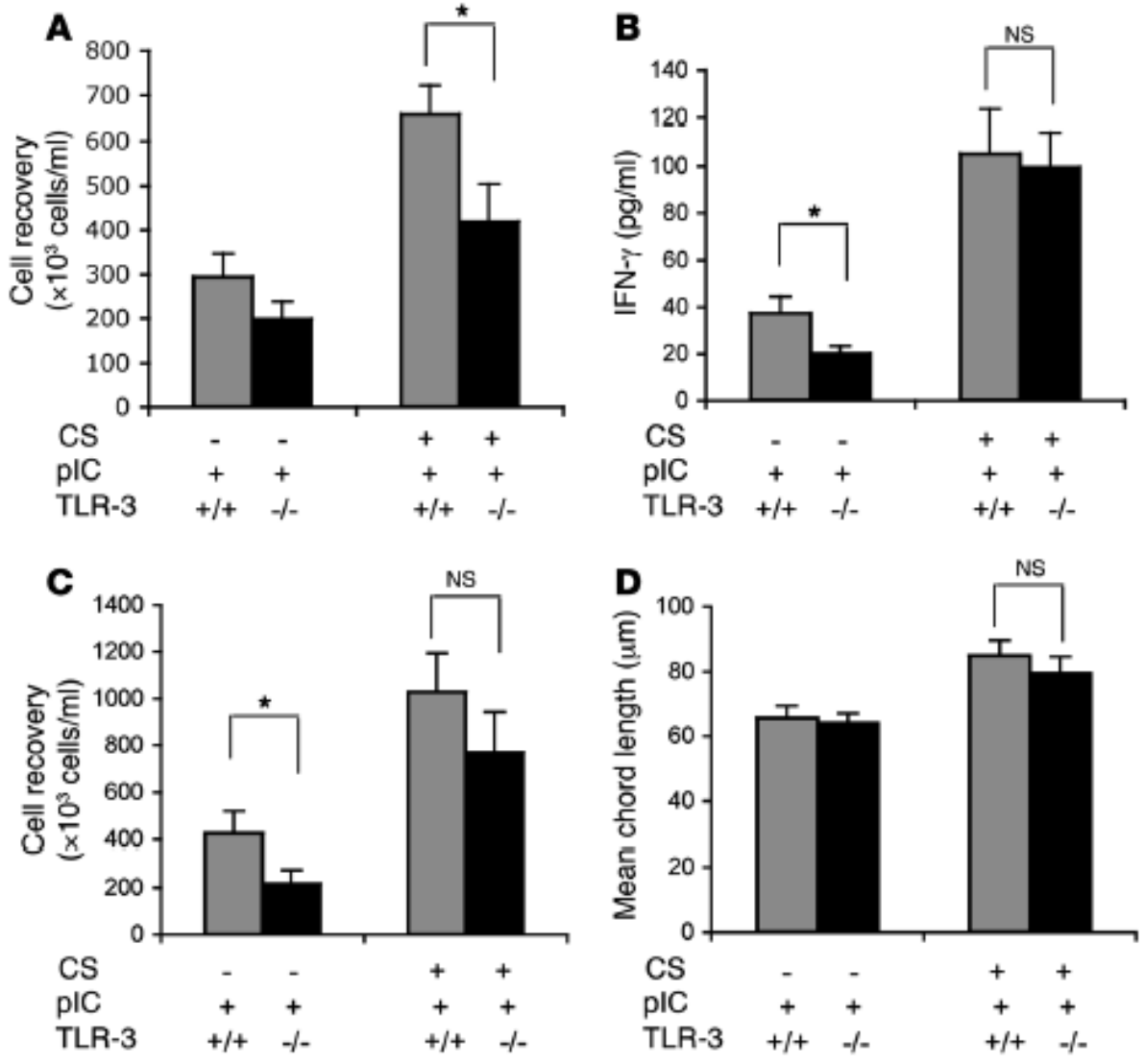


Active IL-18 ELISA (BAL Fluid)



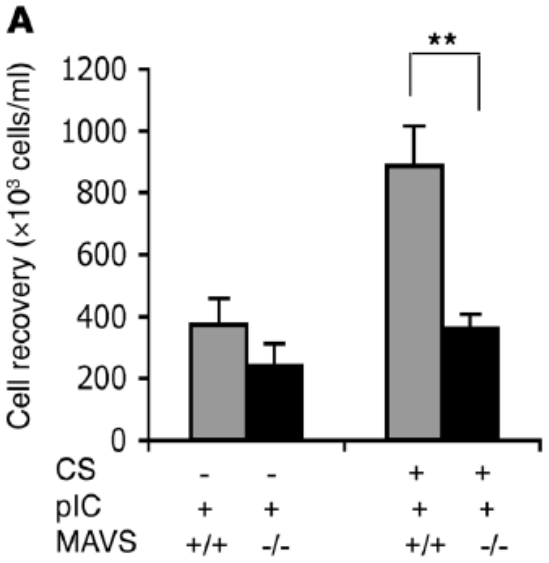
Kang MJ et al. J Clin Invest. 2008; 118(8)

Role of TLR-3 in CS+pIC model : not significant !

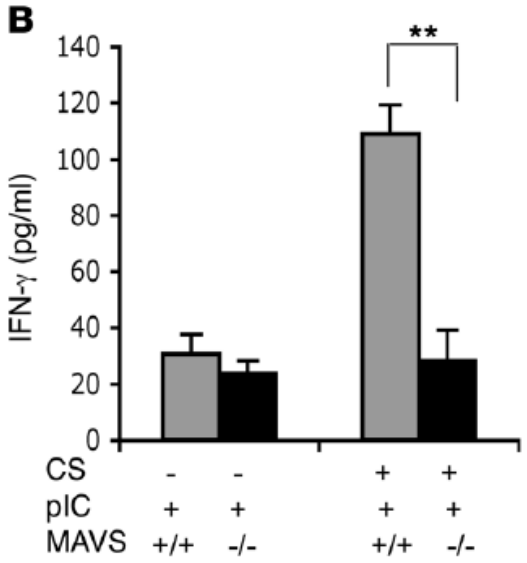


MAVS-dependent Pulmonary Inflammation & Remodeling

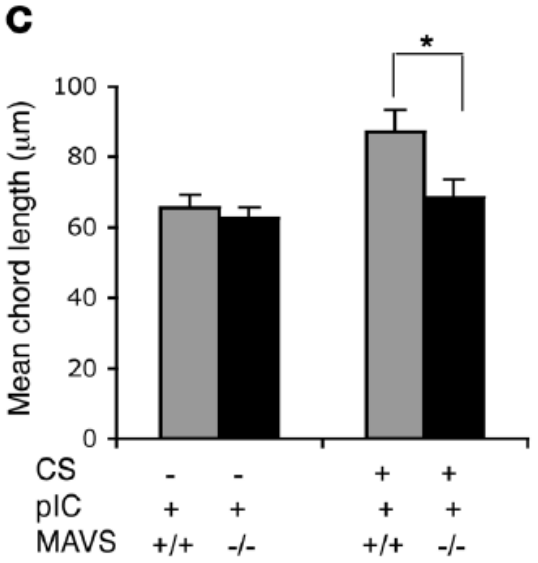
BAL Inflammation



ELISA - BAL

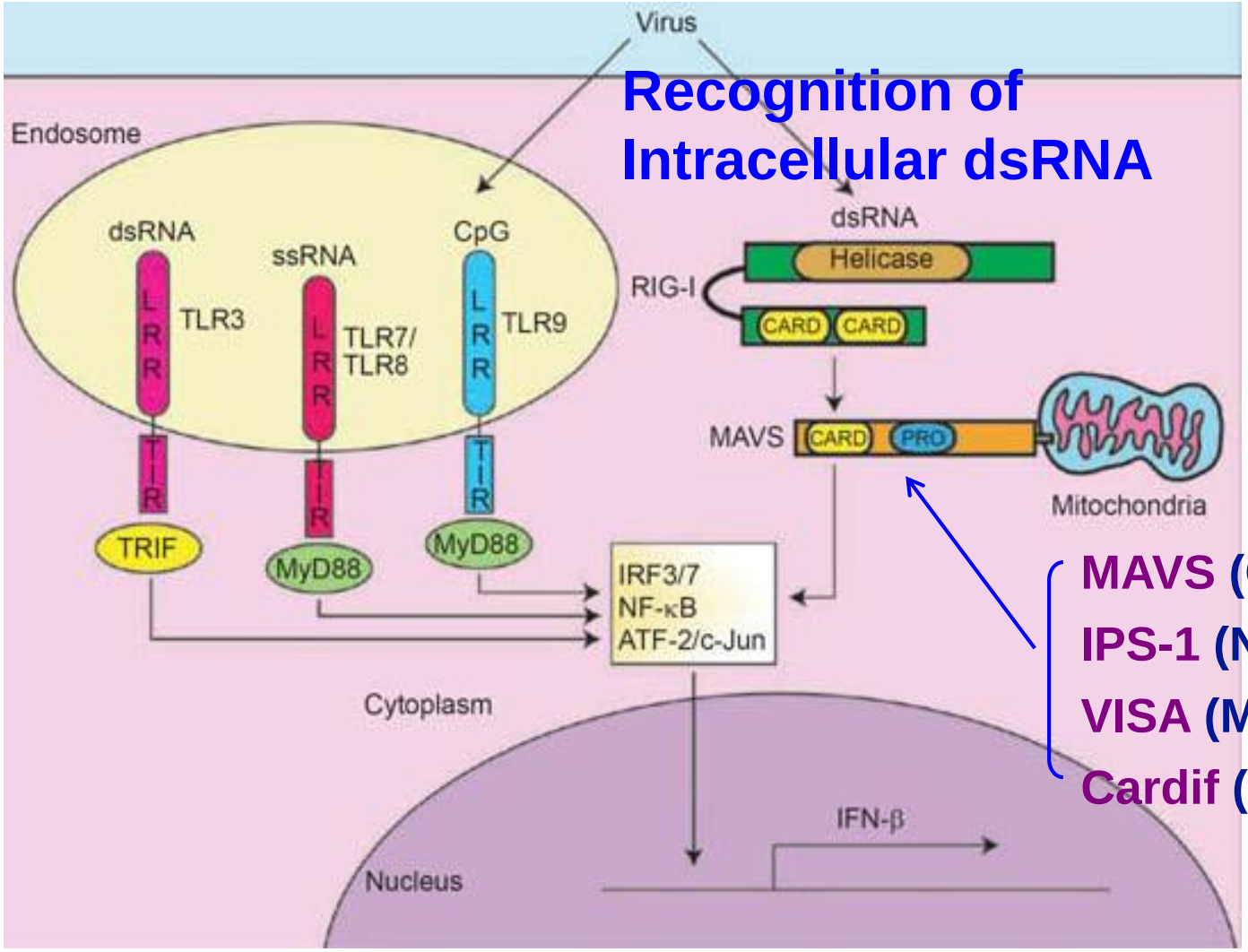


Morphometry



Kang MJ et al. J Clin Invest. 2008

RIG-I like Helicases (RLHs) & Mitochondrial Antiviral Signaling Protein (MAVS)



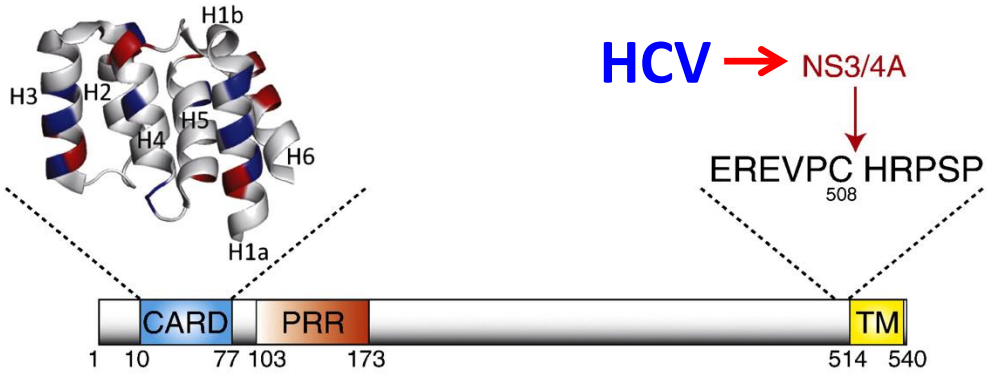
MAVS (Cell. 2005)

IPS-1 (Nat Immunol. 2005)

VISA (Mol Cell. 2005)

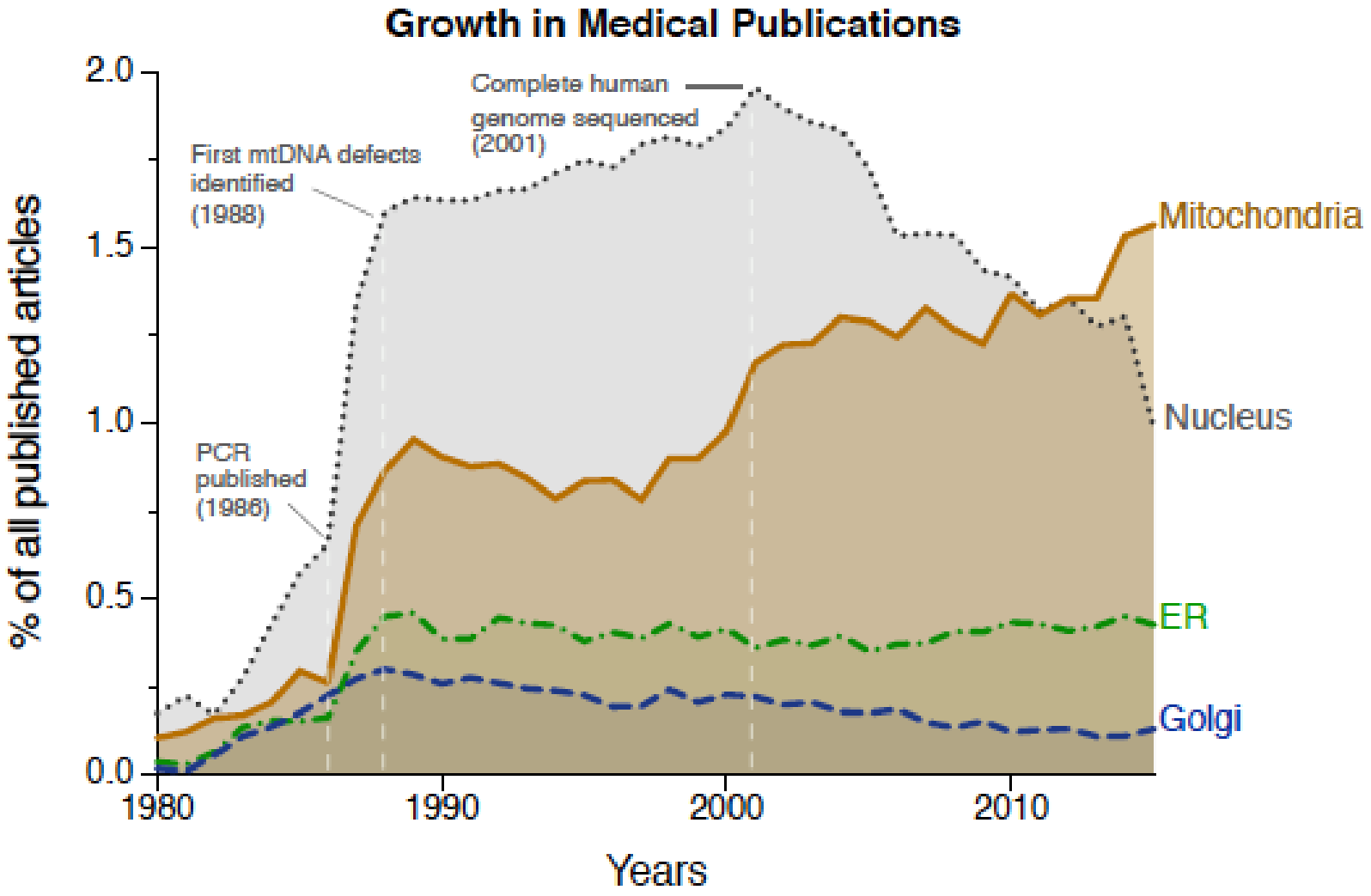
Cardif (Nature. 2005)

Mitochondrial Antiviral Signaling Protein (MAVS)



- The first mitochondrial protein identified in the context of innate immune system.
- Is localized to the outer mitochondrial membrane and its localization on mitochondria is critical for the proper functioning of MAVS.

The rise of Mitochondria in Medicine



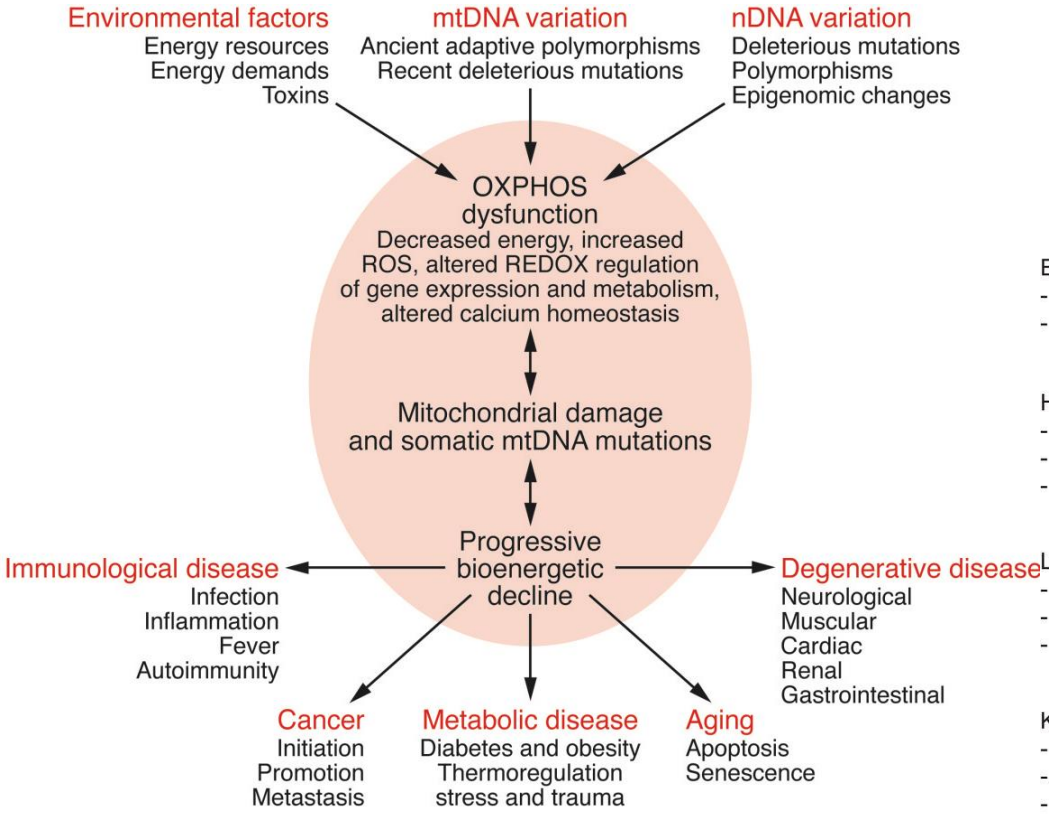
Picard M et al. Mitochondrion. 2016;30:105 - 116

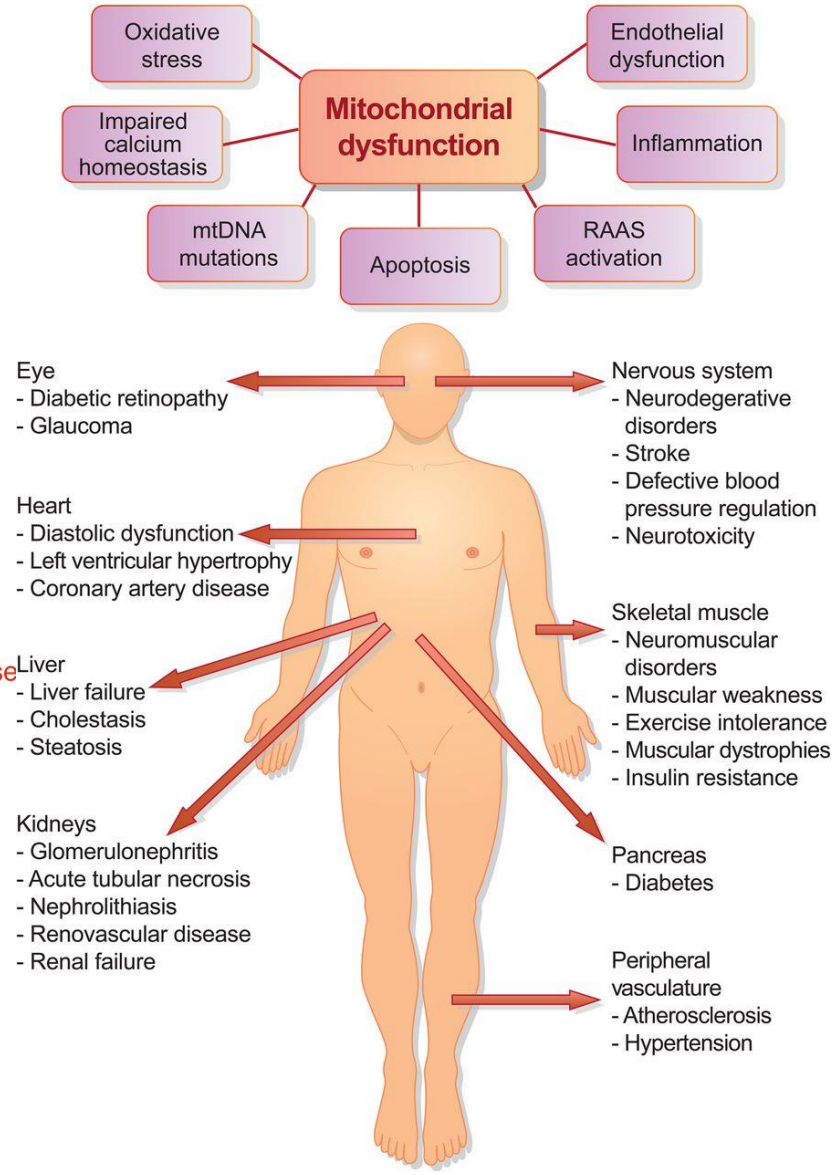
Mitochondria

- organelle controlling fundamental biologic functions

- Historically, mitochondria have been regarded as a powerhouse within a cell.
- Recently, the role of mitochondria has been expanded in vast areas of molecular and cellular biology ..
  - ✓ Cell proliferation, differentiation & death
  - ✓ Metabolism
  - ✓ Redox homeostasis/ Calcium homeostasis
  - ✓ Immune signaling/ regulation...
- "Mitochondrial dysfunction" : implicated to have a major pathogenic role in a wide range of diseases…

Mitochondrial Perspective of Pathogenesis

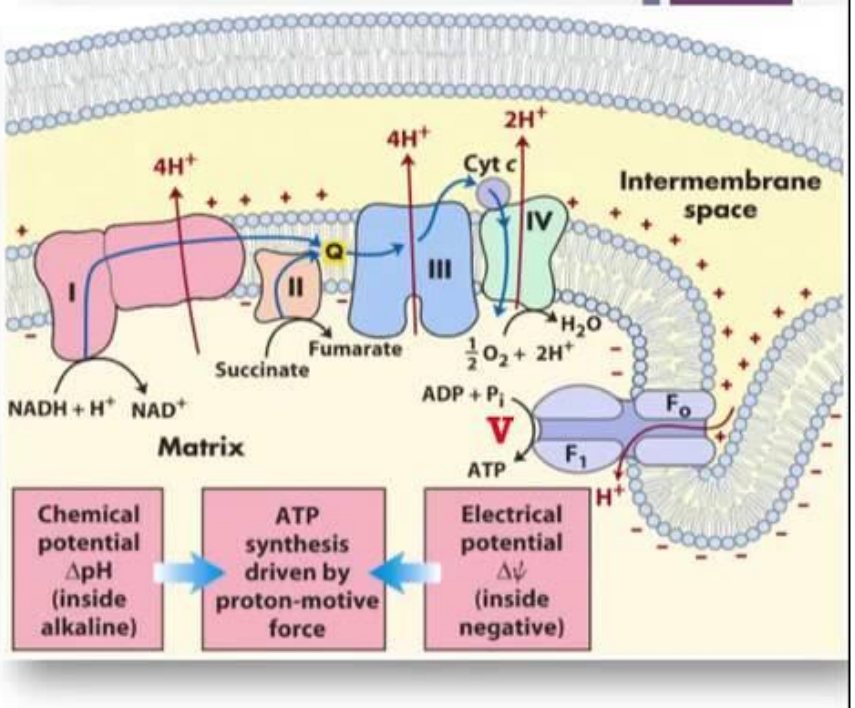




Wallace DC. J Clin Invest. 2013;123:1405-12. A Mitochondrial Bioenergetic Etiology of Disease

Chemiosmotic Model

- Energy stored in "battery" used to drive ATP synthesis
- CHEMI – chemical reaction; OSMOTIC – driven by transport
- Flow of H^+ back into matrix provides energy to synthesize ATP



Peter Mitchell, 1920–1992

Proposed chemi-osmotic model

Coupled with H^+ translocation

$$ADP + P_i + nH^+_P \longrightarrow ATP + H_2O + nH^+_N$$

ATP synthesis

Mitochondrial bioenergetics & Airway Disease

Oxidative stress–induced mitochondrial dysfunction drives inflammation and airway smooth muscle remodeling in patients with chronic obstructive pulmonary disease

Wiegman CH et al. on behalf of COPDMAP. J Allergy Clin Immunol. 2015;136:769 - 80

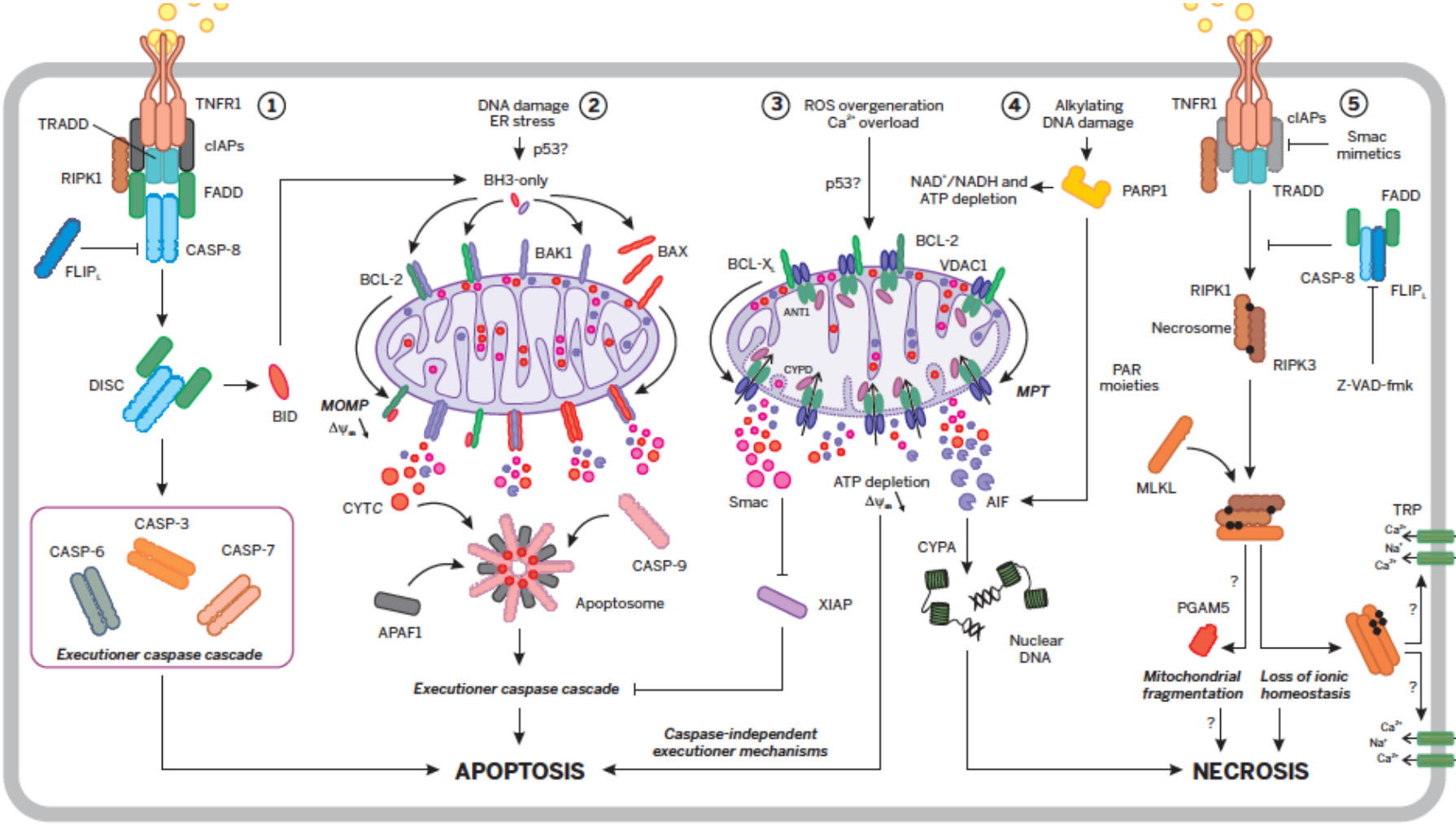
- In mice exposed to ozone, a source of oxidative stress,
  - lung inflammation and AHR associated with mitochondrial dysfunction
  - ΔΨm ↓, mitochondrial oxidative stress ↑, mitochondrial complex I, III, and V expression ↓.
- In ASM cells from patients with COPD
  - ΔΨm ↓, mitochondrial complex expression ↓, basal and maximum respiration levels ↓, respiratory reserve capacity ↓ compared with those from healthy control subjects,
  - In contrast, ↑ mitochondrial reactive oxygen species (ROS)

Mesenchymal stem cells alleviate oxidative stress–induced mitochondrial dysfunction in the airways

Li X et al. J Allergy Clin Immunol. 2018;141:1634 - 45

- Coculture of iPSC-MSCs with human ASMCs attenuated CSM-induced mitochondrial ROS, apoptosis, and ΔΨm loss in ASMCs.
- Mitochondrial transfer from iPSC-MSCs to ASMCs was observed after direct co-culture and was enhanced by CSM.
- iPSC-MSCs attenuated ozone-induced mitochondrial dysfunction, airway hyper-responsiveness, and inflammation in mouse lungs.

Major Signal Transduction Cascades leading to Cell Death



Green DR et al. Science. 2014;345:1466 (1250256)

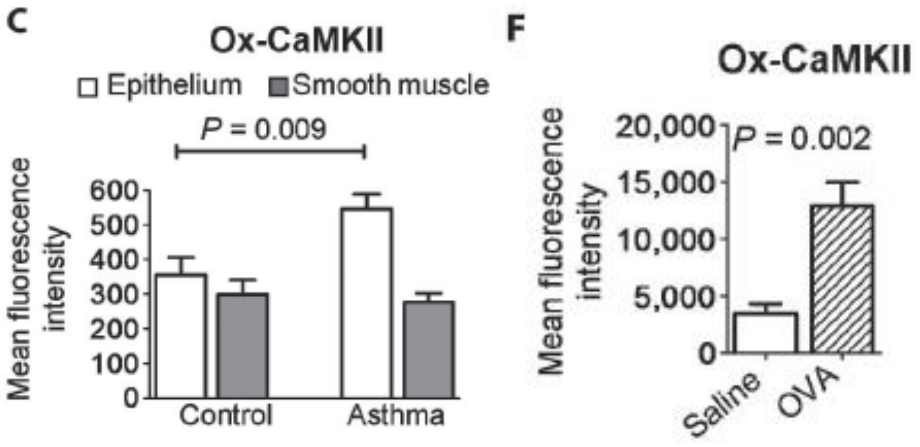
Mitochondrial Ca^{++} Signaling & Airway Disease

Mitochondrial CaMKII inhibition in airway epithelium protects against allergic asthma

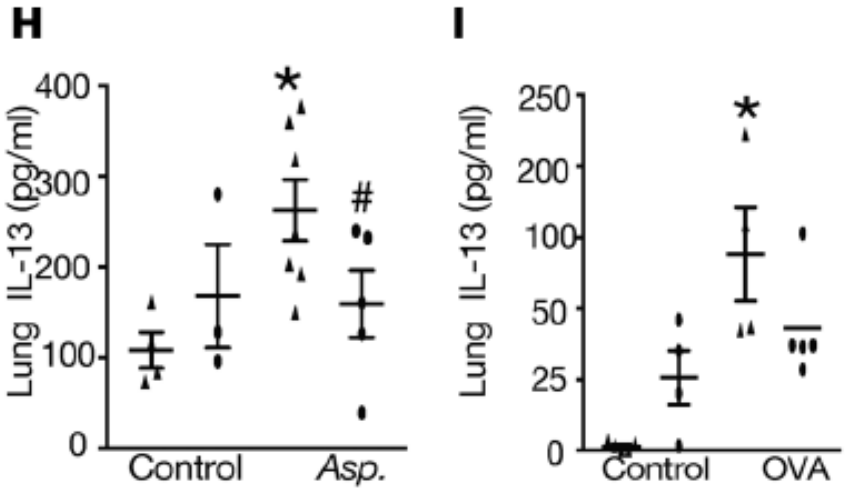
Sebag SC et al. JCI Insight. 2017

CaMKII Is Essential for the Proasthmatic Effects of Oxidation

Sanders PN et al. Sci Transl Med. 2013

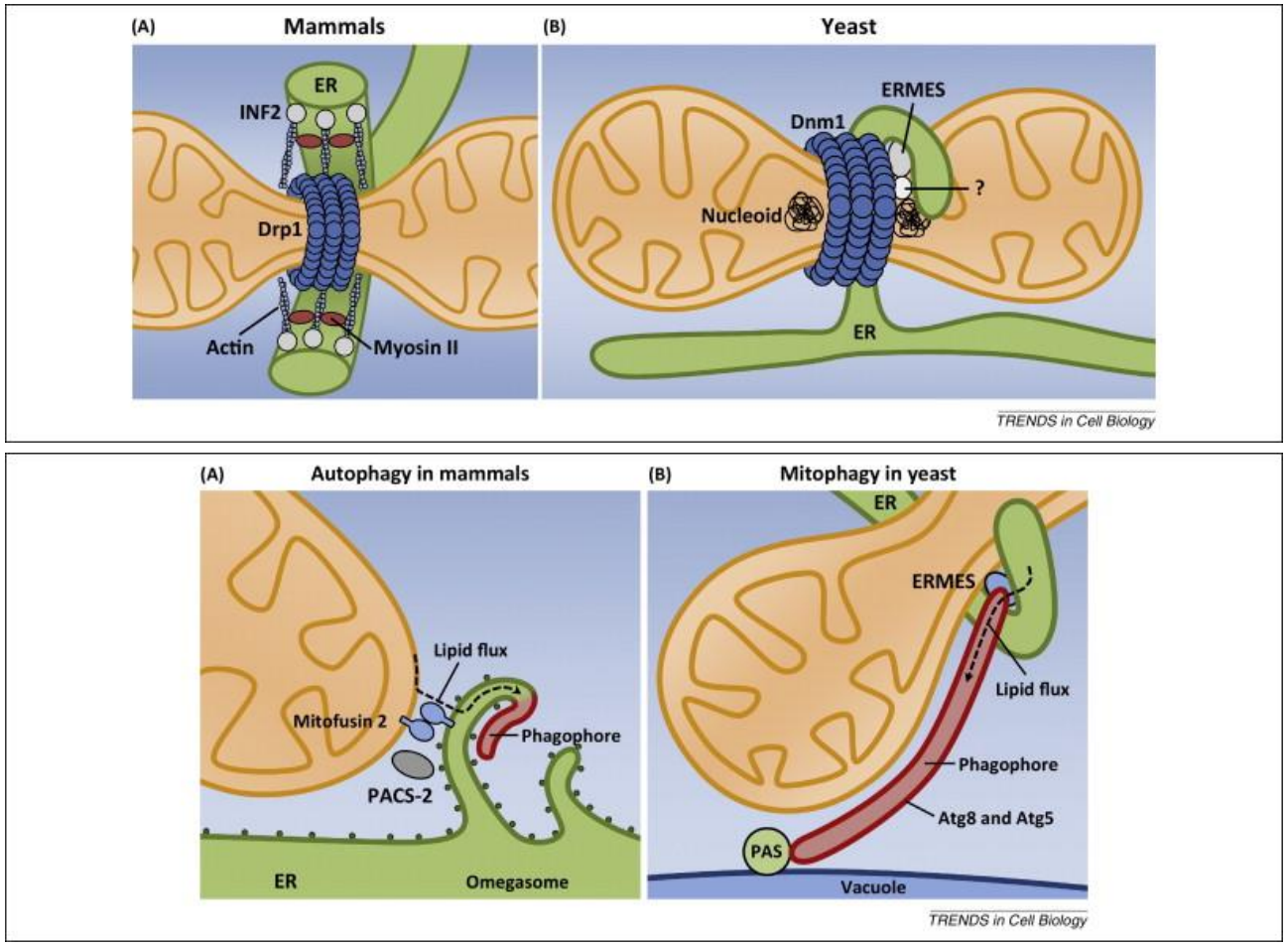


Sanders PN et al. Sci Transl Med. 2013



Sebag SC et al. JCI Insight. 2017

ER-Mitochondria Crosstalk

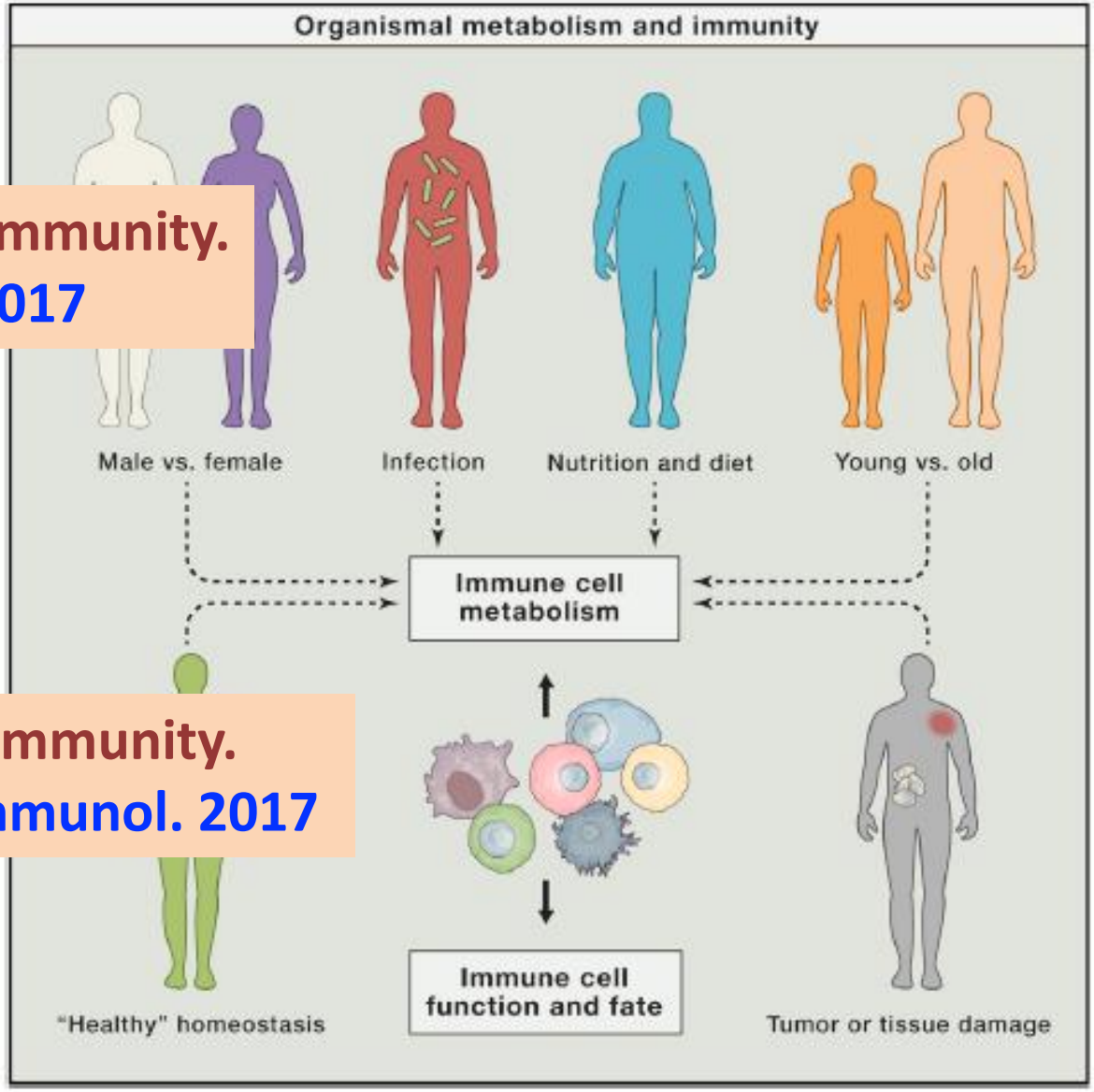


- ER stress and its signaling networks in asthma (Dr. Lee YC et al.)
  - ✓ Allery Asthma Immunol Res. 2015
  - ✓ Exp Mol Med. 2018

Immunometabolism
- Metabolic Control of Immune Cells

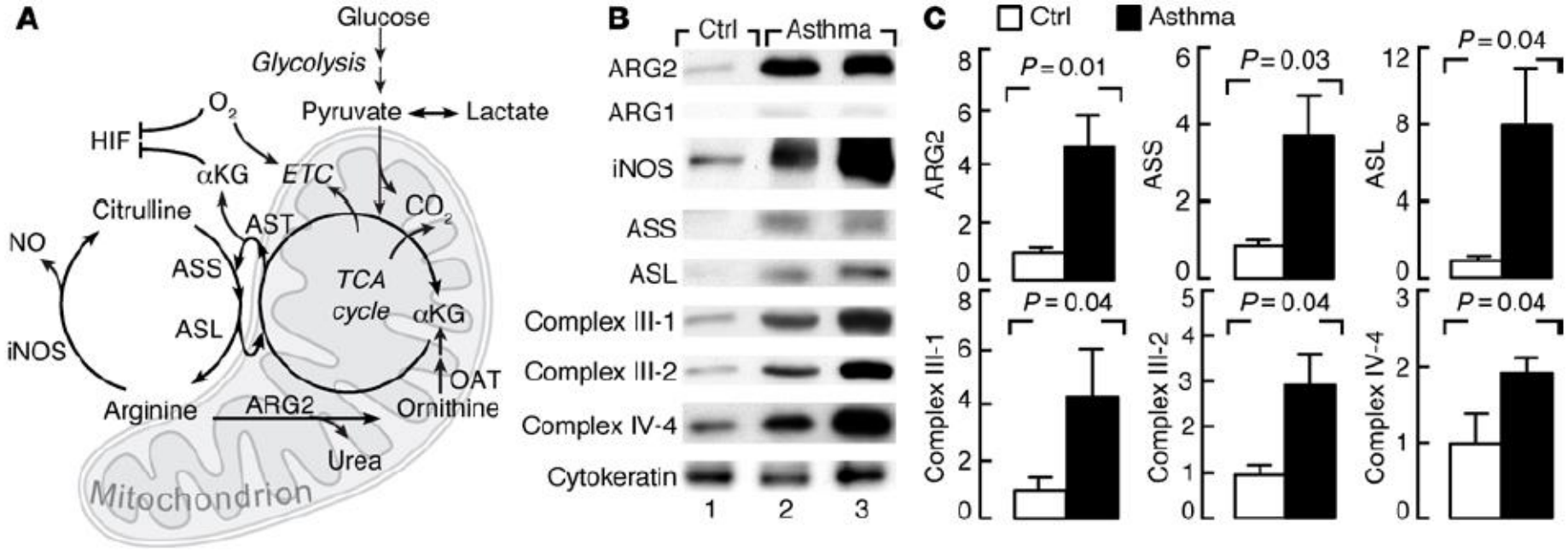
Metabolic Instruction of Immunity.
Buck M et al. Cell. 2017

Mitochondrial Control of Immunity.
Mehta M et al. Nat Rev Immunol. 2017



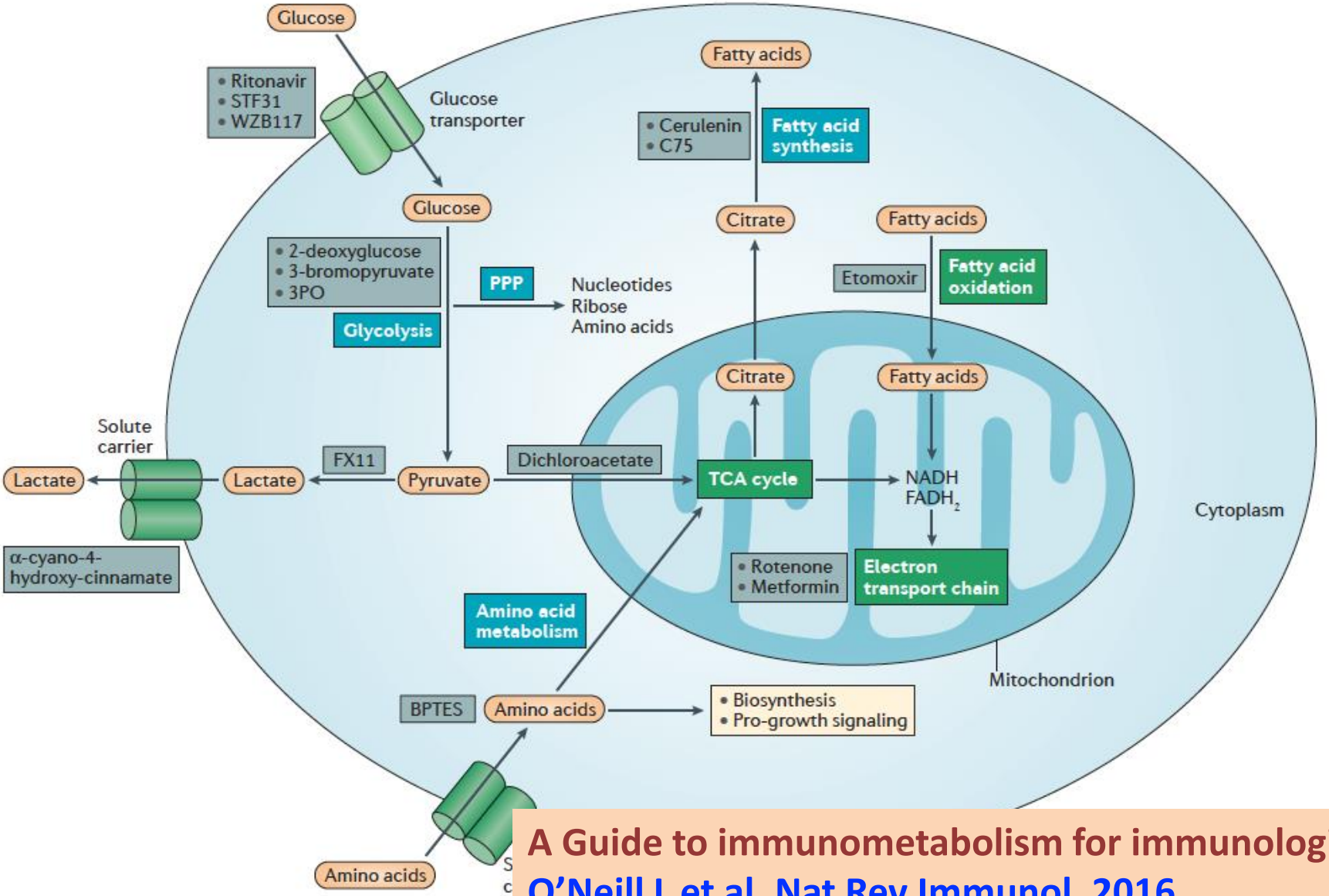
Increased mitochondrial arginine metabolism supports bioenergetics in asthma

Xu W et al. J Clin Invest. 2016



- Mice lacking Arg2 had greater Th2 inflammation than WT mice
- Arginine flux preserves cellular respiration and suppresses pathological signaling events

Six Major Metabolic Pathways

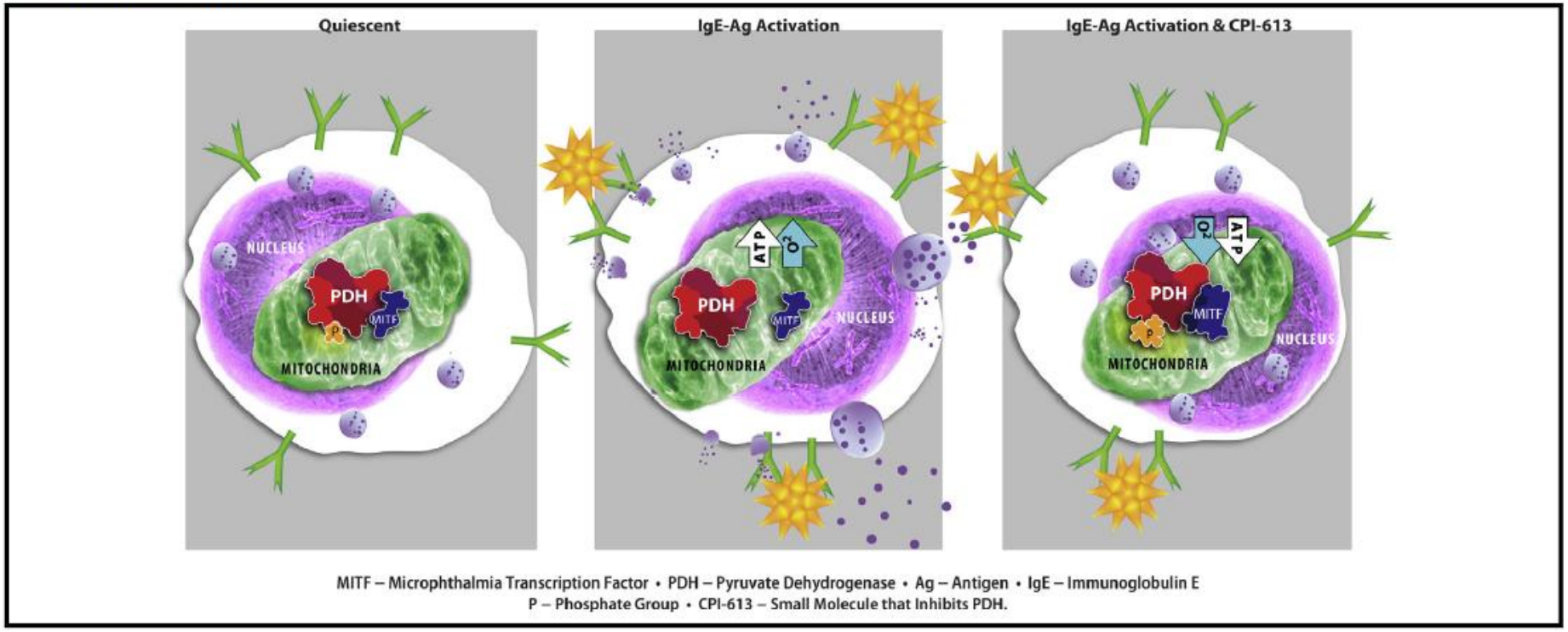


A Guide to immunometabolism for immunologists.
O'Neill L et al. Nat Rev Immunol. 2016

Pyruvate dehydrogenase has a major role in mast cell function, and its activity is regulated by mitochondrial microphthalmia transcription factor

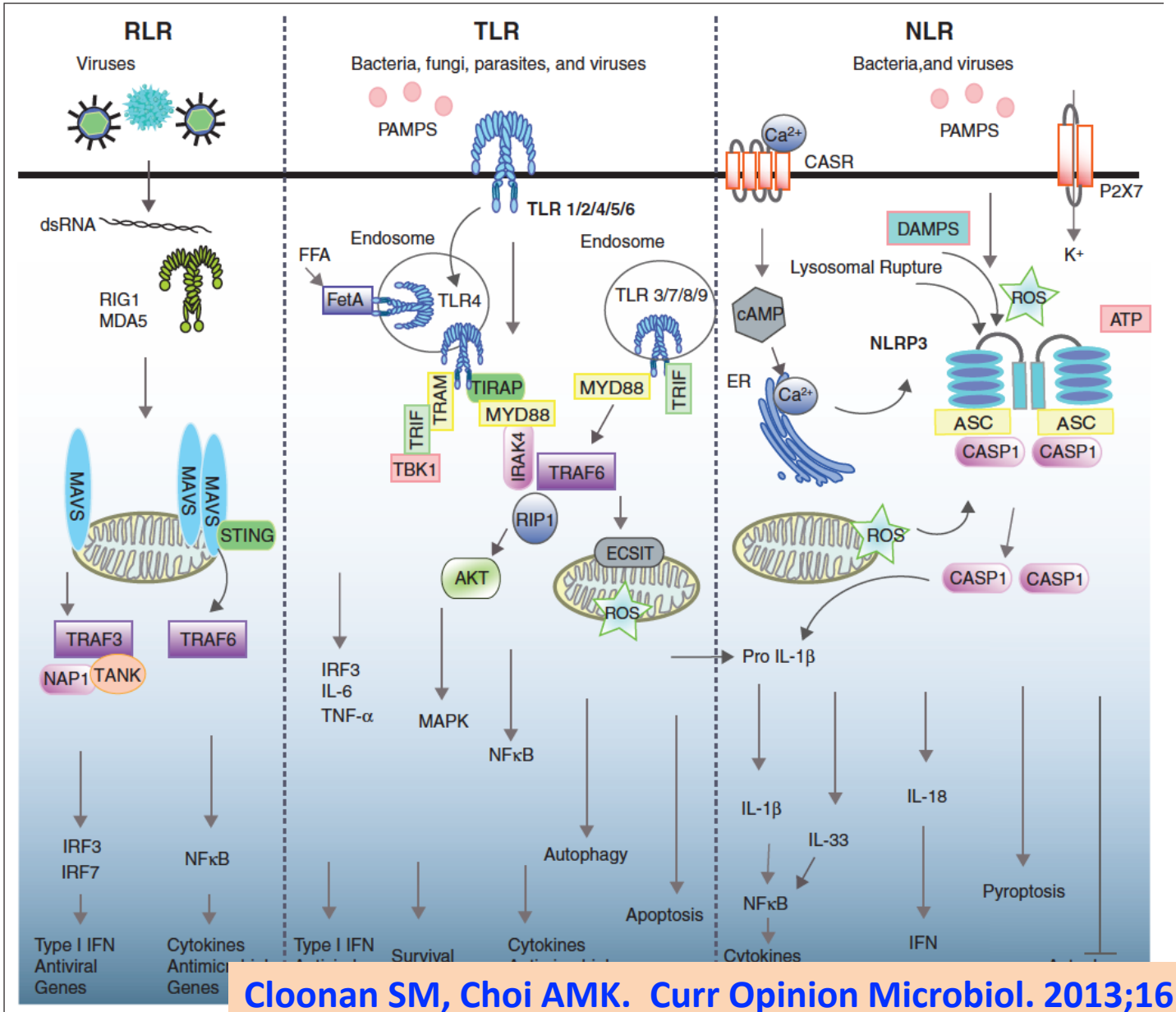
Israa Sharkia, MSc,[a]* Tal Hadad Erlich, PhD,[a]* Nadine Landolina, PhD,[b] Miri Assayag, PhD,[c] Alex Motzik, MSc,[a] Inbal Rachmin, PhD,[a]‡ Gillian Kay, PhD,[a] Ziv Porat, PhD,[d] Sagi Tshori, MD, PhD,[e] Neville Berkman, MD, PhD,[c] Francesca Levi-Schaffer, PharmD, PhD,[b] and Ehud Razin, PhD[a] *Jerusalem and Rehovot, Israel*

GRAPHICAL ABSTRACT



JACI. 2017;140:204

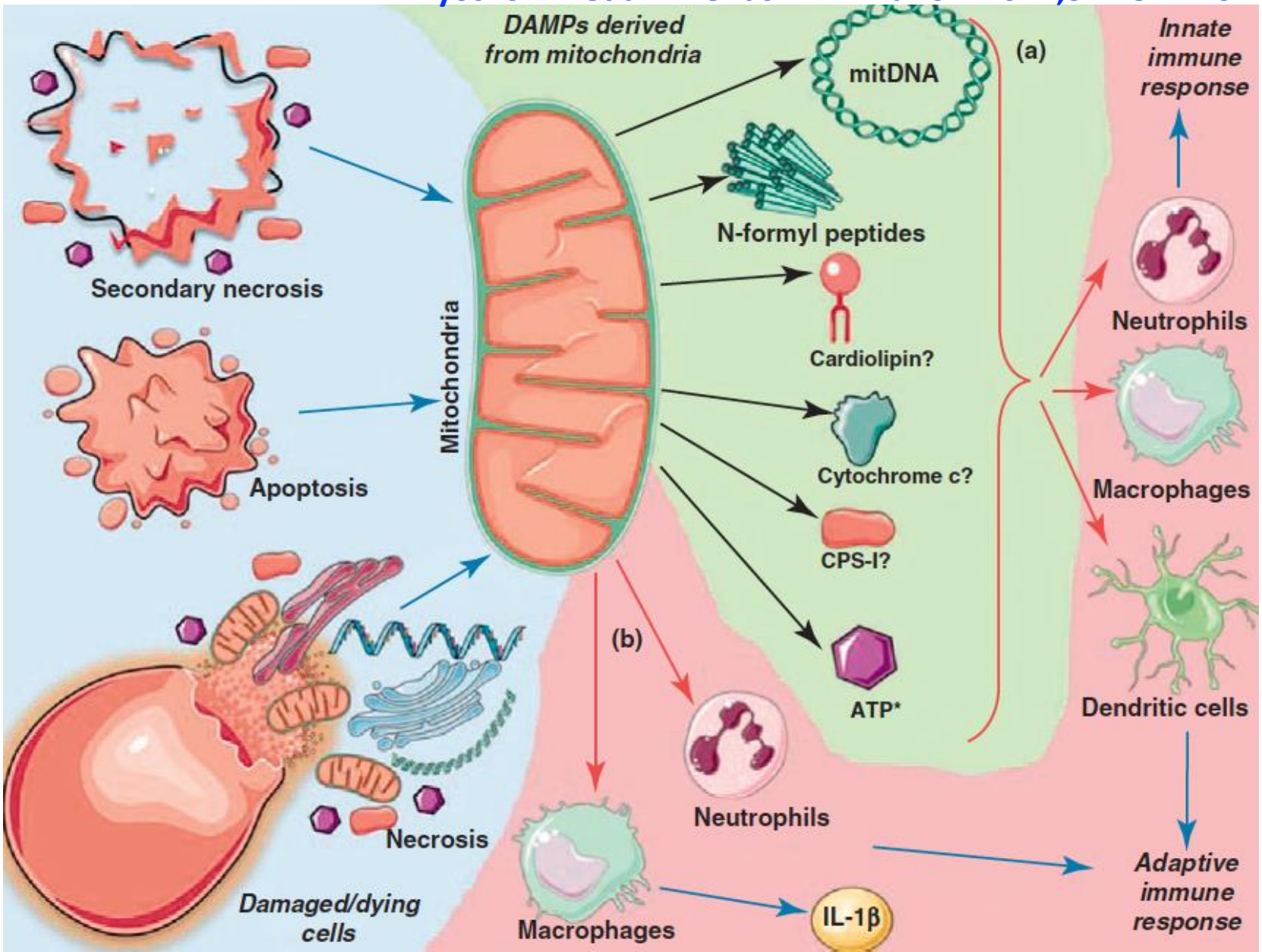
Mitochondria as Immune Signaling Hub



Cloonan SM, Choi AMK. Curr Opinion Microbiol. 2013;16:327 - 338

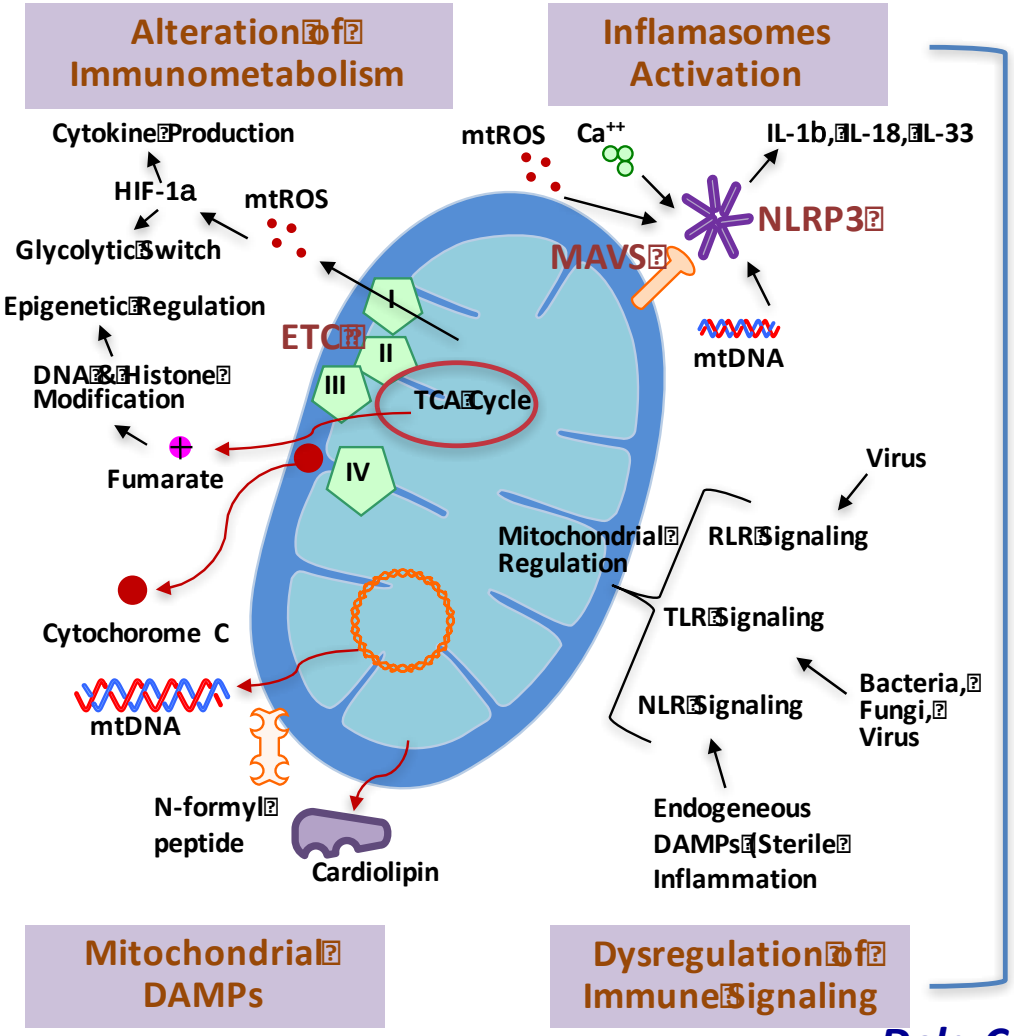
Mitochondrial DAMPs (MitoDAMPs)

Kryosko DV et al. Trends in Immunol. 2011;32:157 - 164



Mitochondrial Innate Immunity & Inflammatory Diseases

Mitochondrial Dysfunction



Chronic Inflammatory Disorders

- Atherosclerosis
- COPD
- Pulmonary Fibrosis
- NAFLD
- Tumorigenesis
- Neuroinflammation
- Inflammageing
- Other...

Dela Cruz C, Kang MJ. Mitochondrion. 2018

The Journal of Clinical Investigation RESEA

Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD

J Clin Invest. 2014;124:3987

nature medicine

VOLUME 22 | NUMBER 2 | FEBRUARY 2016 NATURE MEDICINE

Mitochondrial iron chelation ameliorates cigarette smoke–induced bronchitis and emphysema in mice

Therapeutic Potential of Mitochondrial Targeting

Mitochondrial transfer from bone-marrow–derived stromal cells to pulmonary alveoli protects against acute lung injury

Mohammad Naimul Islam, Shonit R Das, Memet T Emin, Michelle Wei, Li Sun, Kristin Westphalen, David J Rowlands, Sadiqa K Quadri, Sunita Bhattacharya & Jahar Bhattacharya

Bone marrow–derived stromal cells (BMSCs) protect against acute lung injury (ALI). To determine the role of BMSC mitochondria in this protection, we airway-instilled mice first with lipopolysaccharide (LPS) and then with either mouse BMSCs (mBMSCs) or human BMSCs (hBMSCs). Live optical studies revealed that the mBMSCs formed connexin 43 (Cx43)-containing gap junctional channels (GJCs) with the alveolar epithelia in these mice, releasing mitochondria-containing microvesicles that the epithelia engulfed. The presence of BMSC-derived mitochondria in the epithelia was evident optically, as well as by the presence of human mitochondrial DNA in mouse lungs instilled with hBMSCs. The mitochondrial transfer resulted in increased alveolar ATP concentrations. LPS-induced ALI, as indicated by alveolar leukocytosis and protein leak, inhibition of surfactant secretion and high mortality, was markedly abrogated by the instillation of wild-type mBMSCs but not of mutant, GJC-incompetent mBMSCs or mBMSCs with dysfunctional mitochondria. This is the first evidence, to our knowledge, that BMSCs protect against ALI by restituting alveolar bioenergetics through Cx43-dependent alveolar attachment and mitochondrial transfer.

Islam MN et al. Nat Med. 2012

Mitochondrial Innate Immuynity & COPD

Cigarette smoke selectively enhances viral PAMP– and virus-induced pulmonary innate immune and remodeling responses in mice

Min-Jong Kang,[1] Chun Geun Lee,[1] Jae-Young Lee,[1] Charles S. Dela Cruz,[1]
Zhijian J. Chen,[2] Richard Enelow,[1] and Jack A. Elias[1,3]

Kang MJ et al. J Clin Invest. 2008

Suppression of NLRX1 in chronic obstructive pulmonary disease

Min-Jong Kang,[1,2] Chang Min Yoon,[1] Bo Hye Kim,[1] Chang-Min Lee,[2] Yang Zhou,[2] Maor Sauler,[1] Rober Homer,[1,3] Anish Dhamija,[4] Daniel Boffa,[4] Andrew Phillip West,[3] Gerald S. Shadel,[3] Jenny P. Ting,[5] John R. Tedrow,[6] Naftali Kaminski,[1] Woo Jin Kim,[7] Chun Geun Lee,[2] Yeon-Mok Oh,[8] and Jack A. Elias[2]

Kang MJ et al. J Clin Invest. 2015

NLRX1

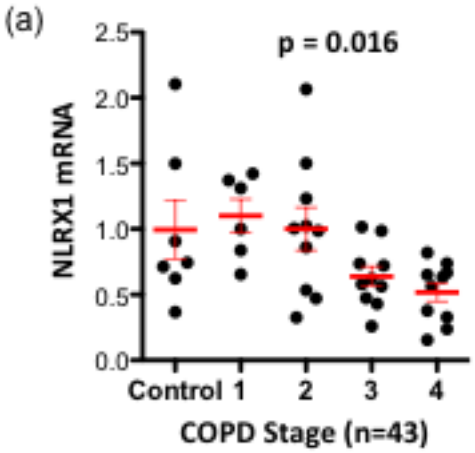
Nucleotide Binding Domain and Leucine-Rich-Repeat-containing Protein X1

- ✓ Identified as a negative regulator of MAVS (Nature 2008)
- ✓ Negatively regulate TLR-induced NF-κB signaling by targeting TRAF6 and IKK (immunity 2011)
- ✓ Located in matrix where NLRX1 interacts with a component of OXPHOS III -> mtROS generation (J Cell Sci 2009)
- ✓ Interact mitochondrial Tu translation elongation factor (TUFM) and promote autophagy (Immunity 2012)

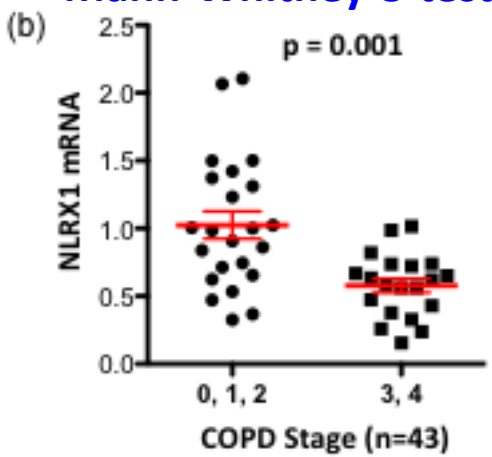
NLRX1 Expression in Humans – LTRC cohort

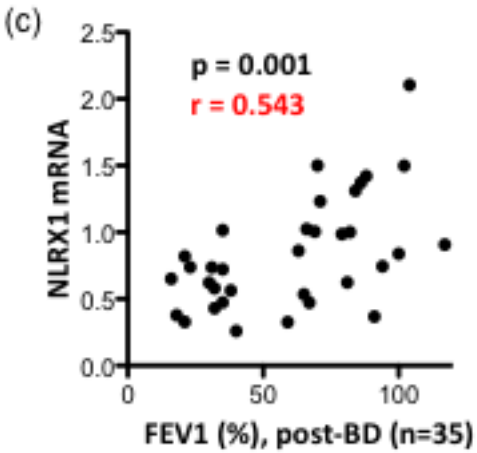
Figure 1. NLRX1 gene expression from patients with COPD

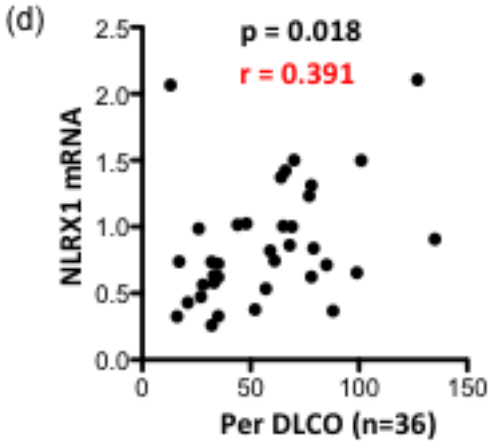
Kruskal-Wallis test



Mann-Whitney U test

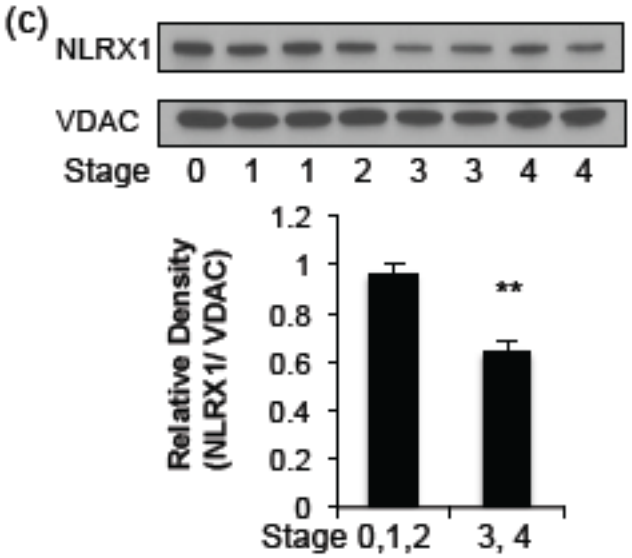






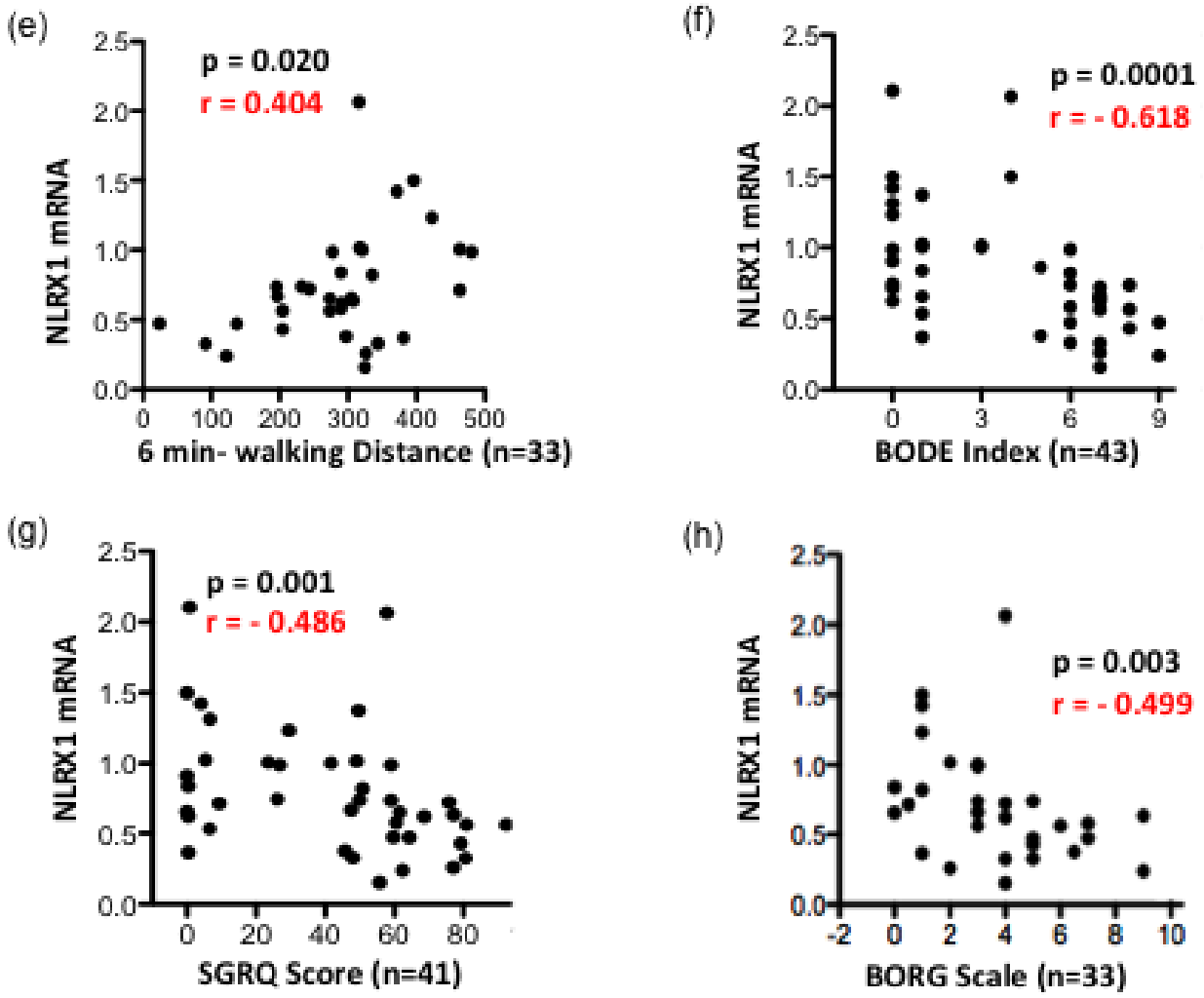
Total 44 fresh frozen tissues

- ✓ **Controls : 7**
- ✓ **COPD/Emphysema : 37**
  - **GOLD stage 1 (7)**
  - **GOLD stage 2 (10)**
  - **GOLD stage 3 (10)**
  - **GOLD stage 4 (10)**



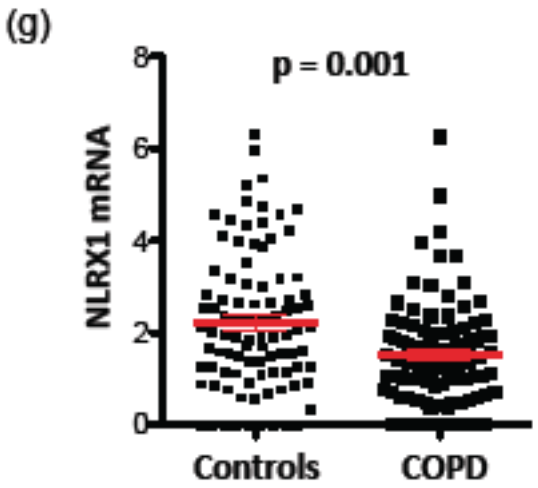
Kang MJ et al. J Clin Invest. 2015

Correlation b/w NLRX1 vs. Disease Severity

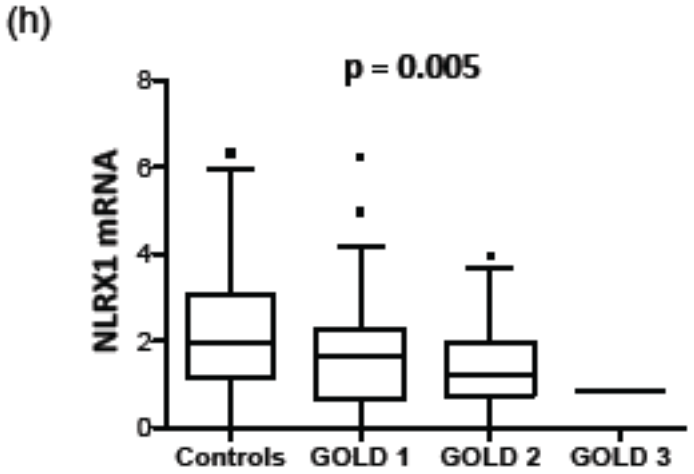


Spearmann's rho correlation

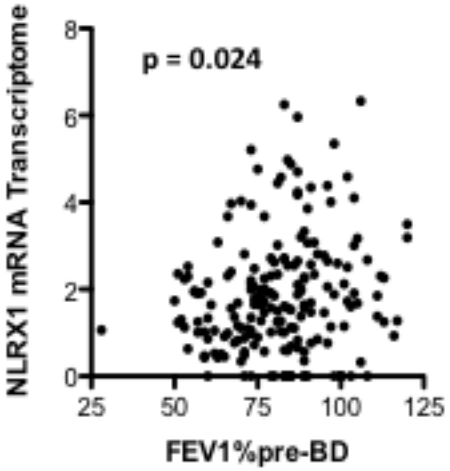
Korean COPD Cohort

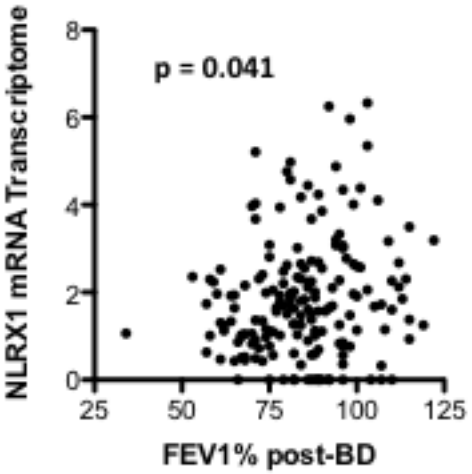


N = 94, 99



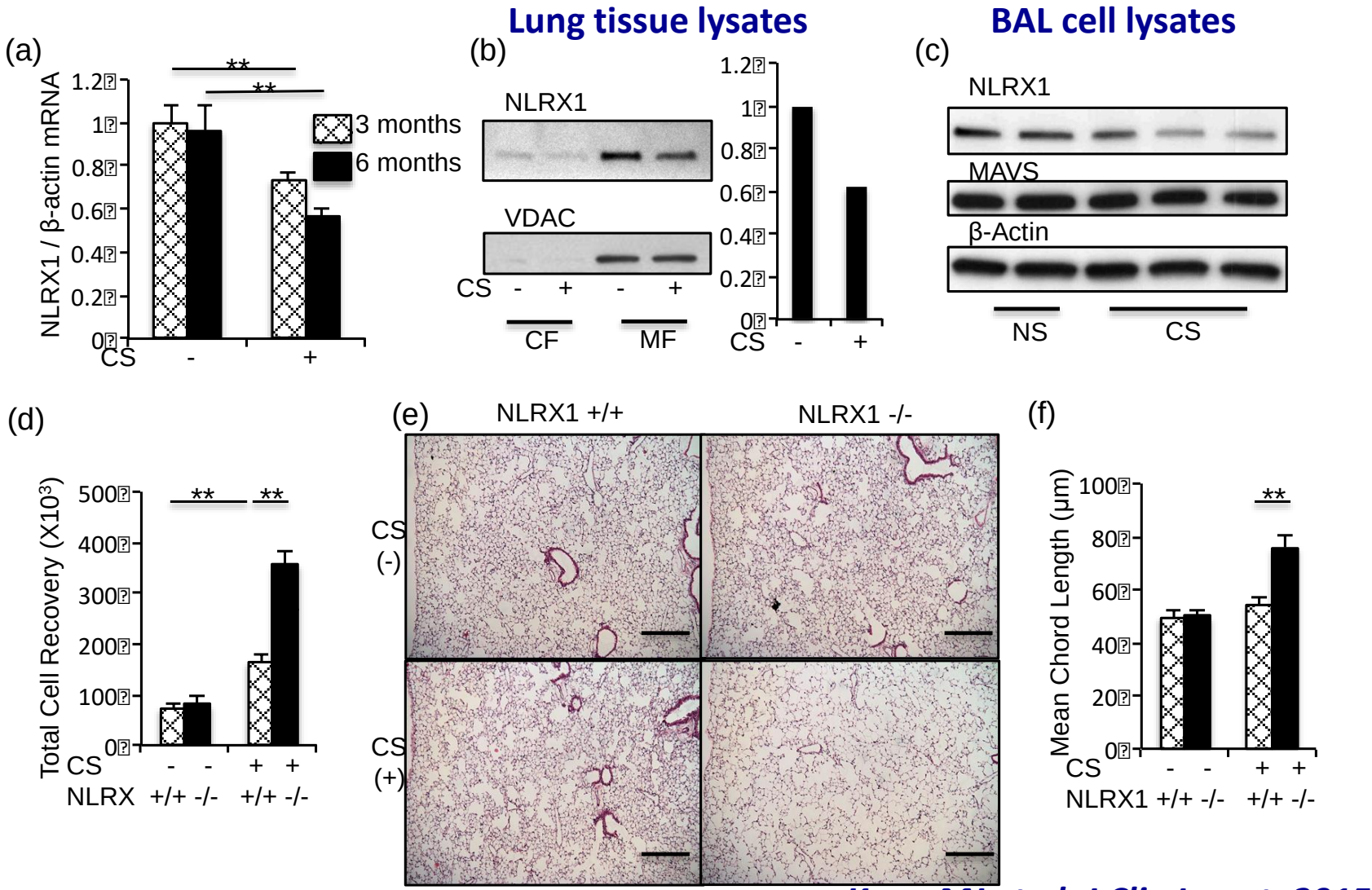
N = 94, 45, 53, 1





Kang MJ et al. J Clin Invest. 2015

Role of NLRX1 in murine COPD model



Kang MJ et al. J Clin Invest. 2015

NLRX1 - Beyond COPD

- ❑ COPD
- ❑ EAE
- ❑ Tumorigenesis
  - ✓ Colon cancer
  - ✓ H. Sarcoma

For further mechanistic understanding..

- ❑ **Inflammasomes**
- ❑ **Senescence**
- ❑ **Mitochondrial autophagy (Mitophagy)**

Senescence-Associated Secretory Phenotype and Its Possible Role in Chronic Obstructive Pulmonary Disease

Manish Kumar[1,2], Werner Seeger[1,2], and Robert Voswinckel[1,2]

AJRCMB. 2014;51:323 - 333

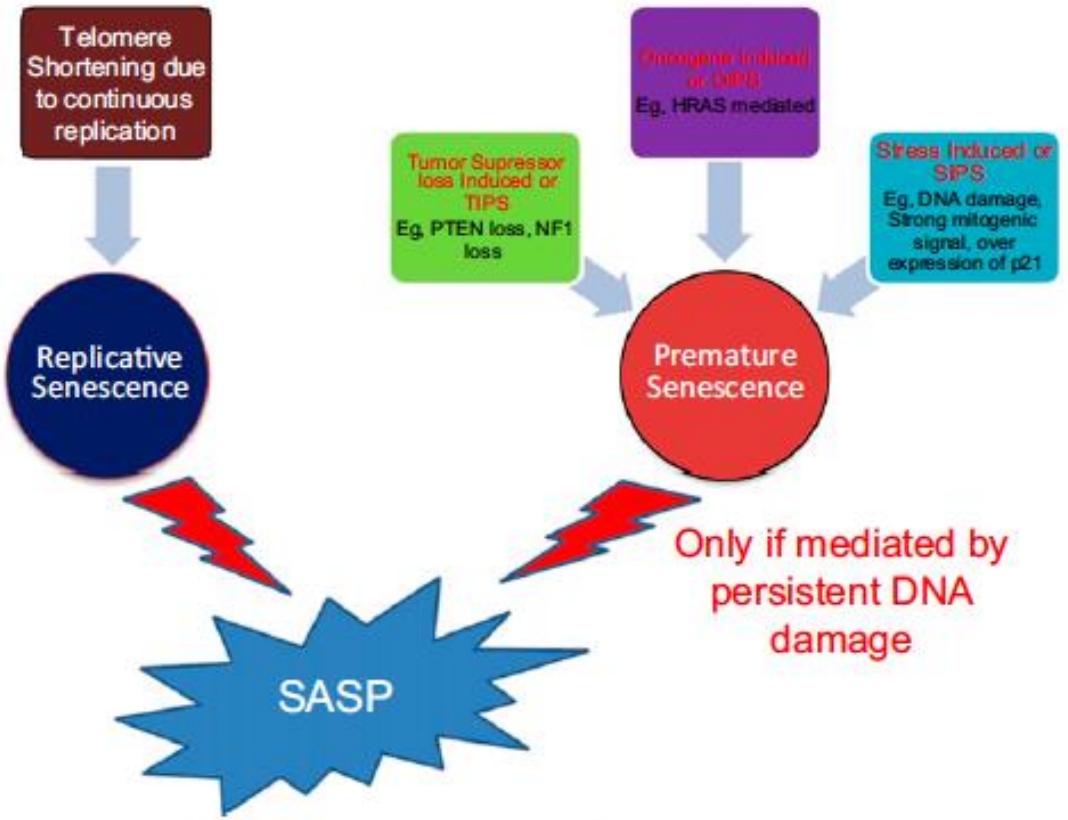
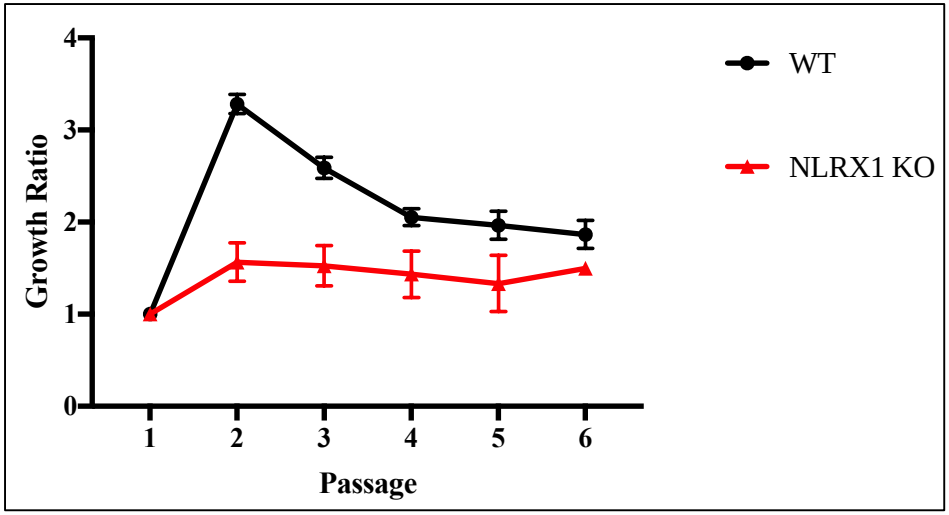
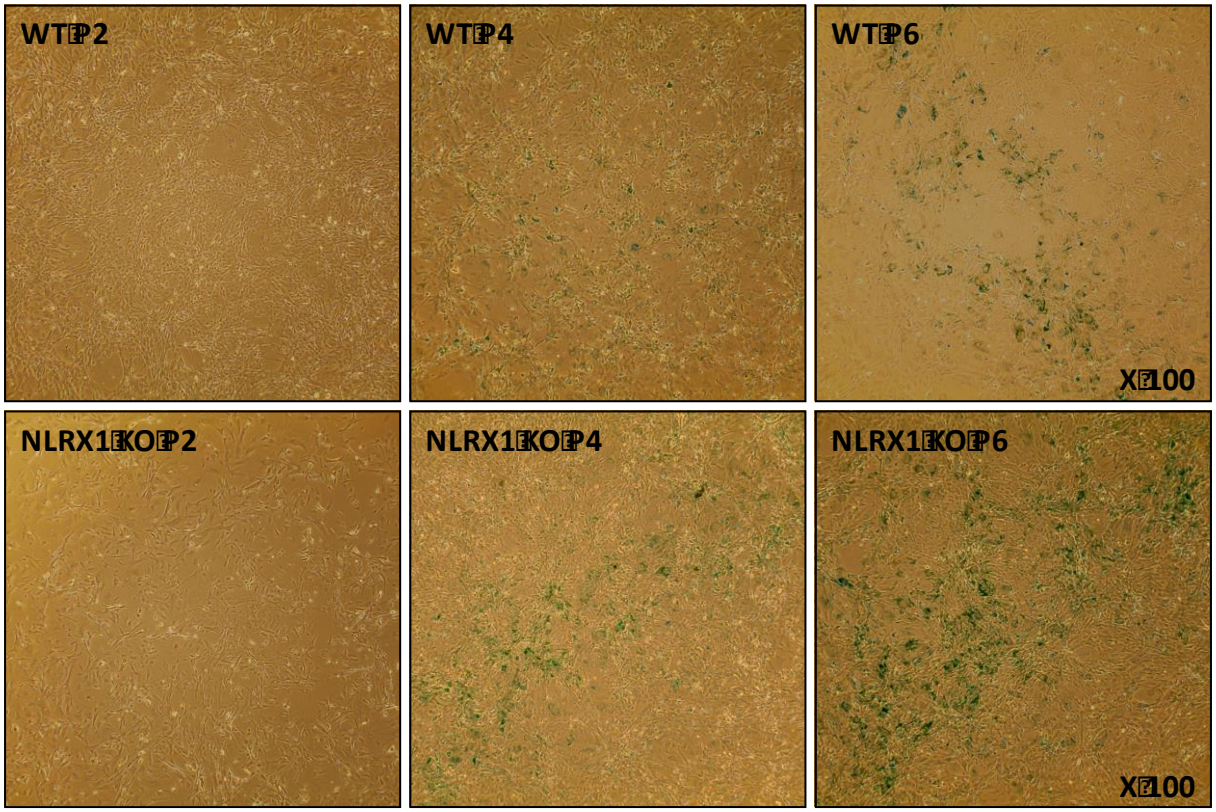


Figure 1. Many roads lead to senescence, but not all cause the senescence-associated secretory phenotype (SASP) response. HRAS, transfection of GTPase HRas; OIPS, oncogene-induced premature senescence; PTEN, phosphatase and tensin homolog; SIPS, stress-induced premature senescence.

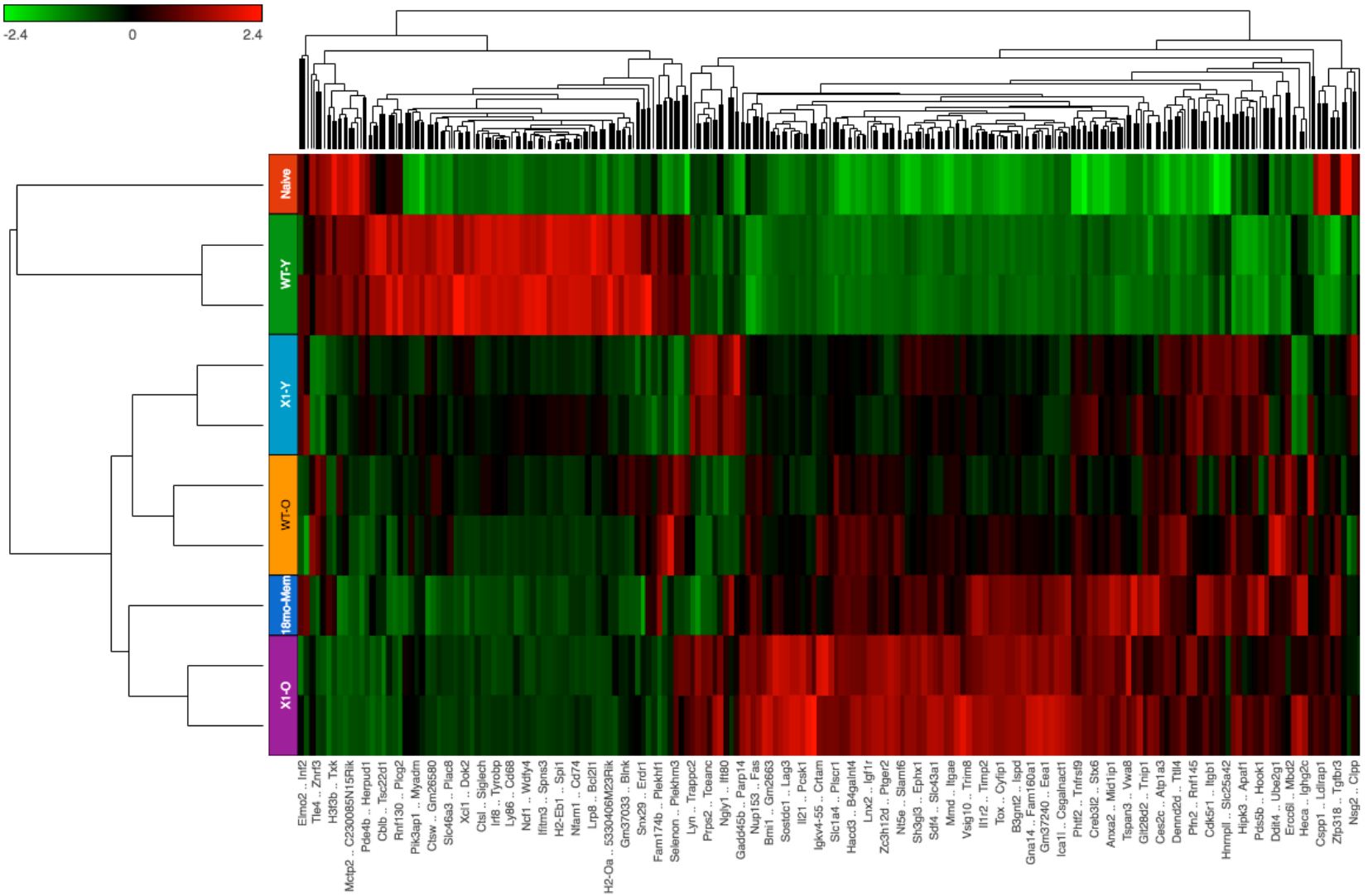
NLRX1 & Cell Senescence



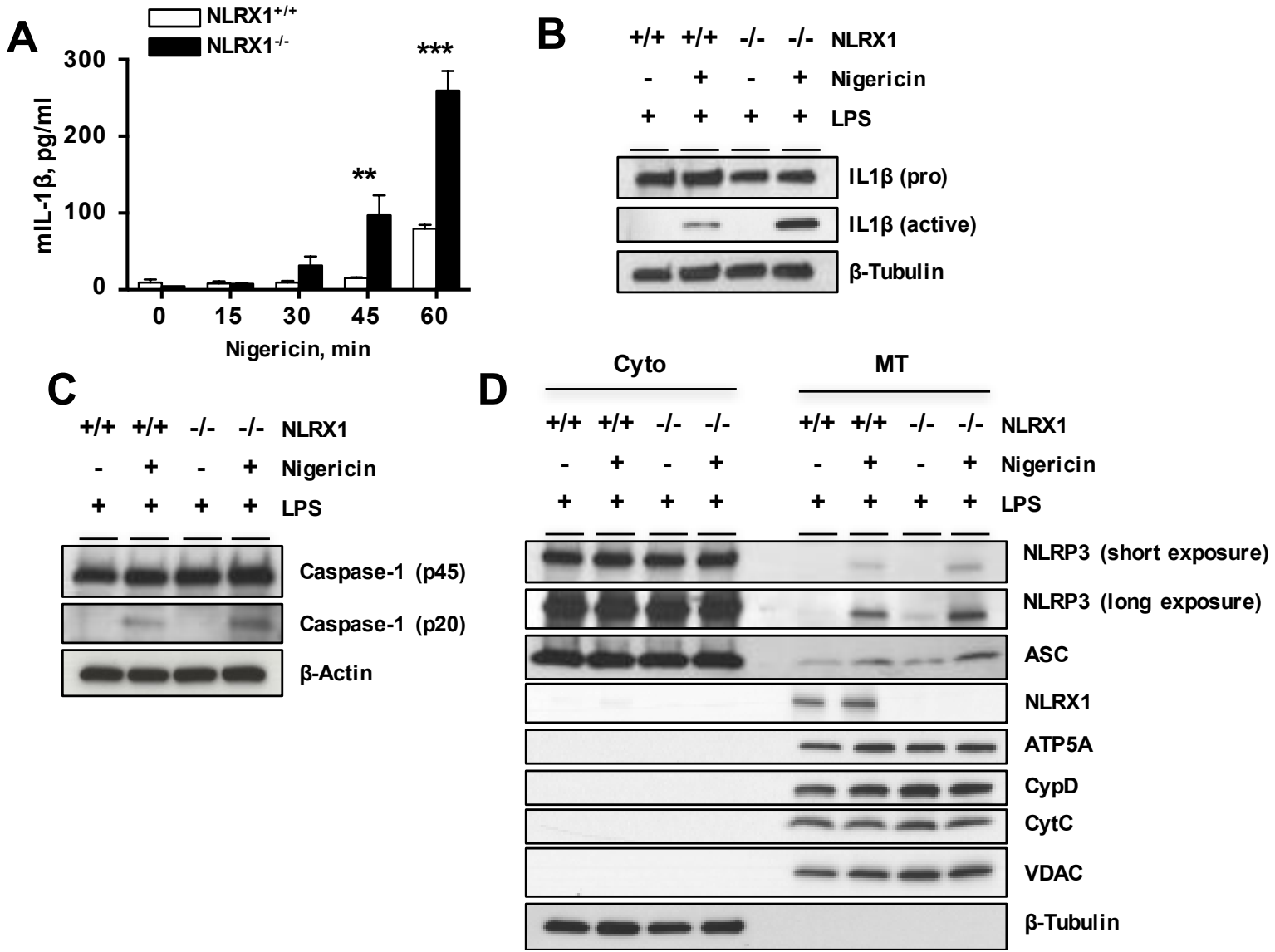


RNA-seq Data set (Heat map generated by Partek)

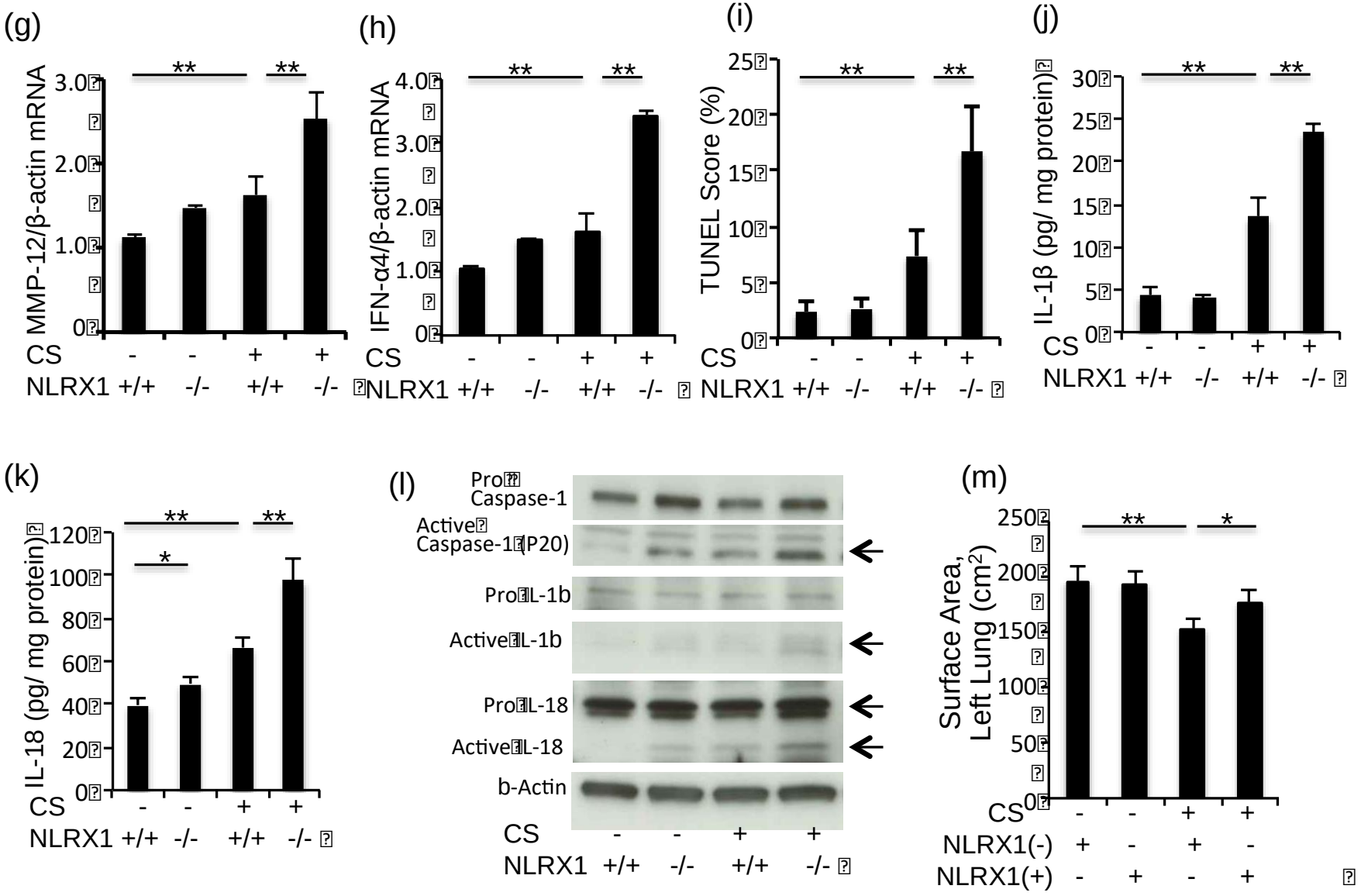
WT CD4 Naïve T cell (3m); WT CD4 Memory T cells (3m); KO CD4 Memory T cells (3m); WT CD4 Memory T cells (12m); KO CD4 Memory T cells (12m); WT CD4 Memory T cells (18m)



Role of NLRX1 in Inflammasomes Activation



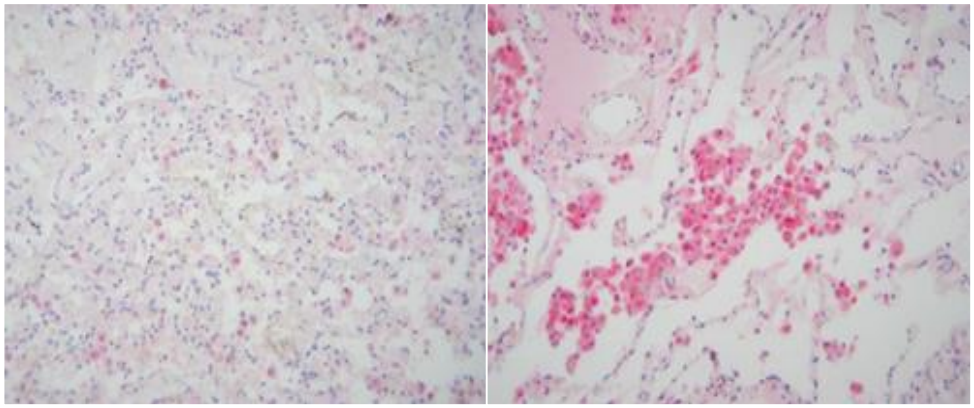
Role of NLRX1 in murine COPD model

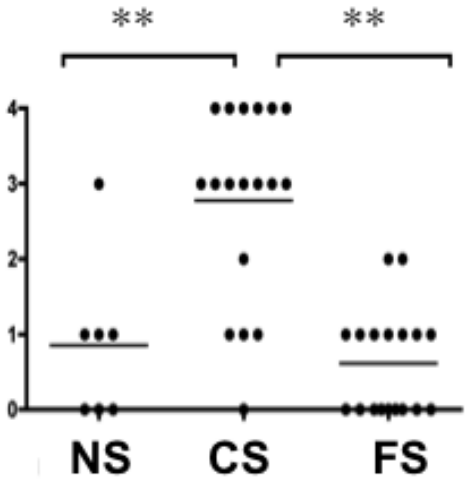


IHC: IL-18

(Human)

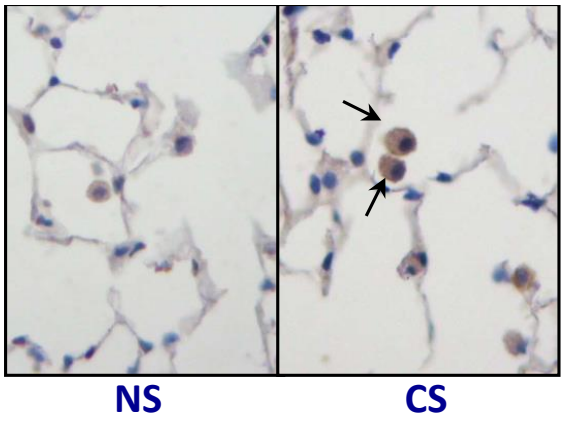
Non-smoker Active smoker



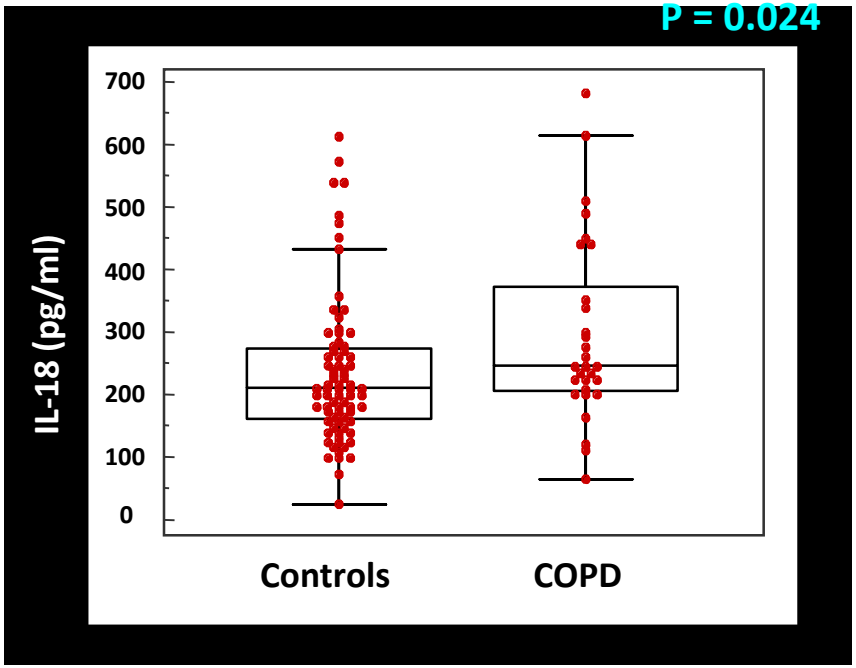


Kang MJ et al. J Immunol. 2007

(Mouse)



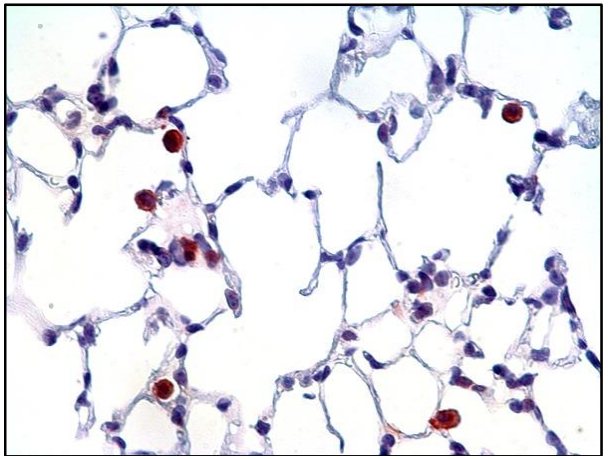
Increase of Serum IL-18 in COPD patients



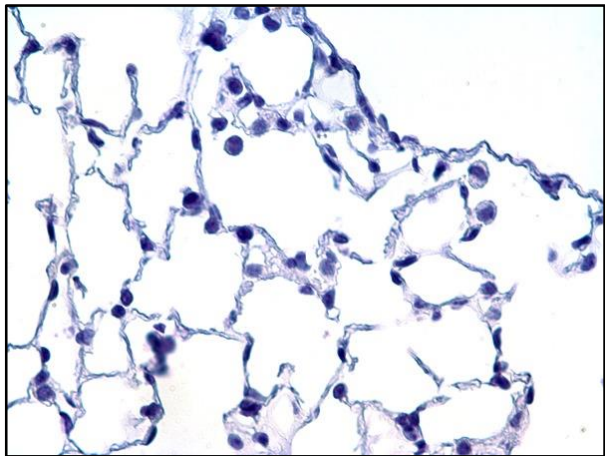
NLRX1 – the site of expression in lungs

Mouse

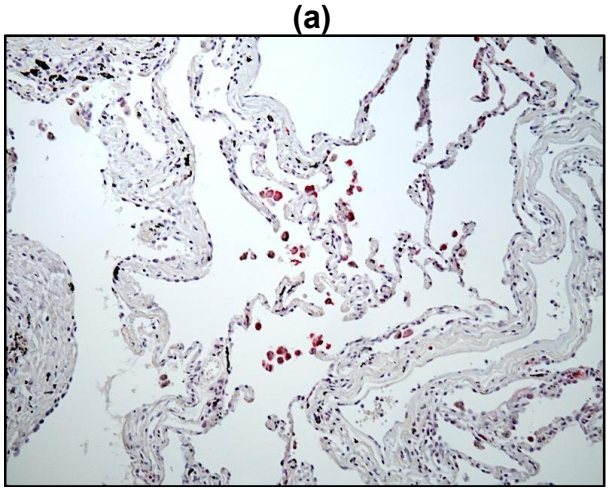
WT non smoking control

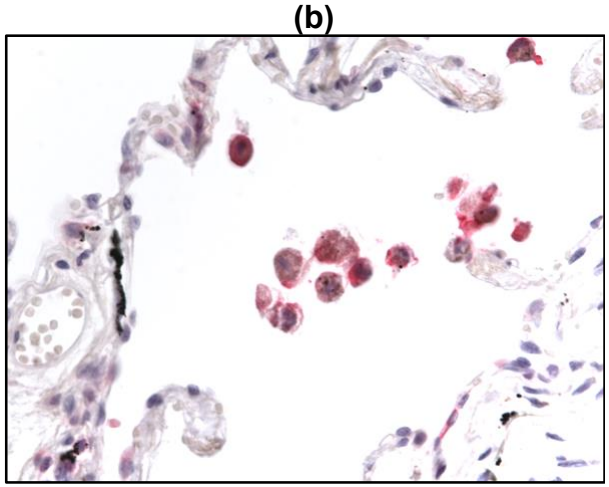


NLRX1$^{-/-}$ control

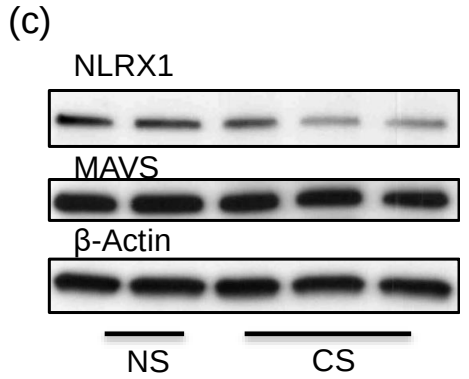


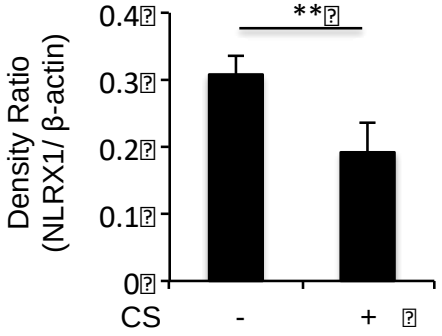
Human





Westernblot Analysis (BAL cells)

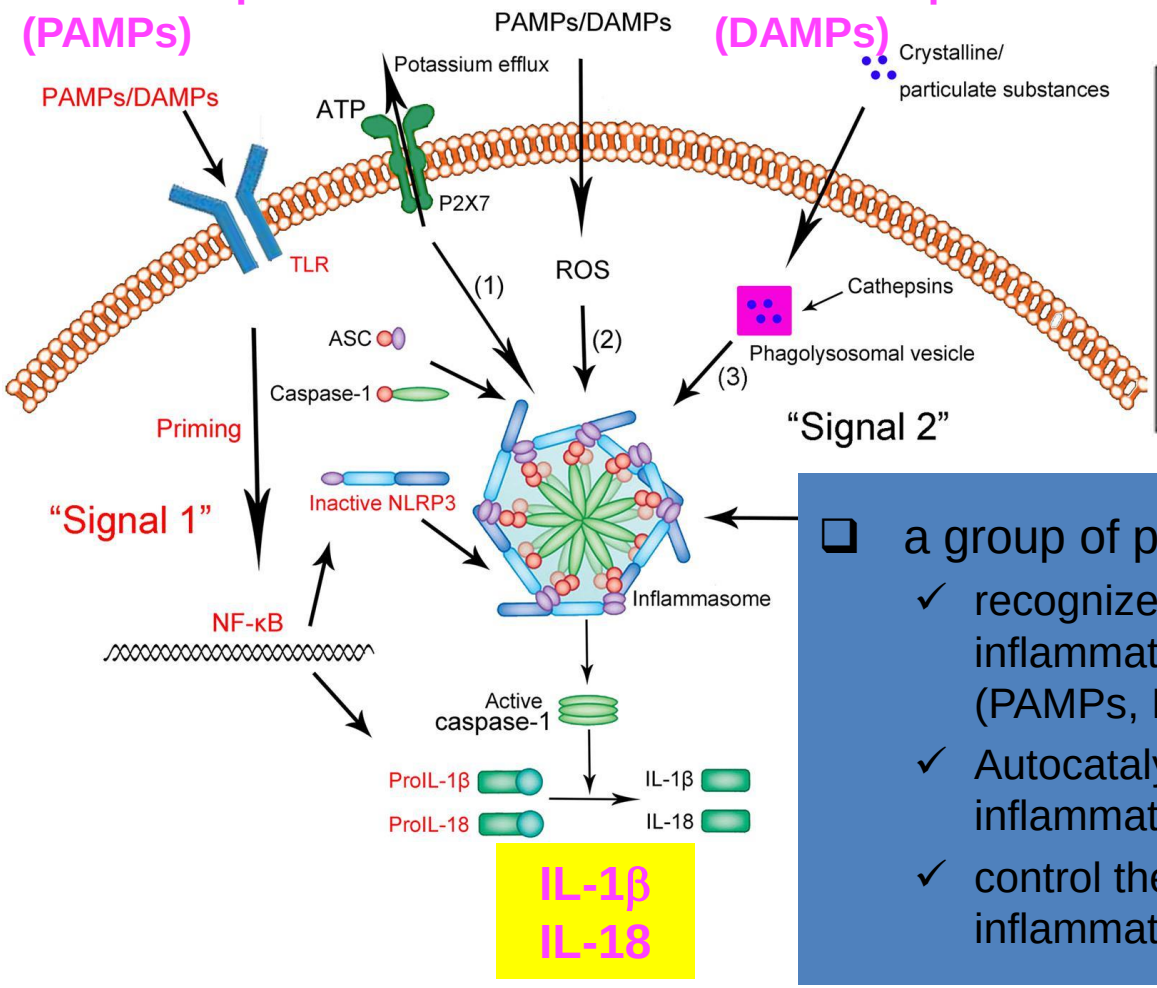


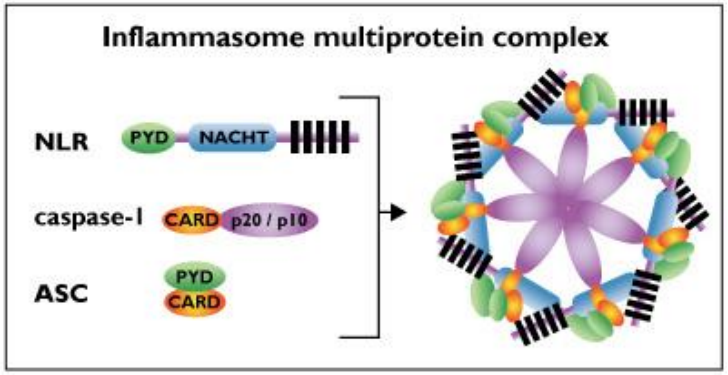


Inflammasome
- assembly mechanism, regulation & signaling

pathogen-associated molecular patterns (PAMPs)

danger-associated molecular patterns (DAMPs)

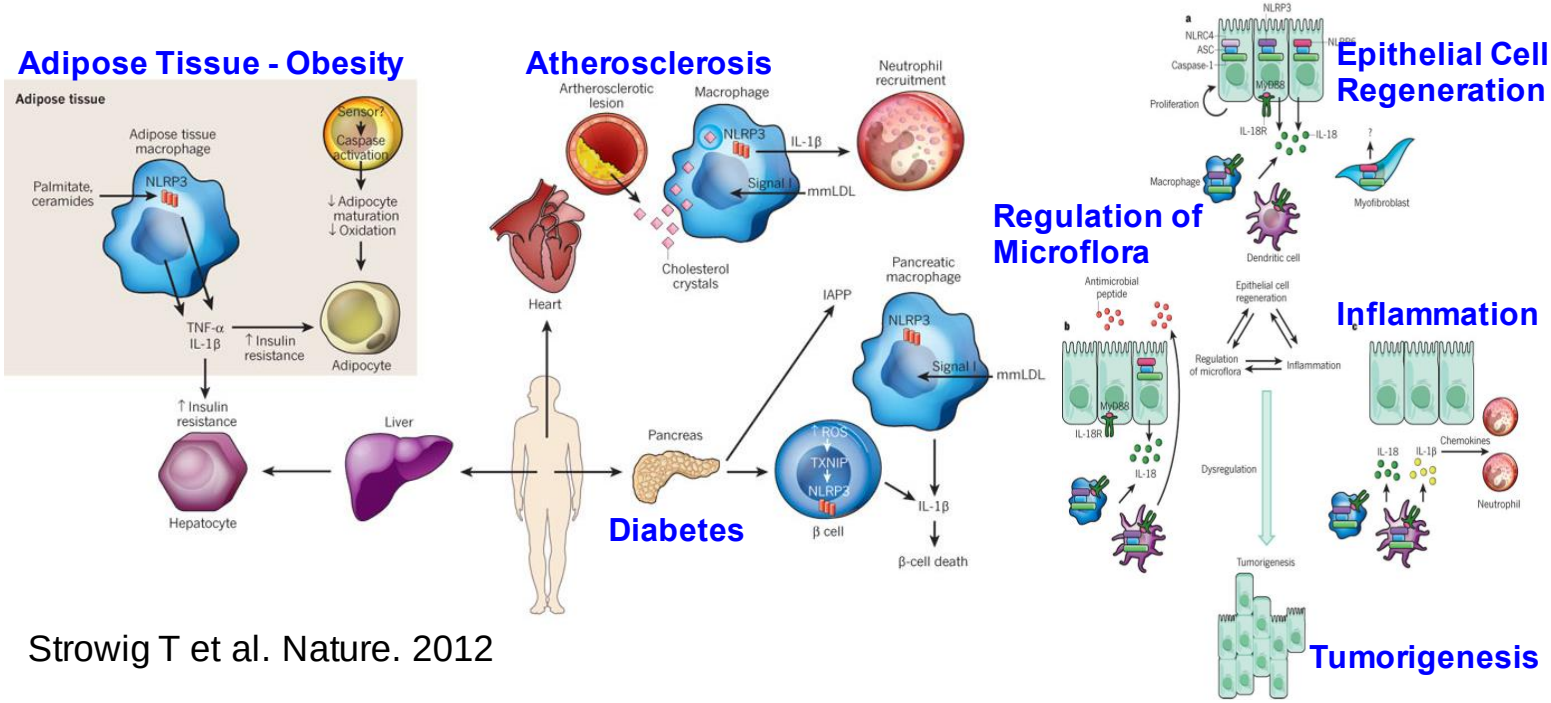




- a group of protein complexes
  - ✓ recognize a diverse set of inflammation-inducing stimuli (PAMPs, DAMPs)
  - ✓ Autocatalytic activation of inflammatory caspases (caspase-1)
  - ✓ control the activation of pro-inflammatory cytokines (IL-1β, IL-18)

Inflammasomes in Health & Disease

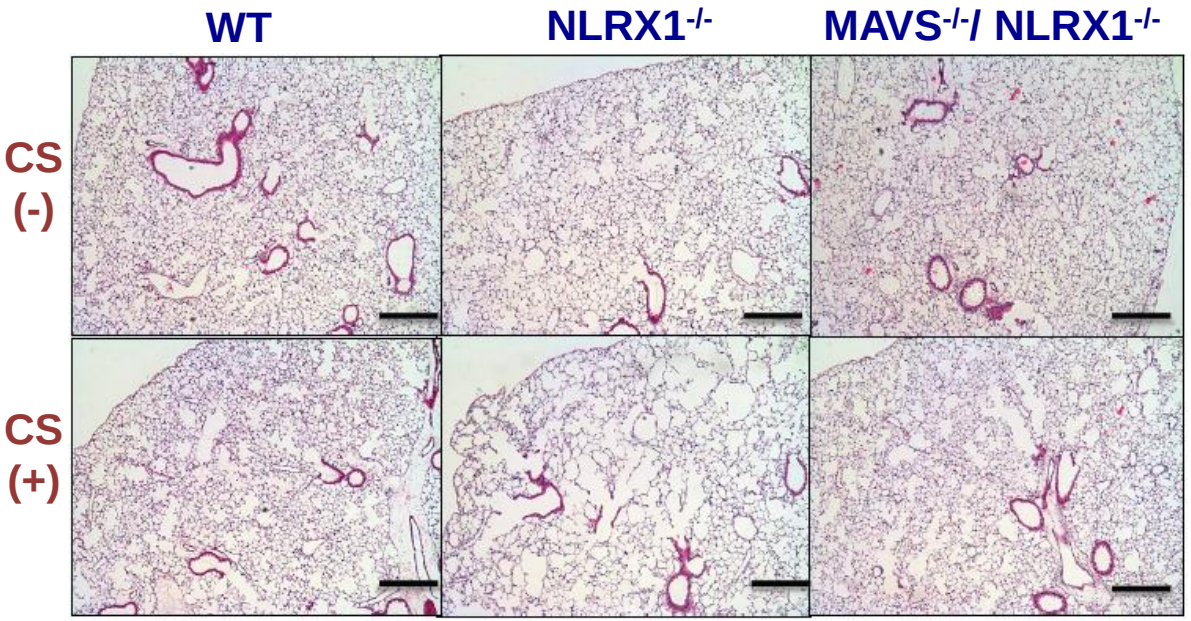
- A central player in innate immune and inflammatory responses.
- During infection or injury, inflammasomes are activated and, under normal circumstances, culminate in the resolution of infection or inflammation and return to homeostasis. However, inappropriate or chronic activation of inflammasomes can lead chronic inflammation and autoimmune disease states.

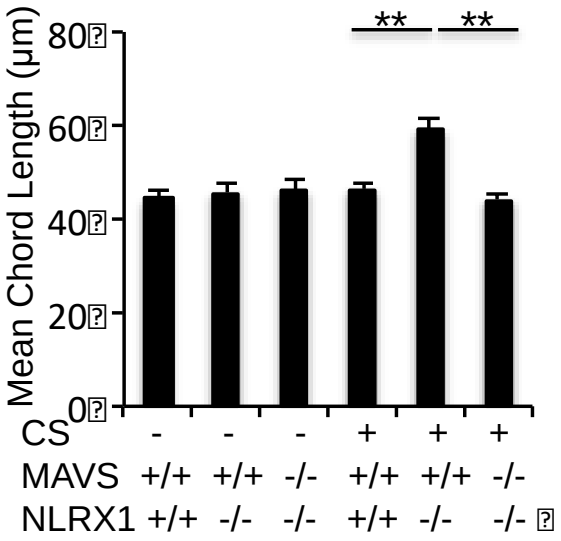


Strowig T et al. Nature. 2012

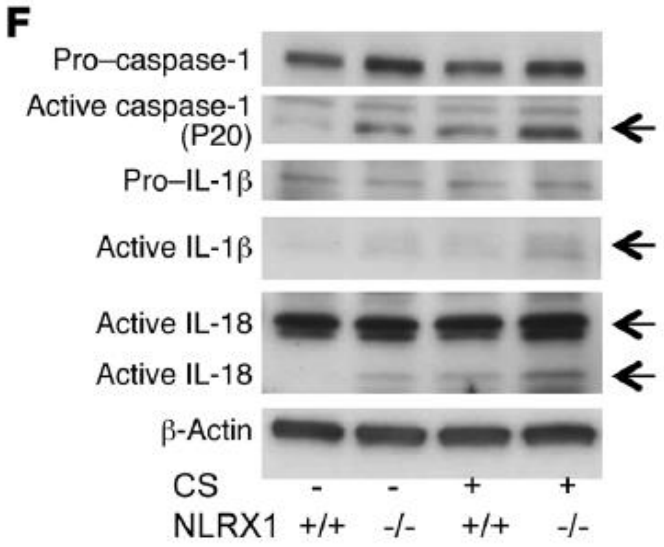
MAVS-dependent Emphysema

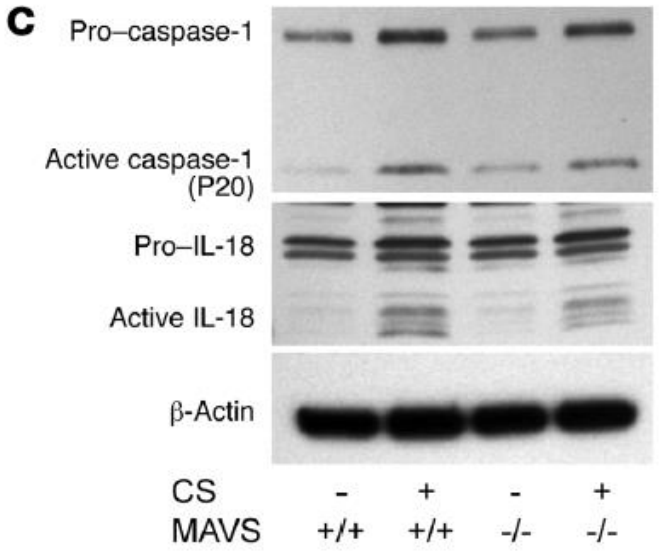
Figure. Representative histologies and measurements of alveolar surface area after 3-month-CS-exposure in wild type (WT) controls, NLRX1$^{-/-}$ and NLRX1$^{-/-}$/MAVS$^{-/-}$ mice (** p < 0.01, two-way ANOVA test; size bar = 400μm).





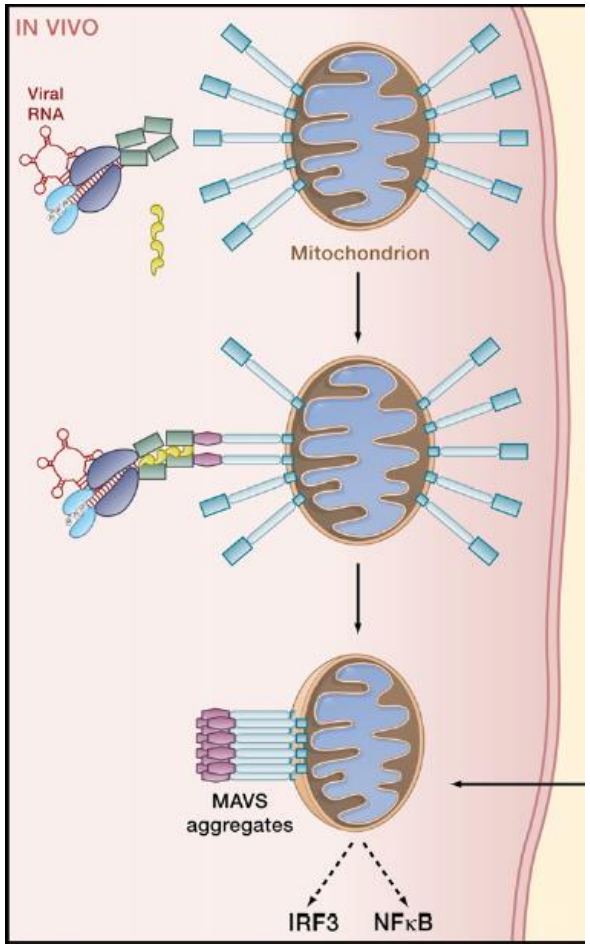
MAVS-dependent Inflammasomes in CS-induced Inflammation *in vivo*



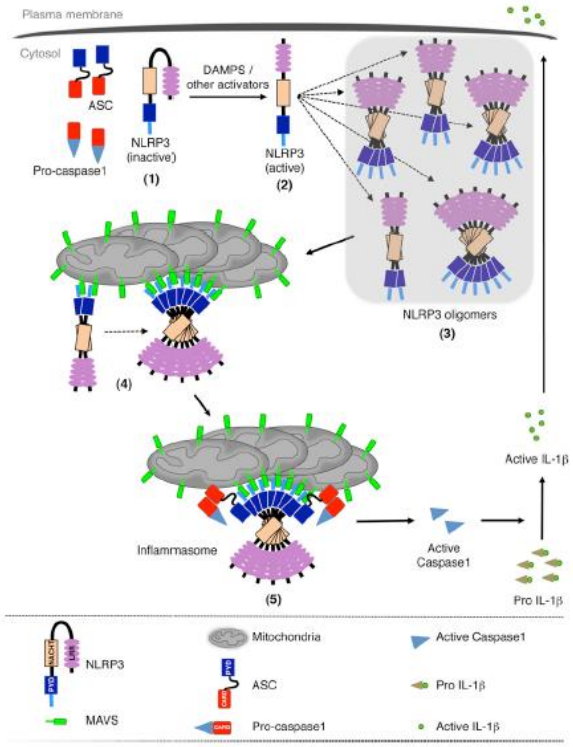


-> To explore further mechanism(s) by which **NLRX1 inhibits inflammasomes activation in the context of *in vivo* CS-induced inflammation**

Multimeric aggregation of MAVS : a critical event of its signaling

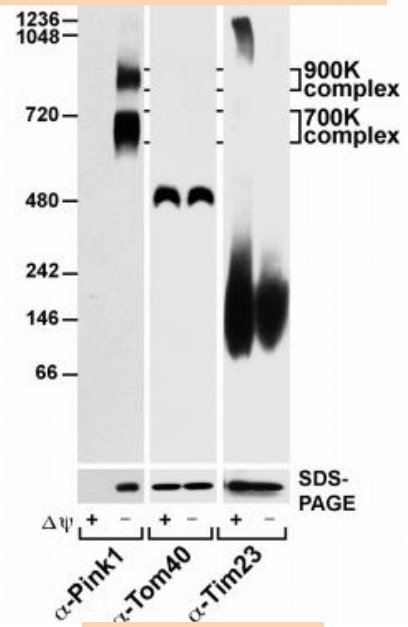


Hou F et al Cell. 2011

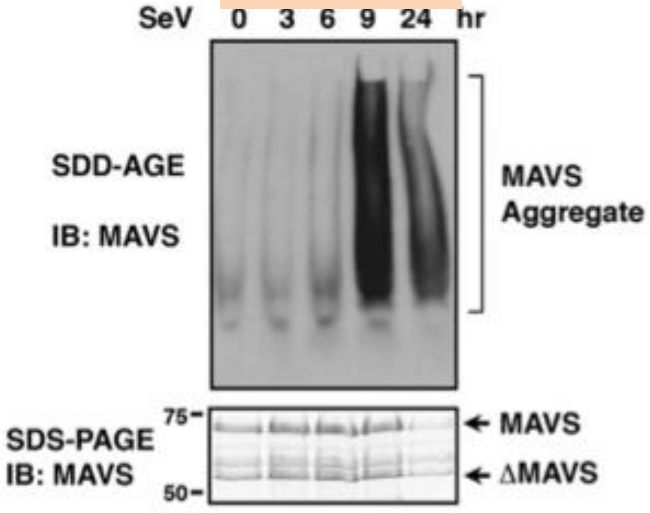


*Cell.*2013;153:348– 361

Blue Native PAGE

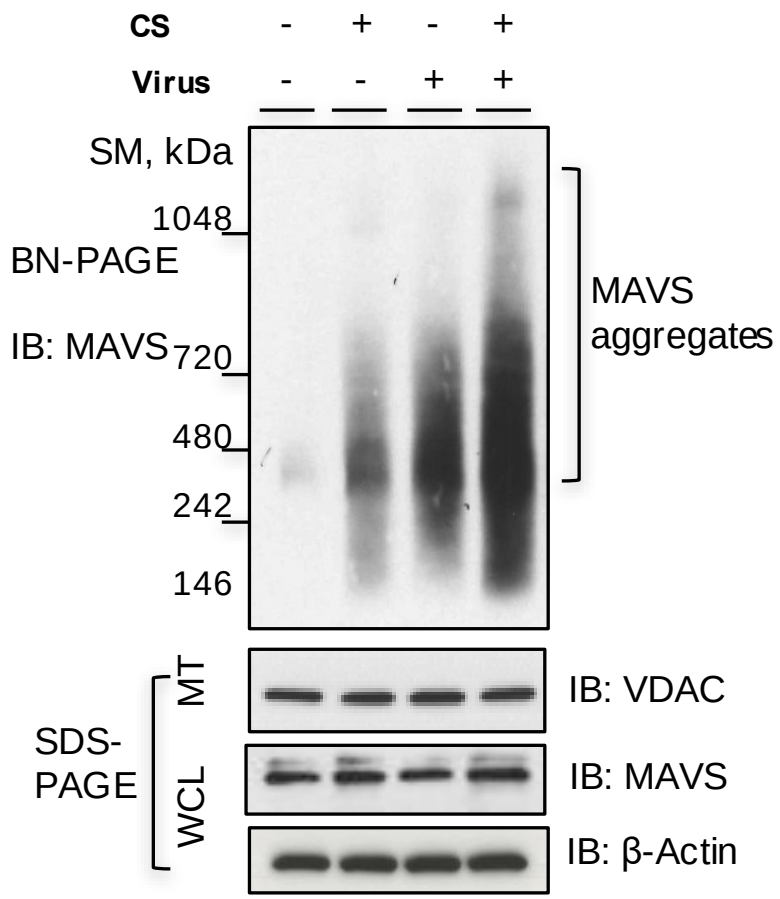


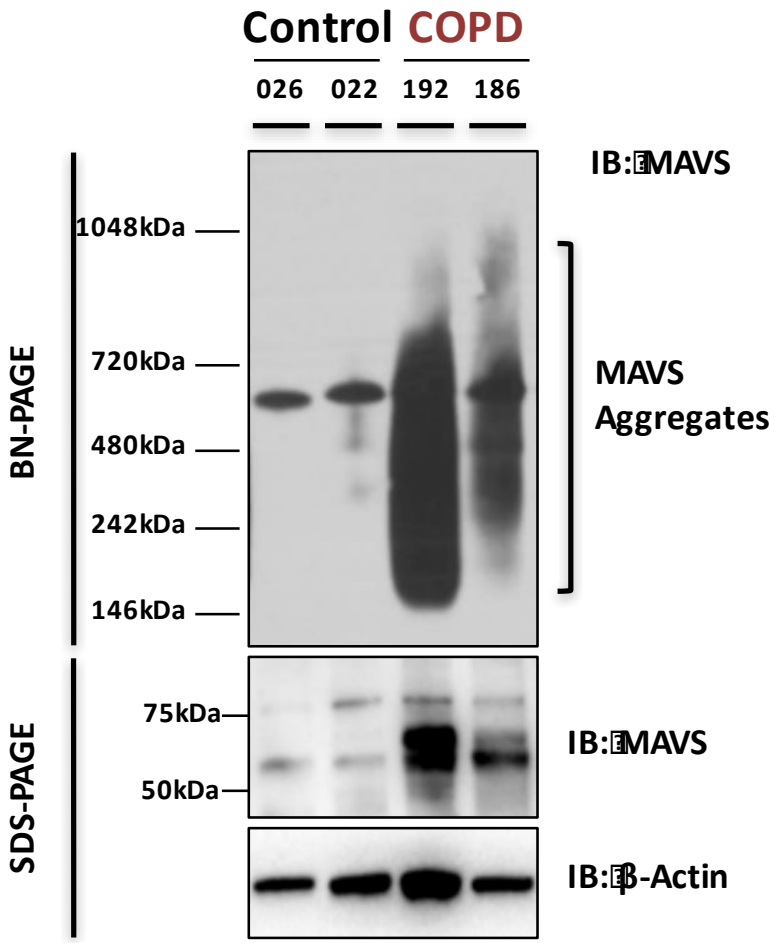
SDD-AGE

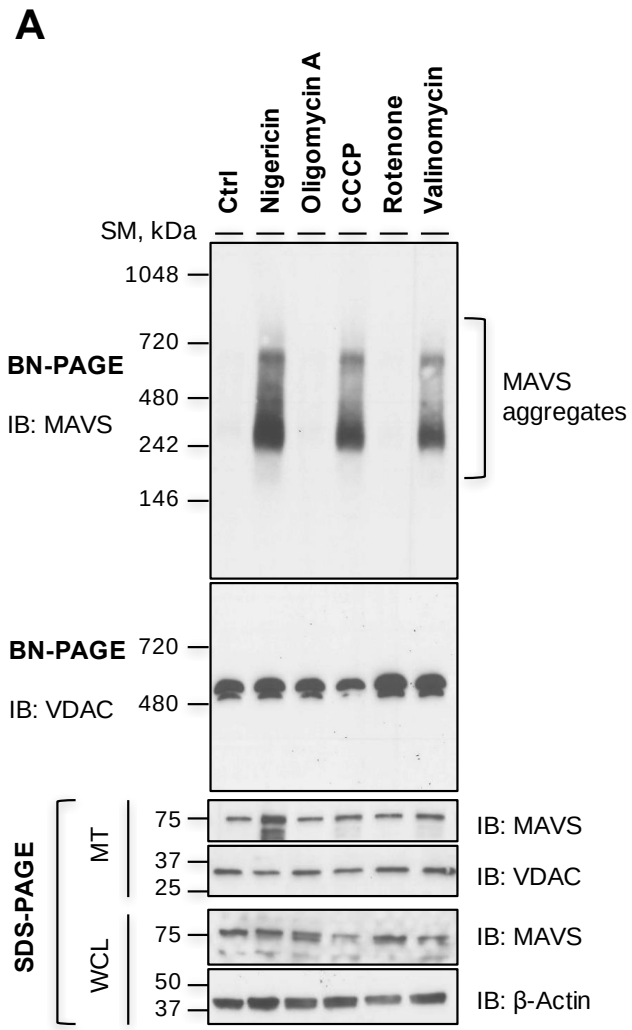


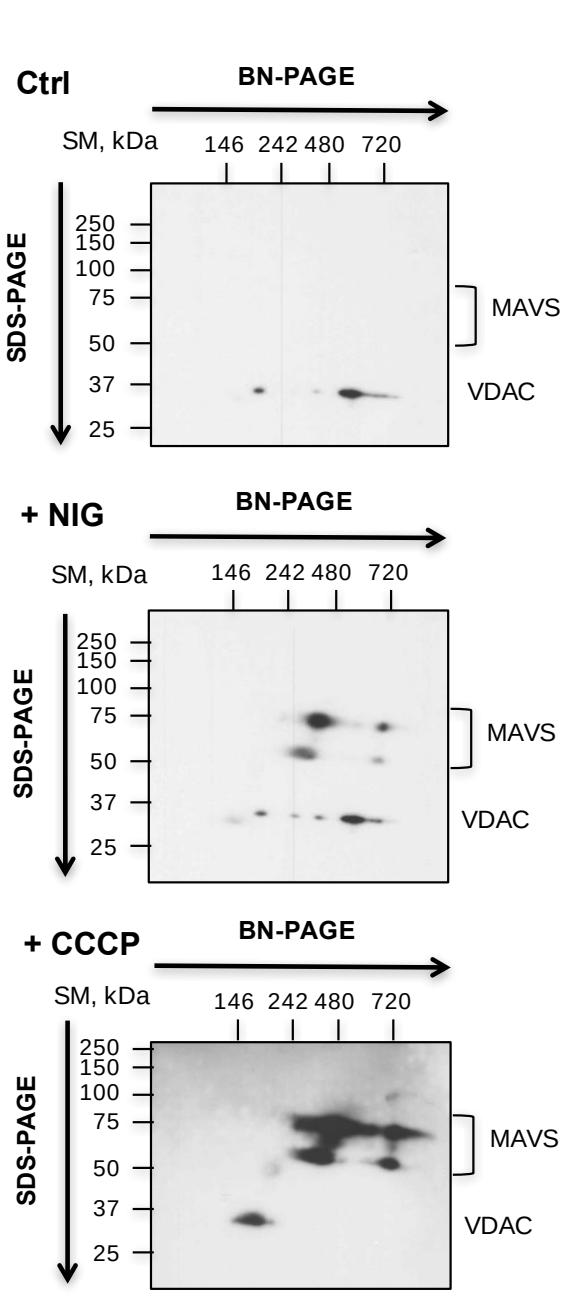
Human Relevance ?

Fig. 8 The exaggerated MAVS aggregation in CS-induced or associated inflammation



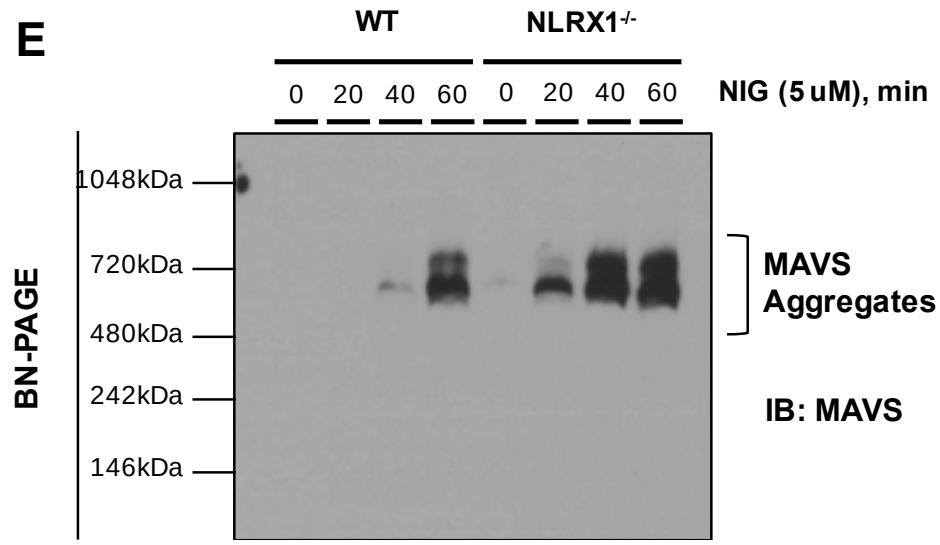


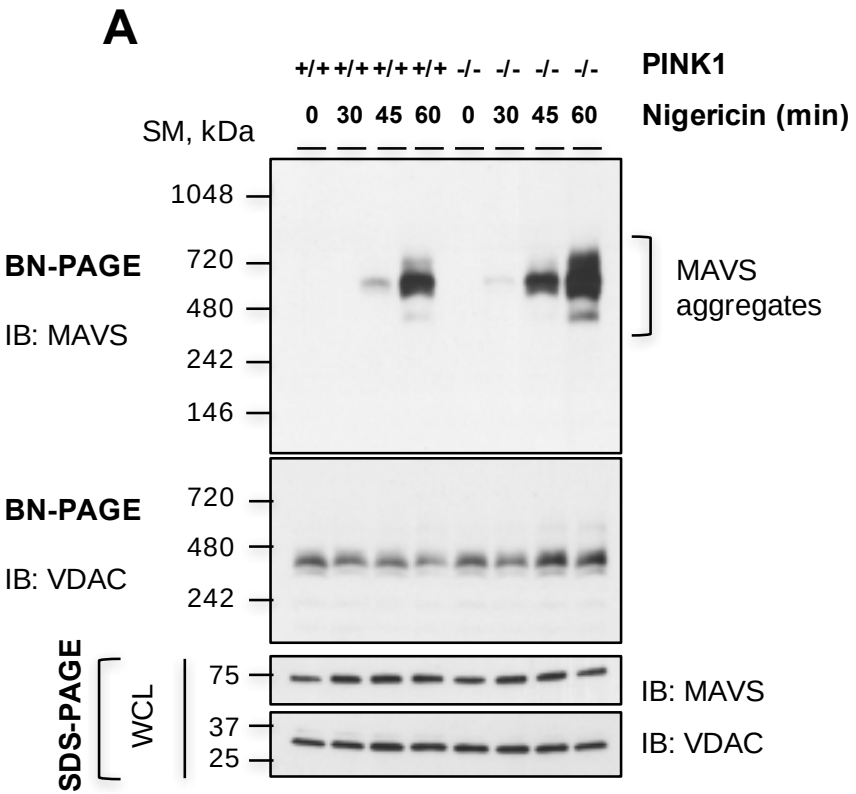


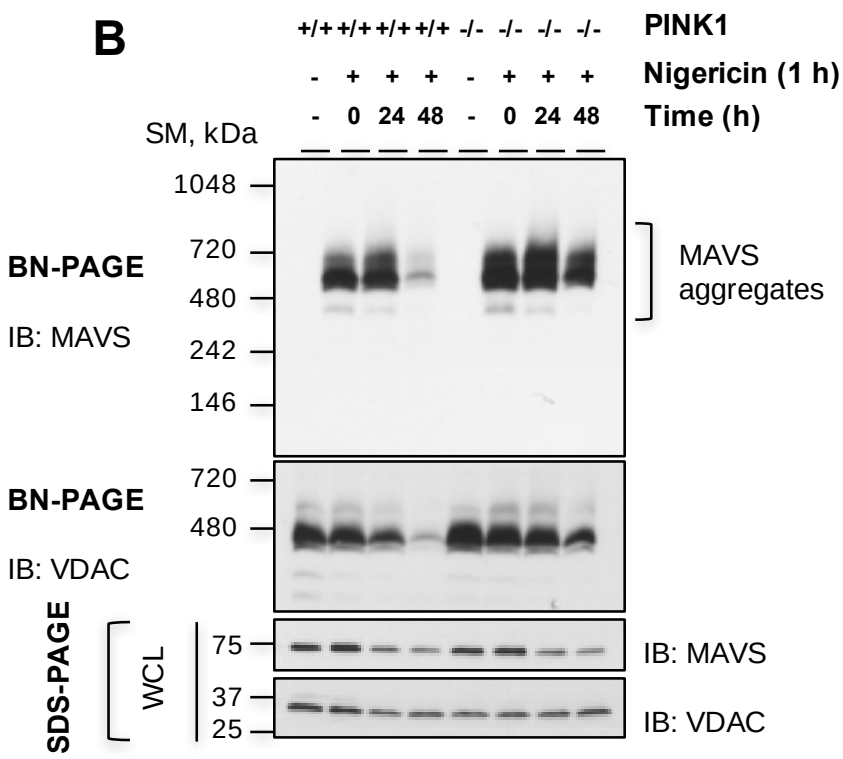


MAVS aggregation-inducing mitochondrial stimuli

Alteration of MAVS aggregation

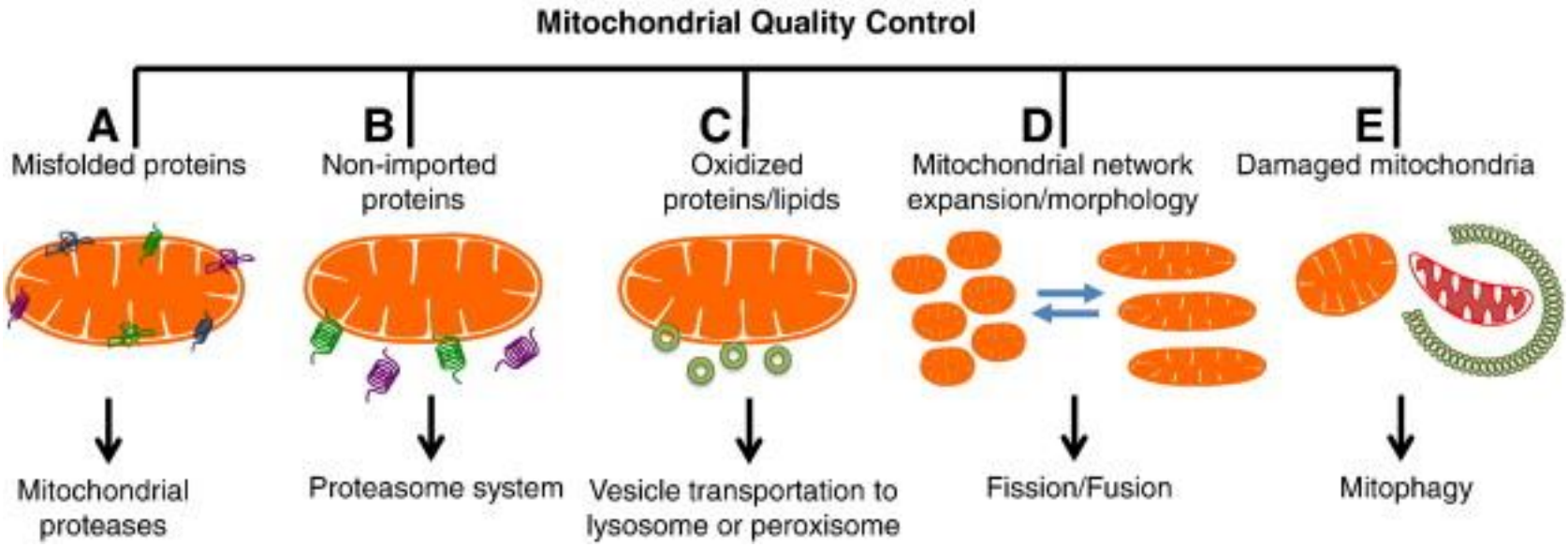




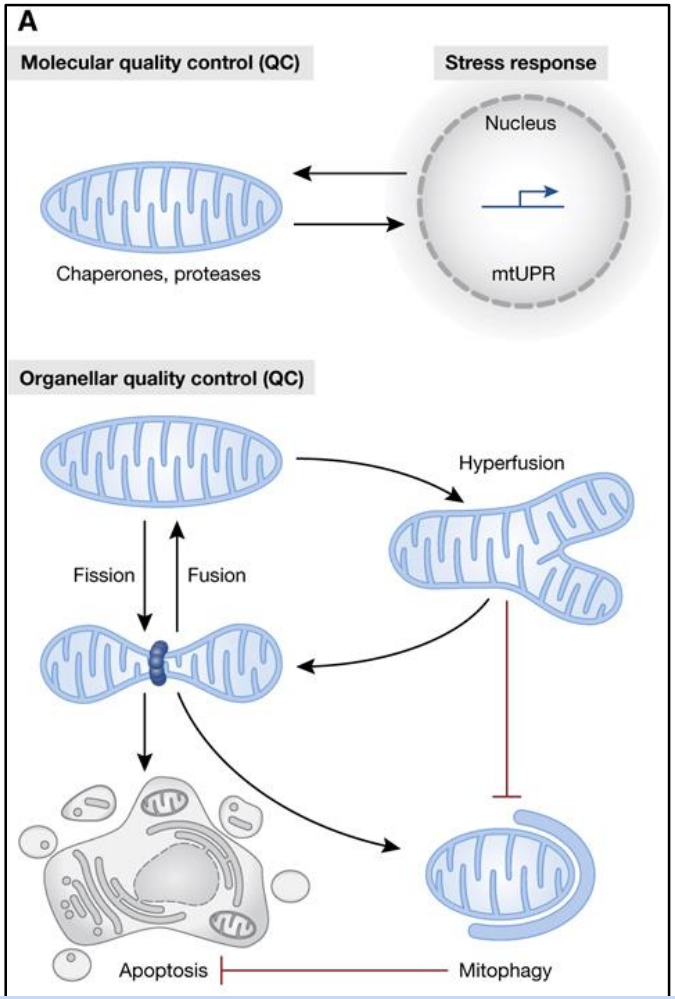


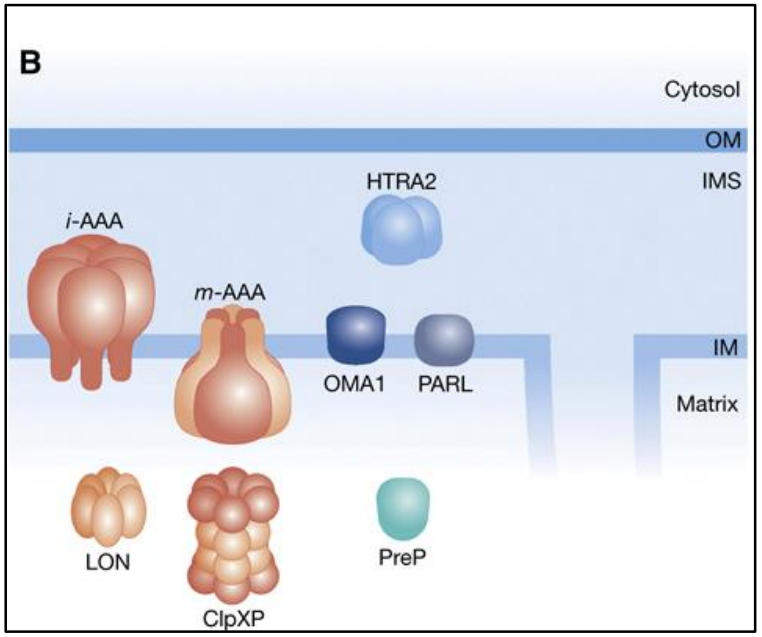
Mitochondrial Quality Control (MQC)

- MQC: A set of evolutionary conserved mechanisms to maintain mitochondrial health



MQC: a matter of life and death for cells





(A) The hierarchical network of mitochondrial QC mechanisms.
(B) Submitochondrial localization of proteases with functions in mitochondrial QC.

Rugarli E et al. Embo J. 2012

Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance

Sarah Pickles[1], Pierre Vigié[2,3], and Richard J. Youle[1,*]
[1]Biochemistry Section, Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA
[2]CNRS, IBGC, UMR5095, 1 rue Camille Saint-Saëns, F-33000 Bordeaux, France

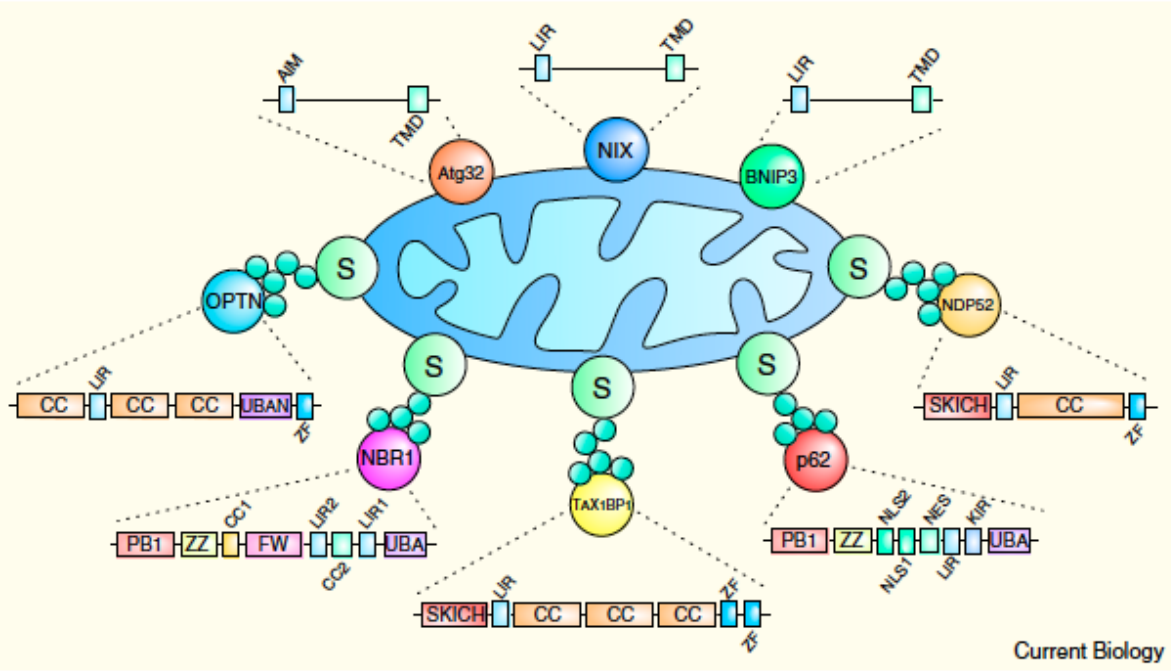
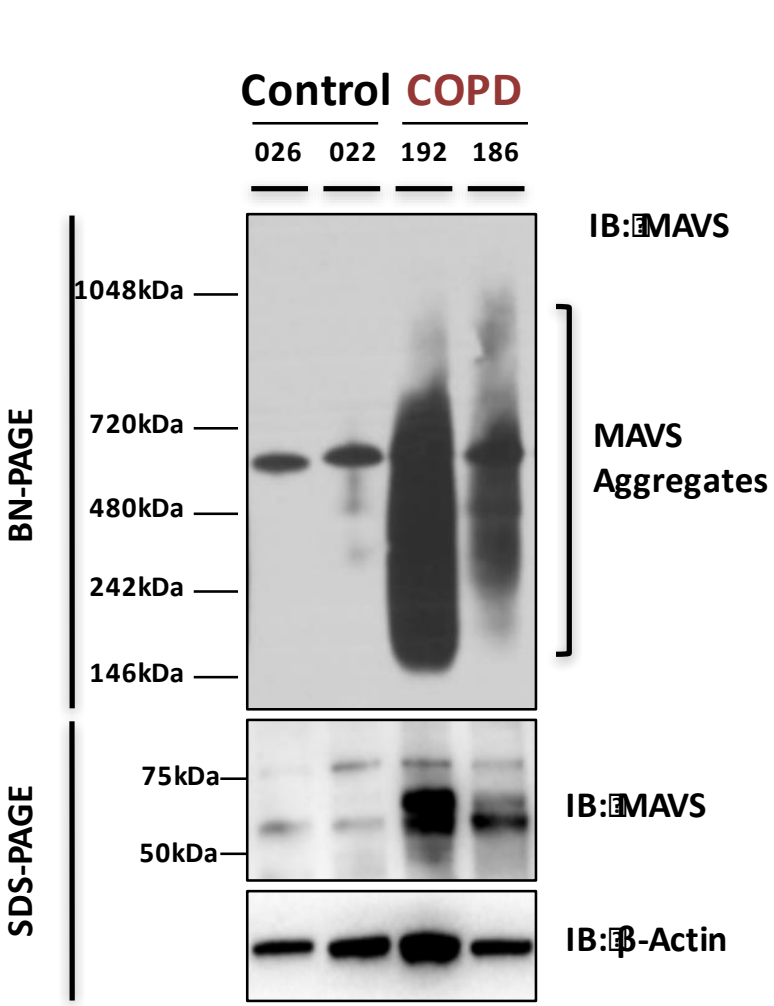
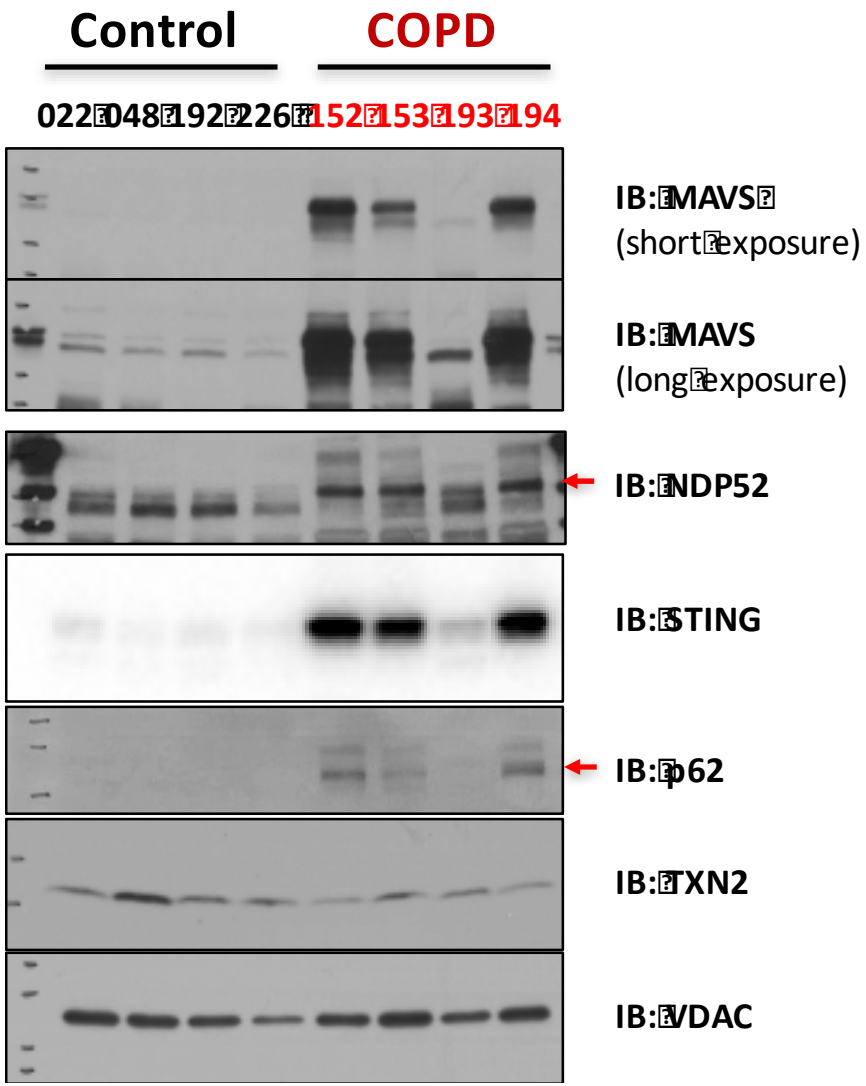


Figure 1. Functional domains of autophagy receptor proteins that operate in mitophagy.
The mitophagy receptors Atg32, NIX and BNIP3 are localized to the mitochondrial outer membrane and schematics of their functional domains are depicted: AIM, Atg8 family interacting motif; TMD, transmembrane domain; LIR, LC3-interacting region. Autophagy receptor proteins involved in mitophagy are shown bound to ubiquitinated mitochondrial substrates (S) and similarly their functional domains are shown: CC, coiled-coil domain; UBAN, ubiquitin binding in ABIN and NEMO domain; ZF, zinc-finger domain; PB1, Phox and Bem1 domain; ZZ, ZZ-type zinc finger domain; FW, four tryptophan domain; UBA, ubiquitin associated domain; SKICH, SKIP carboxyl homology domain; NLS, nuclear localization signals; KIR, Keap interacting region.

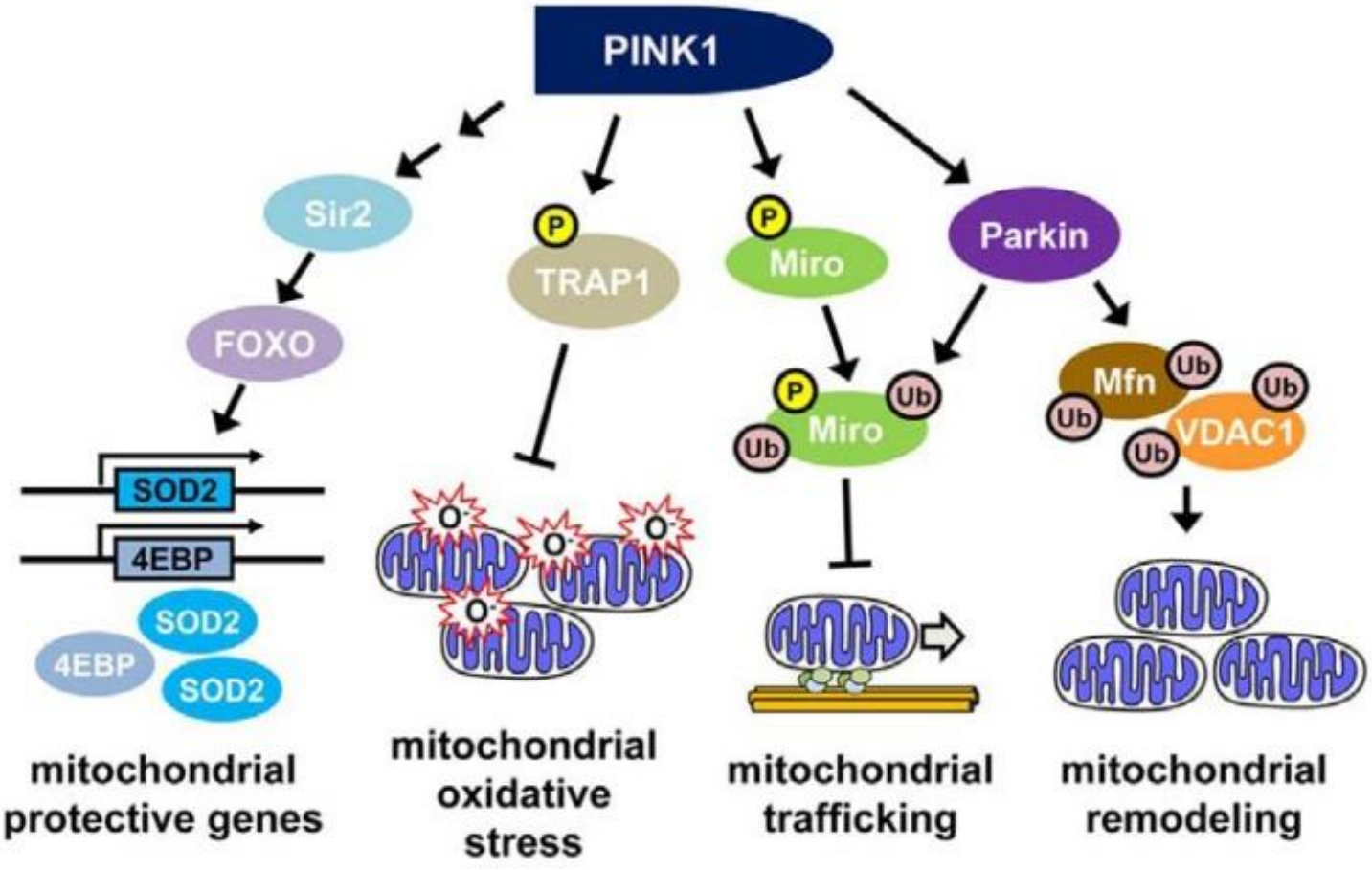
- Mitophagy: a selective removal of mitochondria via autophagy
- During autophagic process, cytoplasmic components are selected and tagged before being sequestered into an autophagosome by means of , so called, "autophagy receptors."
- The recognition of target mitochondria by the autophagosome occurs often through similar receptors, for which a term called mitophagic receptors has been designated.

Accumulation of Mitophagic Receptors on Mitochondria

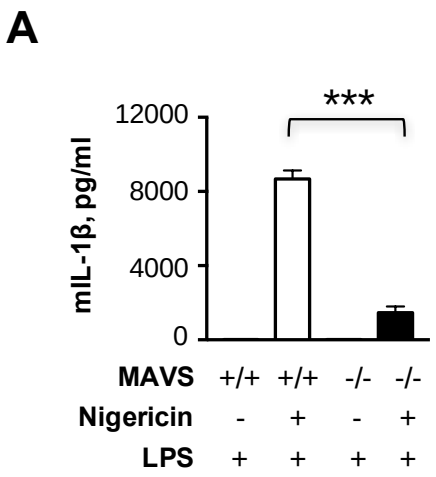


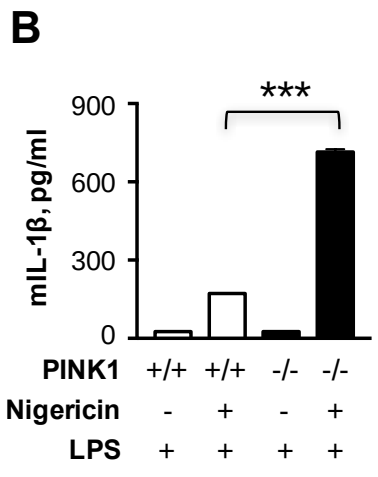


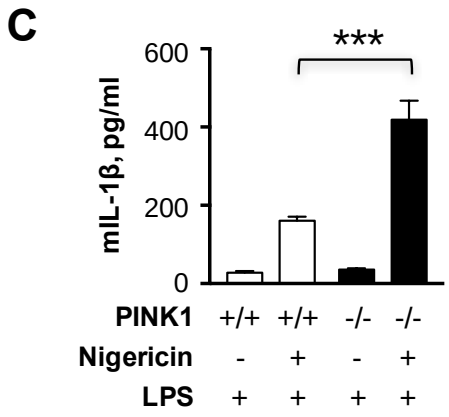
PINK1
– a Regulator of Mitochondrial Health

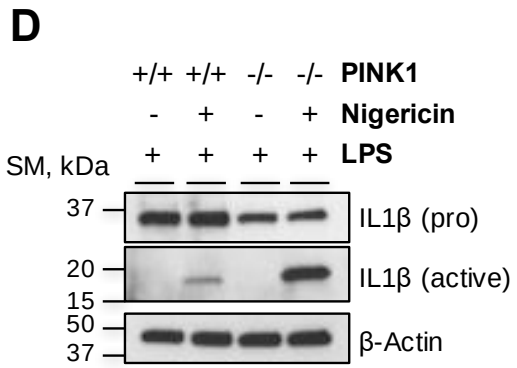


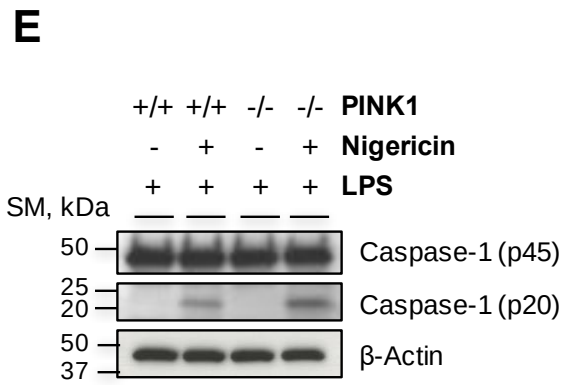
PINK1 inhibits MAVS-mediated inflammasomes activation and its signaling

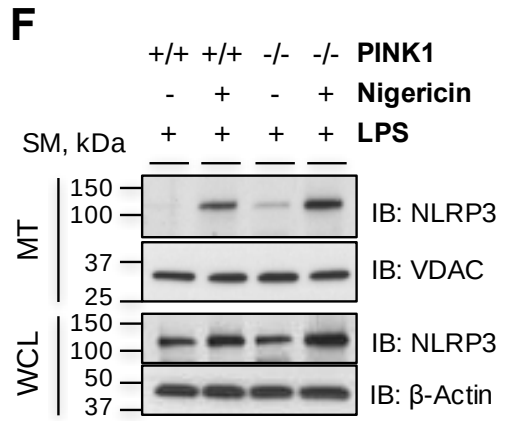




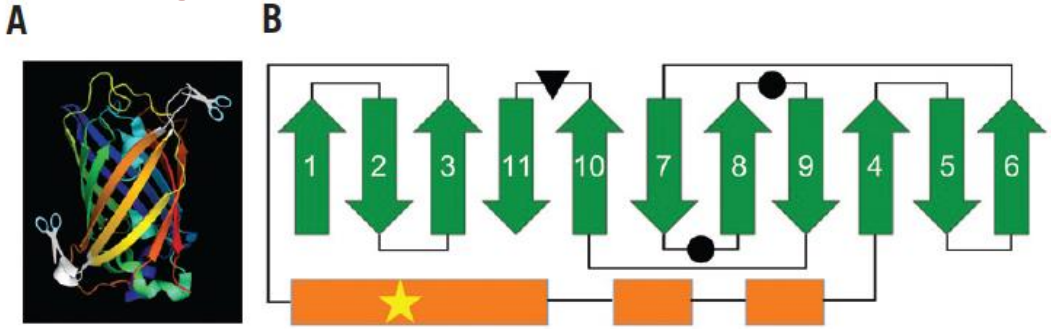




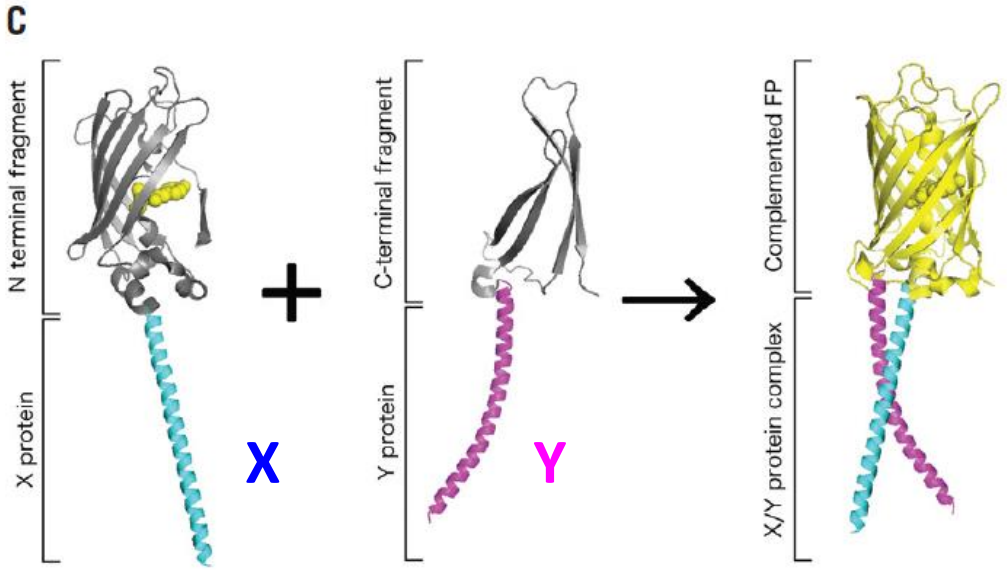




BiFC (Bimolecular Fluorescence Complementation)



Over the past decade, BiFC has emerged as a key technique to visualize protein-protein interactions in a variety of model organisms.



A. 3-dimensional structure of a fluorescent protein, Venus (β-strands & α-helices)

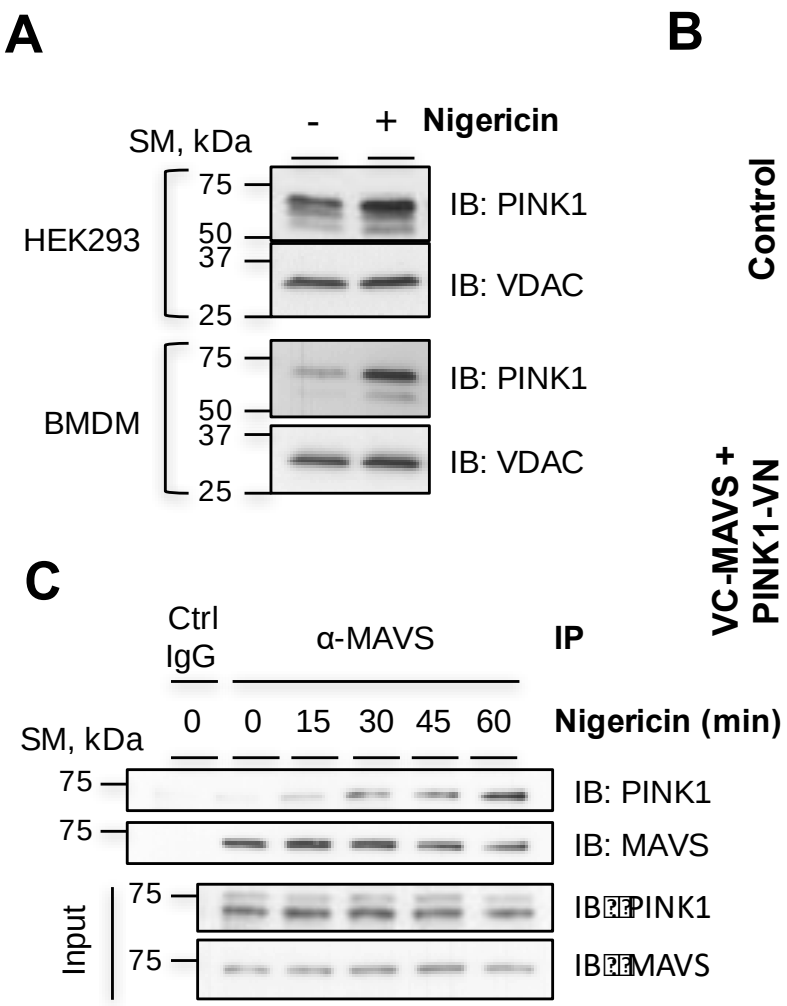
B. Folding topology

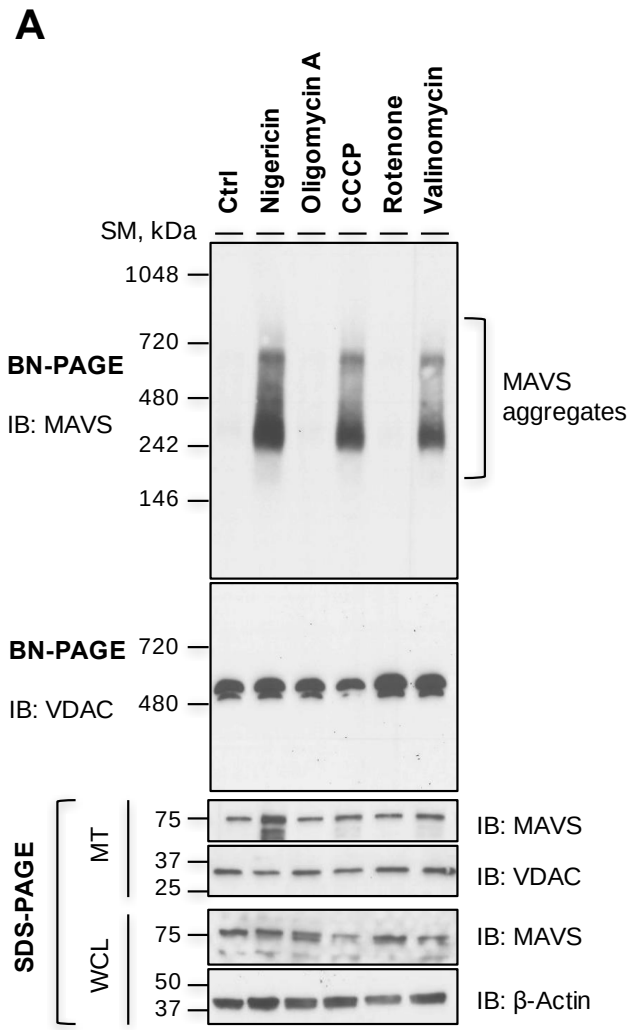
- **β-strands (green arrows)**
- **α-helices (orange boxes)**

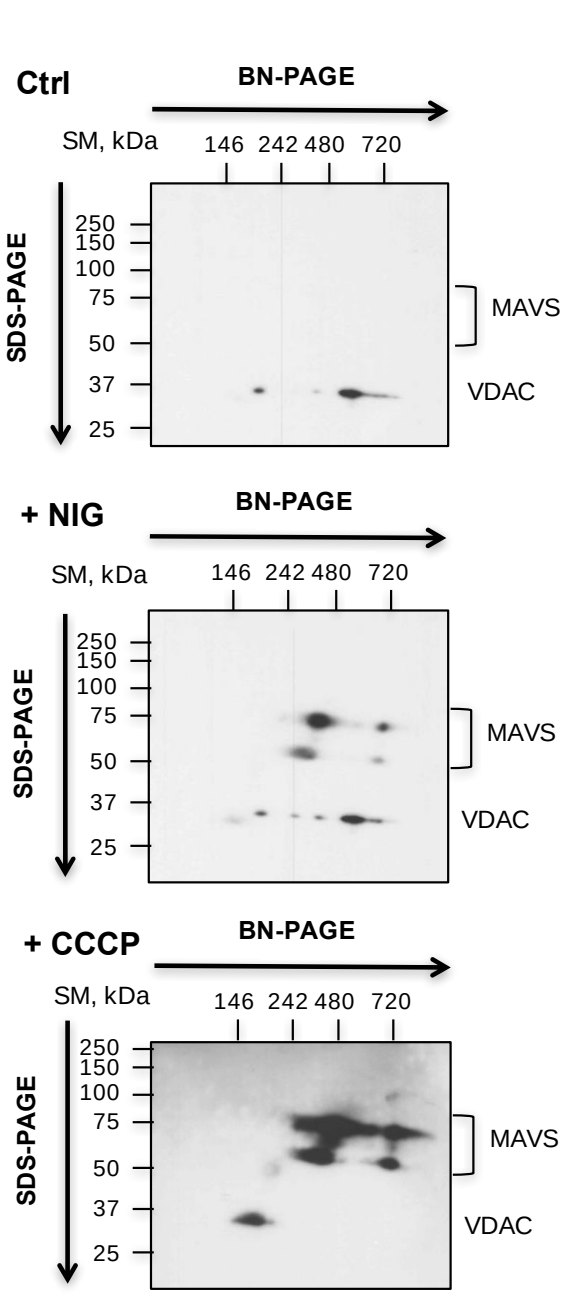
C. Principle of BiFC

- The BiFC assay is based on reconstitution of an intact fluorescent protein when two complementary non-fluorescent fragments are brought together by a pair of interacting proteins.

Dynamic Interaction of PINK1 with MAVS

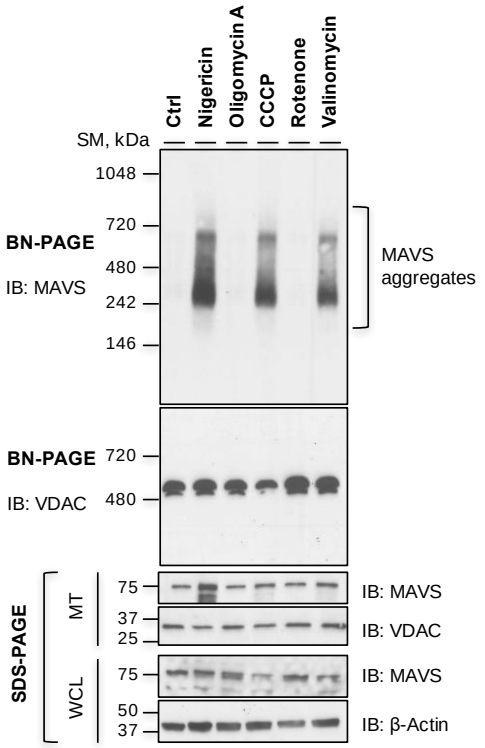


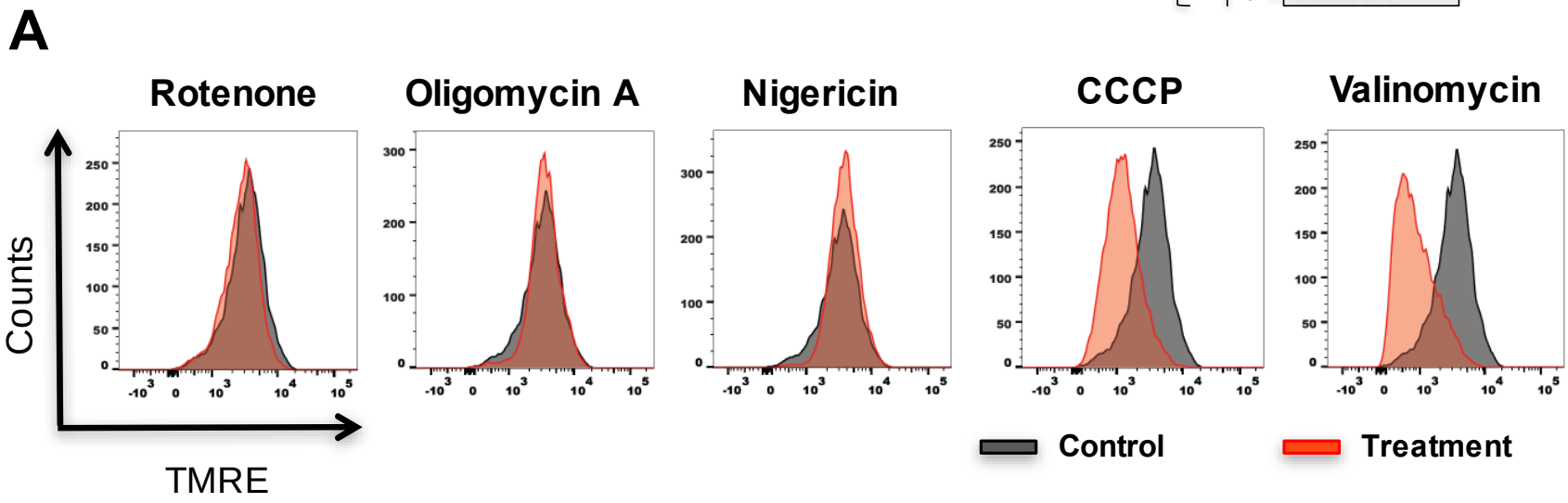




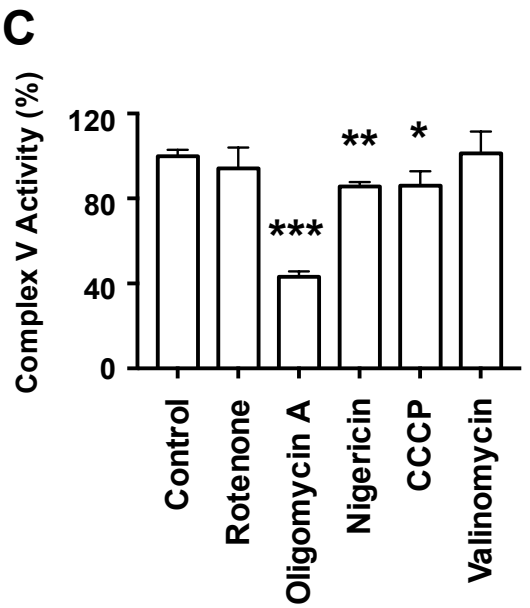
MAVS aggregation-inducing mitochondrial stimuli

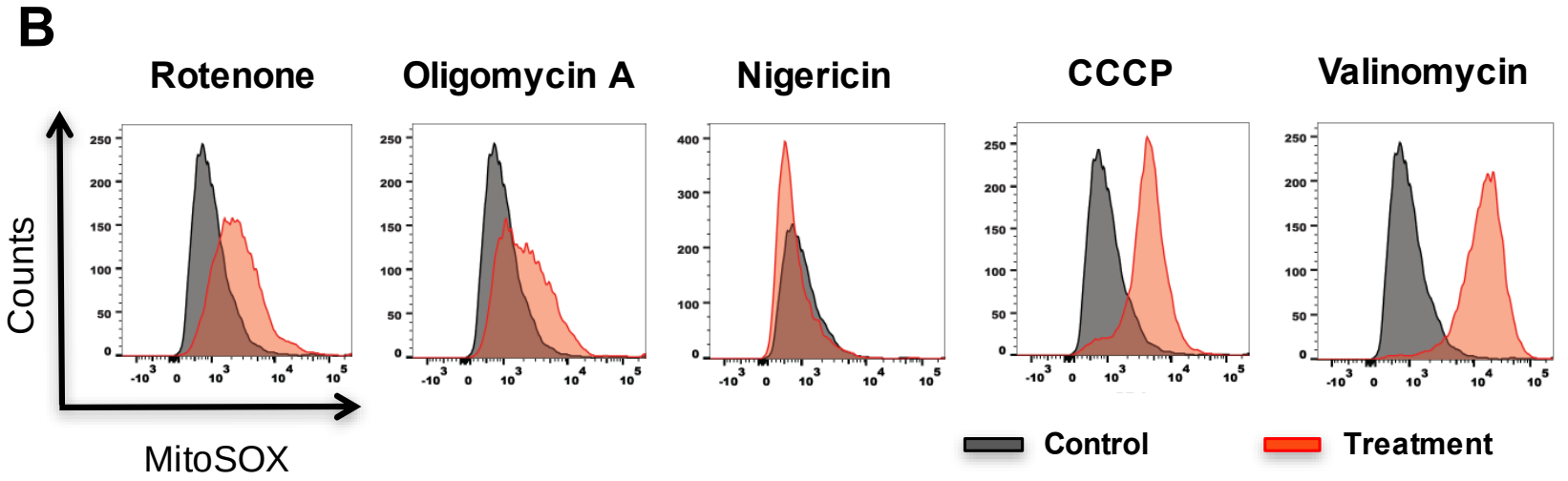
What is the trigger of MAVS aggregation ?





Role of Mitochondrial ROS or Complex V activity ?



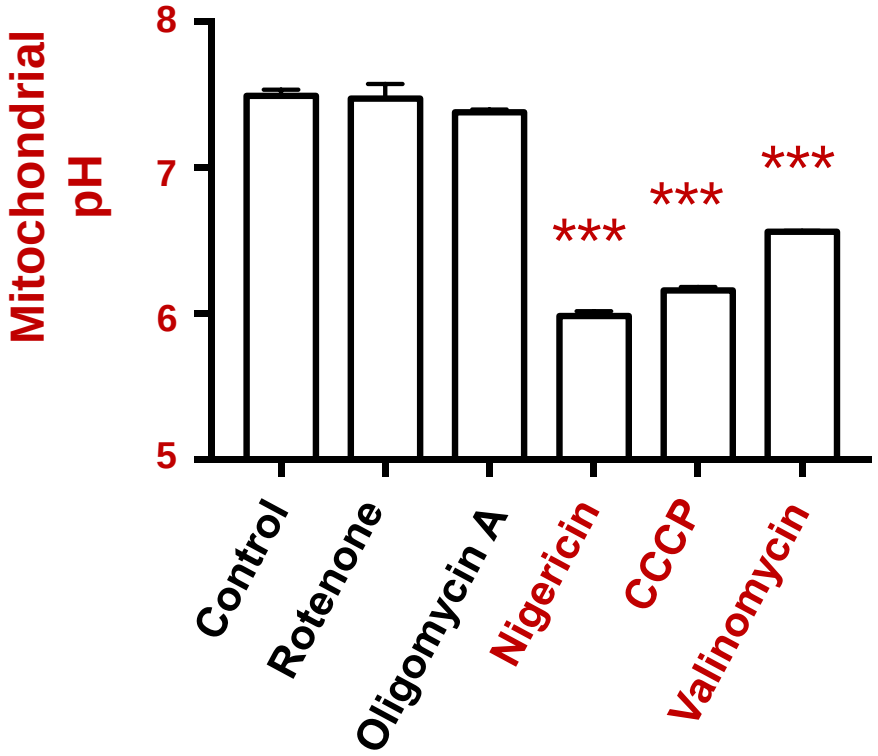


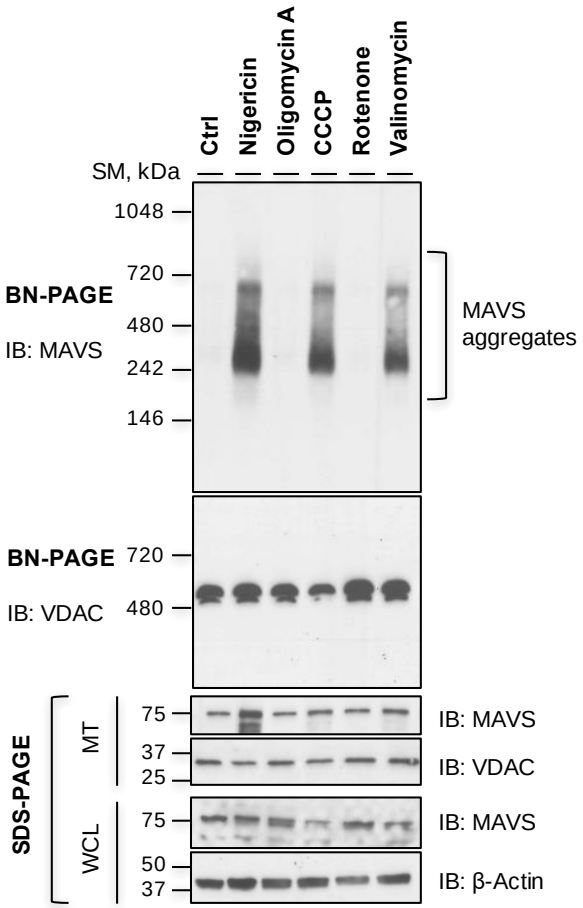
Mitochondrial pH-dependent MAVS aggregation

Santo-Domingo J et al. J Gen Physiol. 2012;139:415 - 423

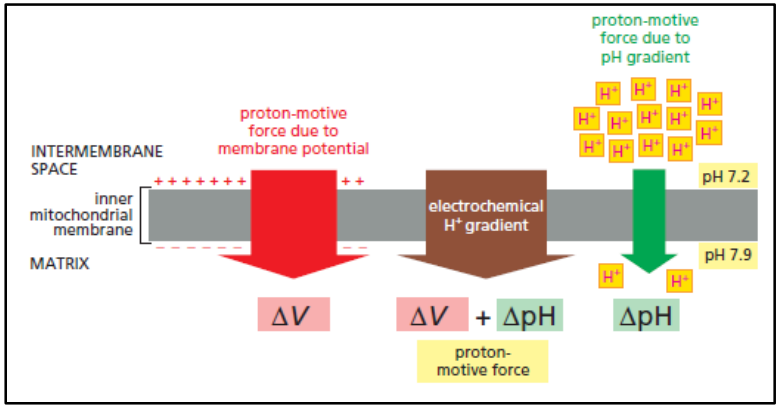
Perspectives on: SGP Symposium on Mitochondrial Physiology and Medicine

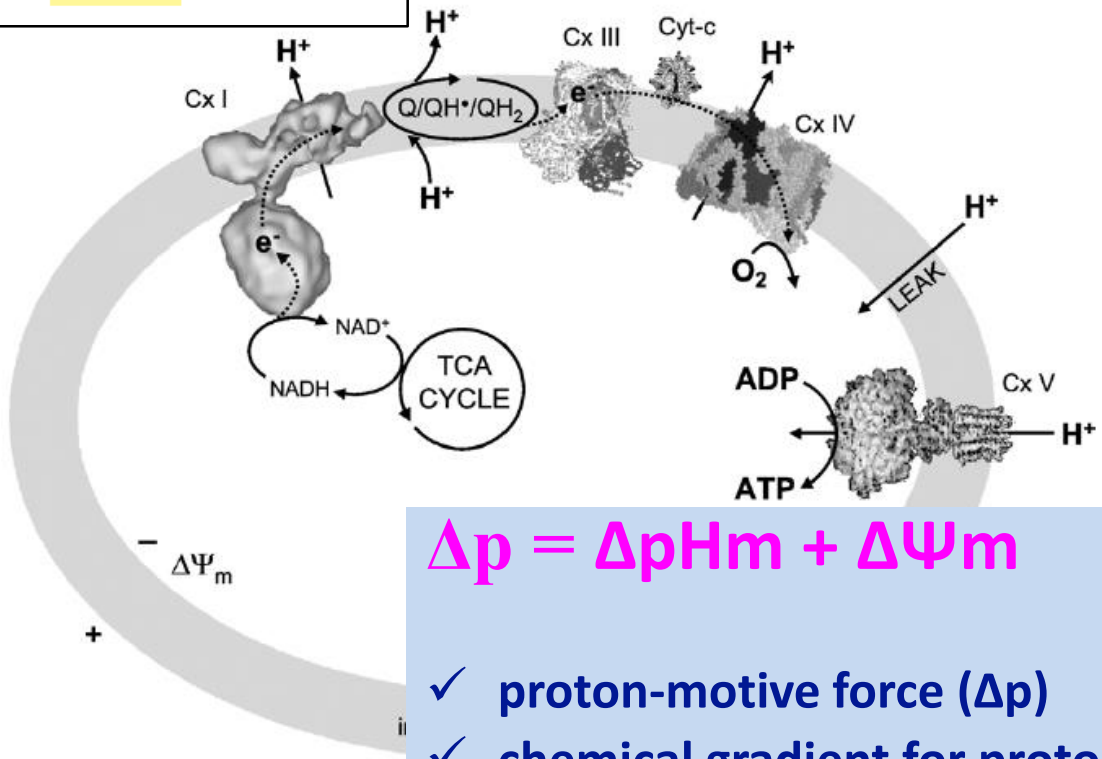
The renaissance of mitochondrial pH





Proton-motive Force & Chemiosmotic Coupling

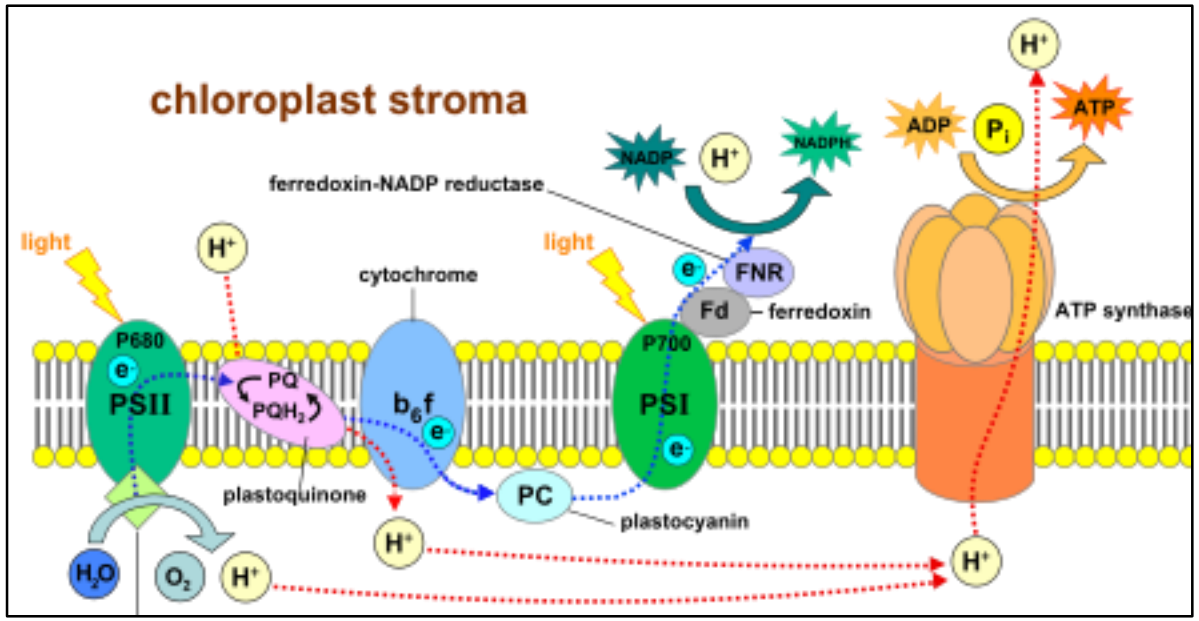


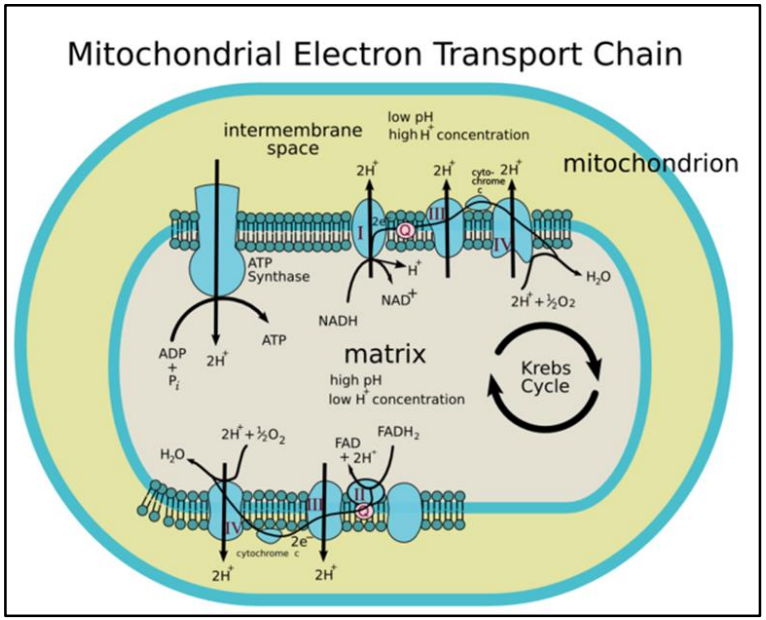


$$\Delta p = \Delta pHm + \Delta \Psi m$$

- ✓ proton-motive force (Δp)
- ✓ chemical gradient for protons (ΔpHm)
- ✓ mitochondrial membrane potential (ΔΨm)

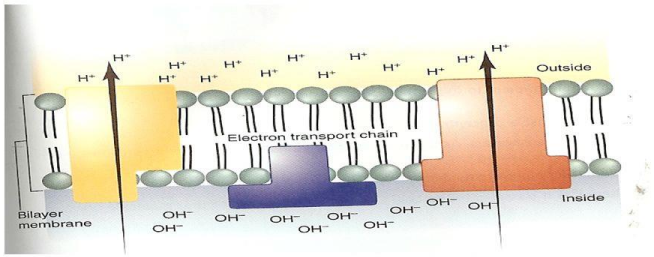
Deeper Meaning of Proton-motive Force (1)



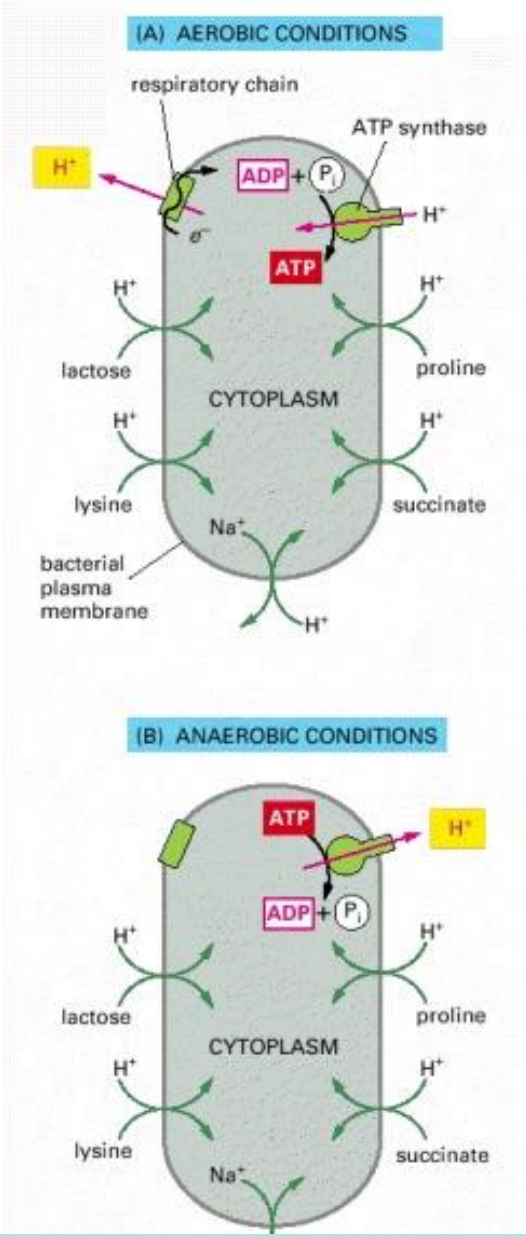


Deeper Meaning of Proton-motive Force (2) - Bacteria

Proton motive force



- The bacterial flagellum is driven by a rotary engine. The engine is powered by **proton motive force**, i.e., by the flow of protons (hydrogen ions) across the bacterial cell membrane due to a concentration gradient set up by the cell's metabolism

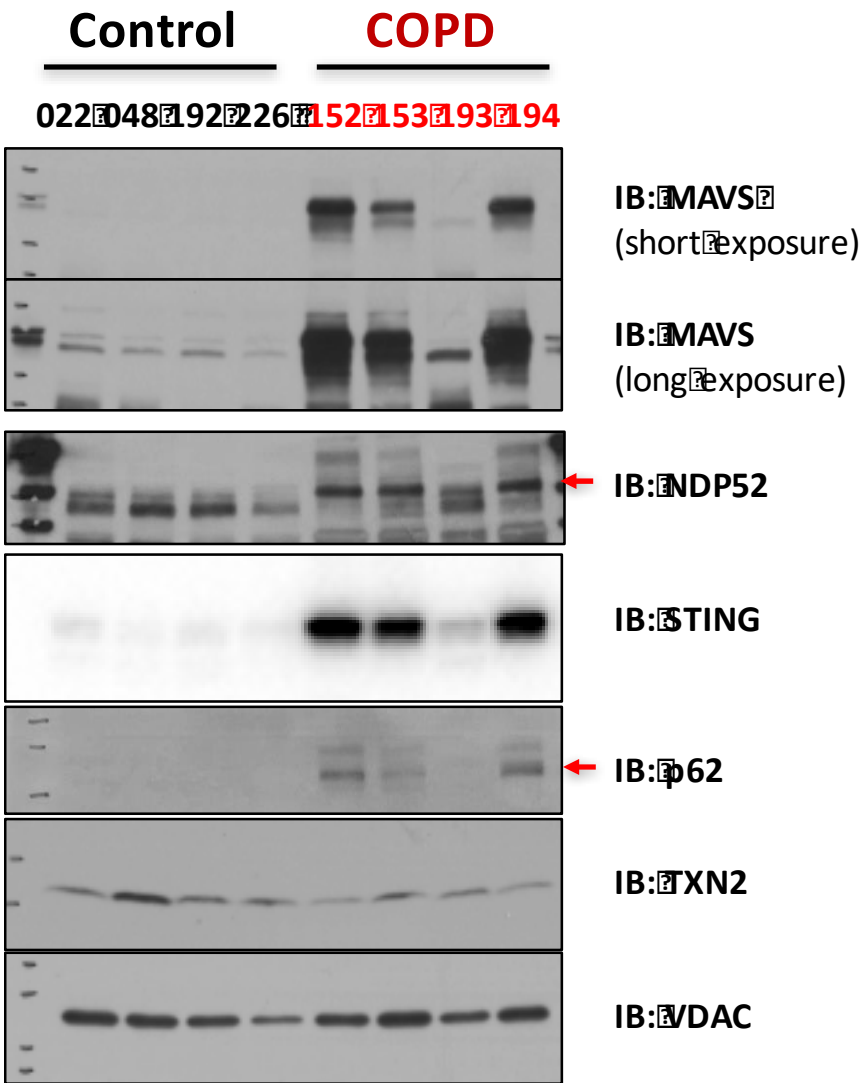


H^+-driven transport of nutrients in bacteria

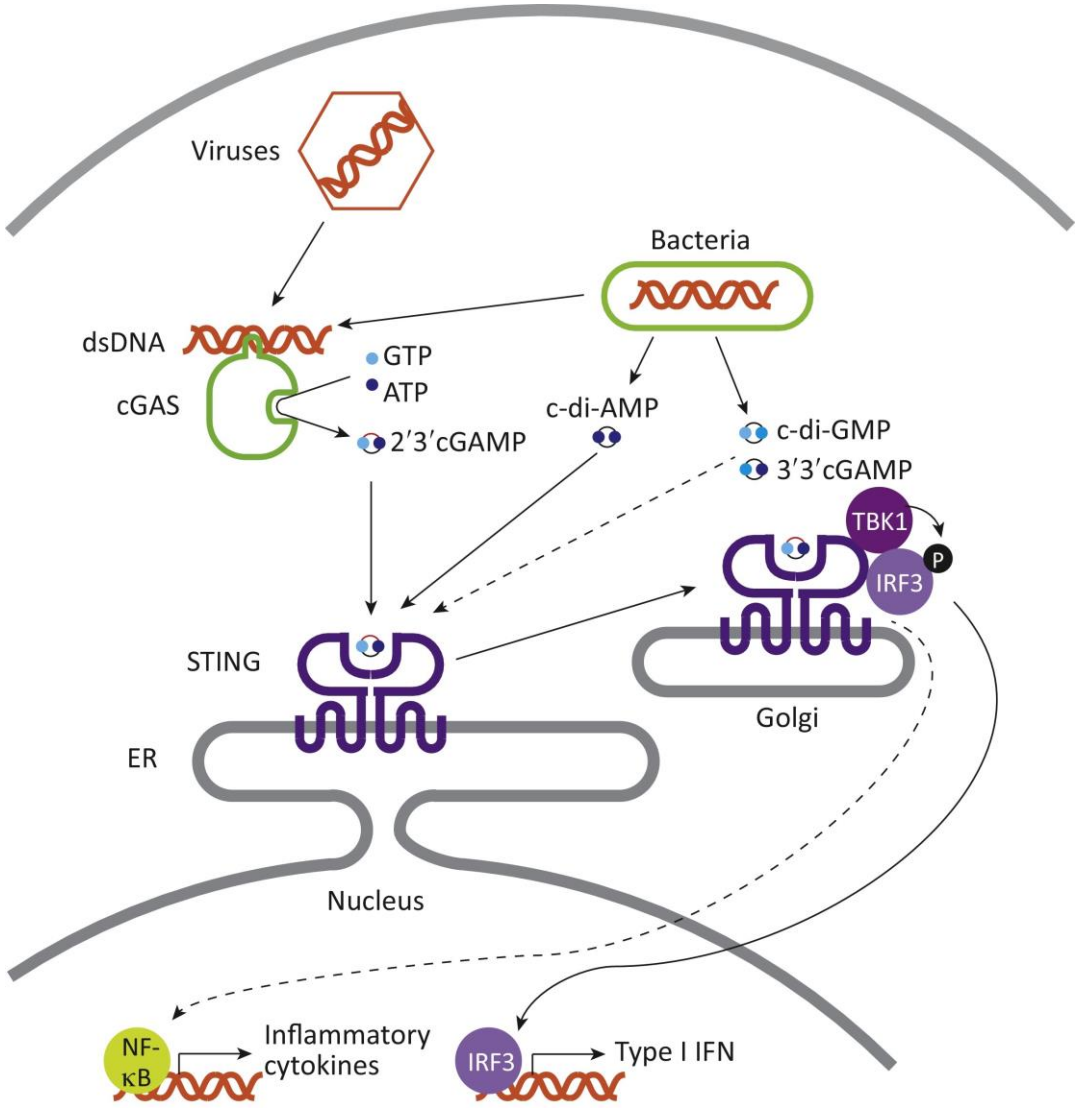
Strength of electric field across membrane of mitochondria (equal to that of lightning bolt)

Value	3e+7 V/m
Organism	Generic
Reference	Lane N, Martin W. The energetics of genome complexity. Nature. 2010 Oct 21 467(7318):929-34. p.931 right colum paragraph **PubMed ID** 20962839
Method	Dividing values in Comments section: 0.15V/(5×10^-9m)=3×10^7V/m

Human Relevance ?

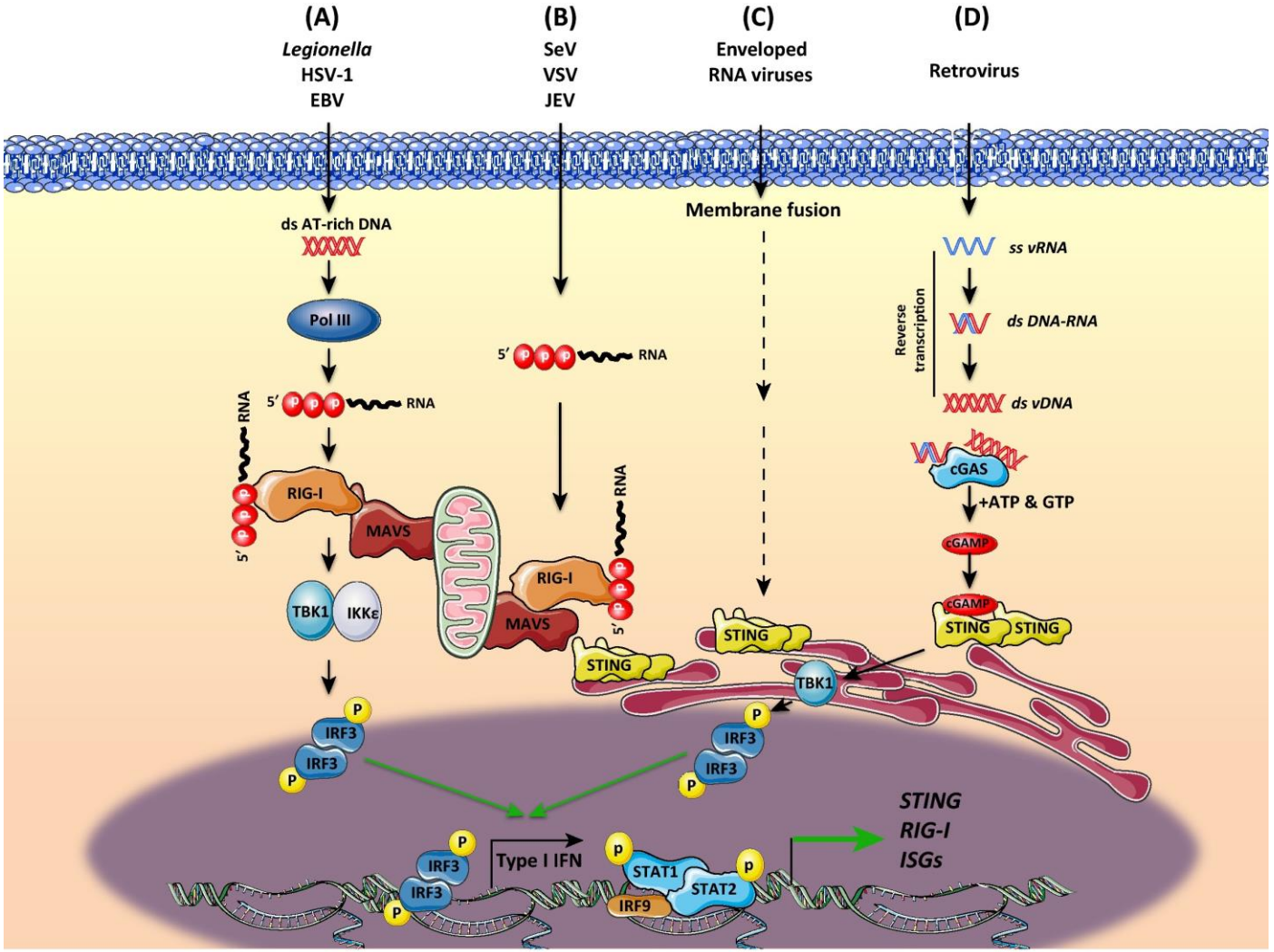


cGAS-STING Pathway

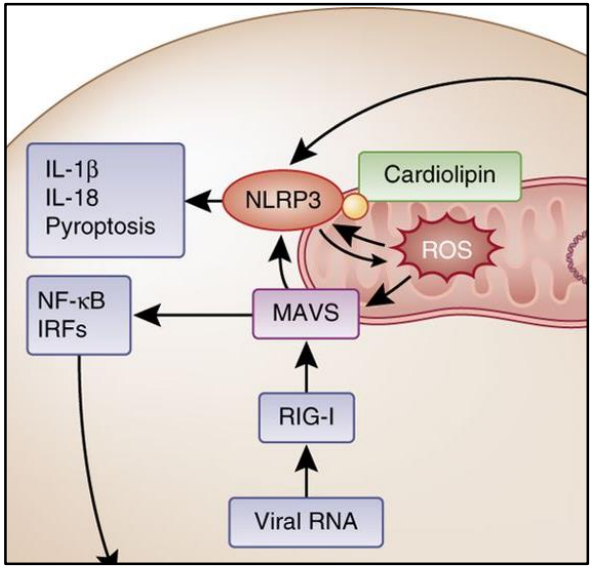


Evolutionary Origins of cGAS-STING Signaling. Trends Immunol. 2017

Crosstalk b/w RLHs & STING Pathways



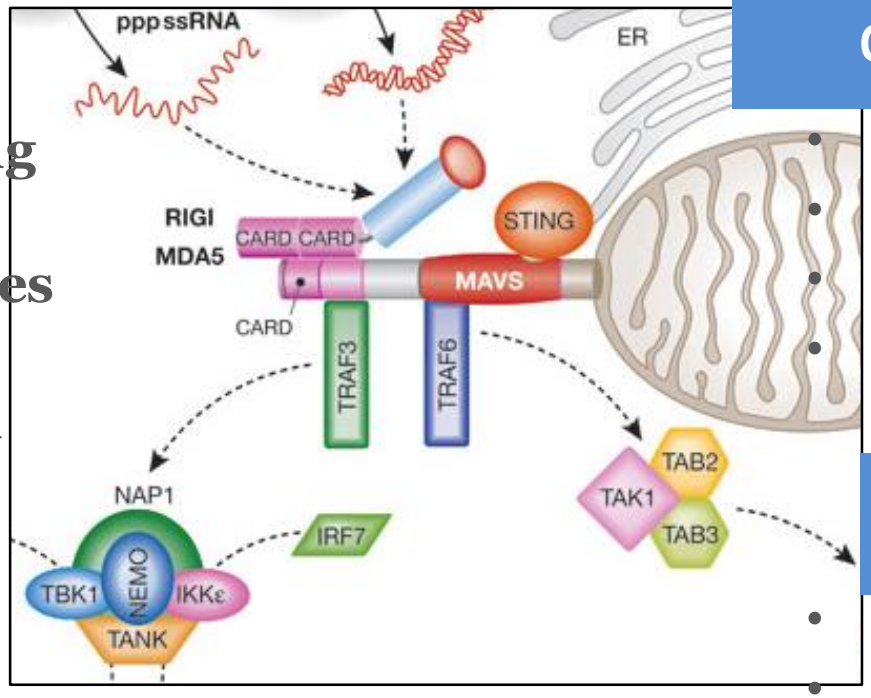
Zevini A et al. Trends Immunol. 2017



MAVS: beyond antiviral signaling

Sensing

- RLHs signaling
- NLRP3 inflammasomes
- cGAS-STING cytosolic DNA sensing



Arnoult D et al. Embo Report. 2011

Coordinated by

- ER
- Autophagy
- Mito Dynamics
- Mitophagy, etc...

Involved in

- Innate Immunity
- Inflammation
- Apoptosis, etc..

PEABODY MUSEUM OF NATURAL HISTORY
YALE UNIVERSITY

Travels in the Great Tree of Life

HOME

LEARN ABOUT THE TREE OF LIFE!

- What is the Tree of Life?
- What is a Phylogenetic Relationship?
- Evolution Along the Branches
- Extreme Divergence!
- Convergent Evolution
- Convergent Insect Eaters
- A Succulent Convergence
- Big Surprises
- Elephant Shrews
- Afrotheria
- Rafflesia
- A Monumental Scientific Challenge
- Computational Complexity
- Why Study the Tree of Life?
- Phylogentic Predictions

ELEPHANT SHREWS

FILMS

A TREE OF LIFE ADVENTURE GAME!

MORPHING ARACHNIDS

FURTHER RESOURCES

CREDITS

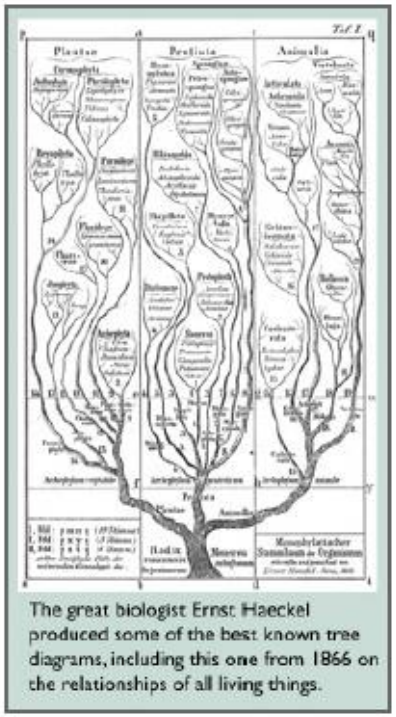
What is the Tree of Life?

In his 1859 masterpiece *On the Origin of Species*, Charles Darwin included just one illustration — a "tree" depicting branching and extinction through time.

With this he crystallized the idea that species share common ancestors at various points back in time. He referred to the genealogical relationships among all living things as "the great Tree of Life."

A detail from Darwin's notebook, drawn in 1837, showing his first sketch of a tree depicting phylogenetic relationships among species.

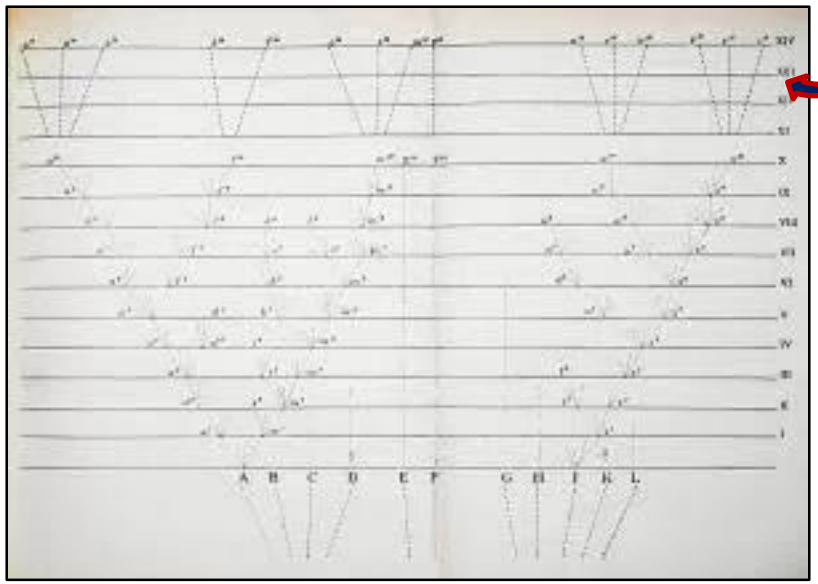
The Syndics of Cambridge University Library



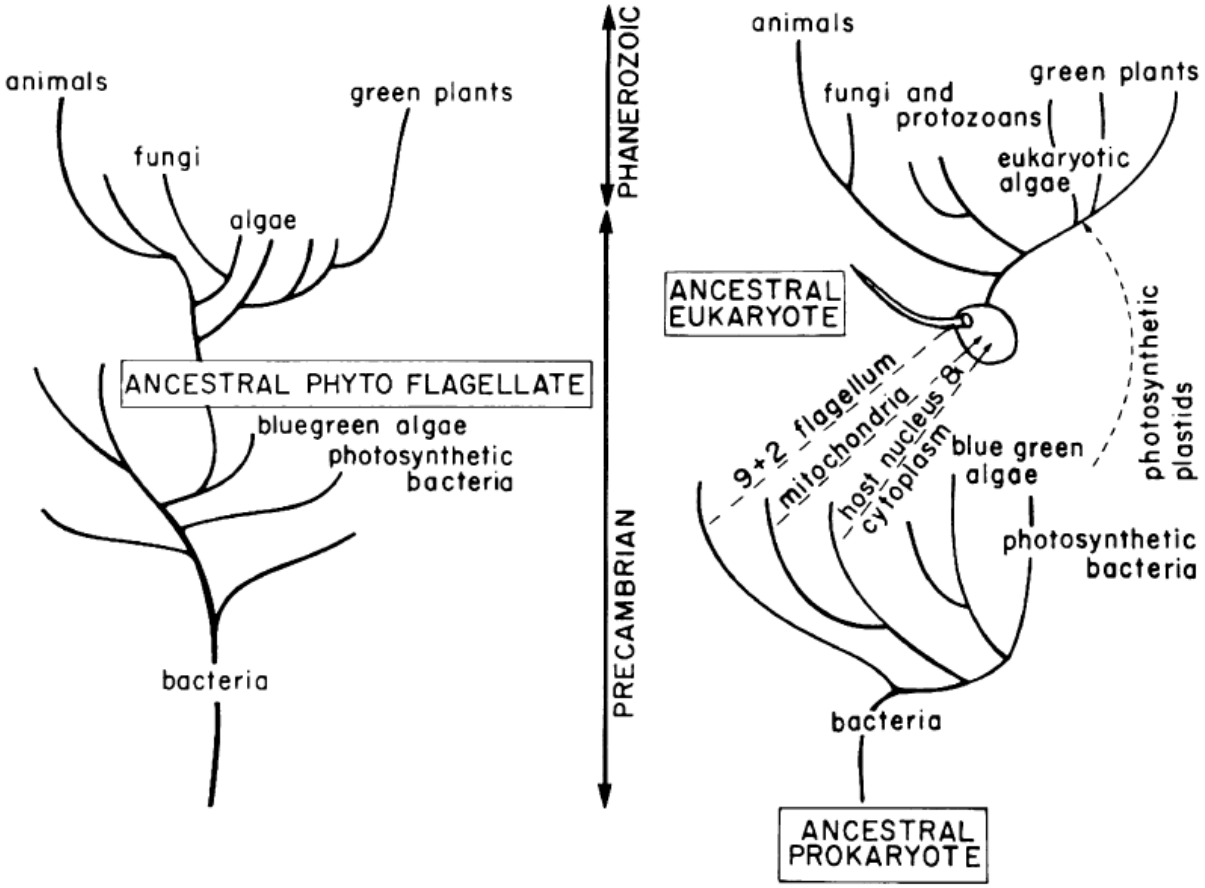
The great biologist Ernst Haeckel produced some of the best known tree diagrams, including this one from 1866 on the relationships of all living things.

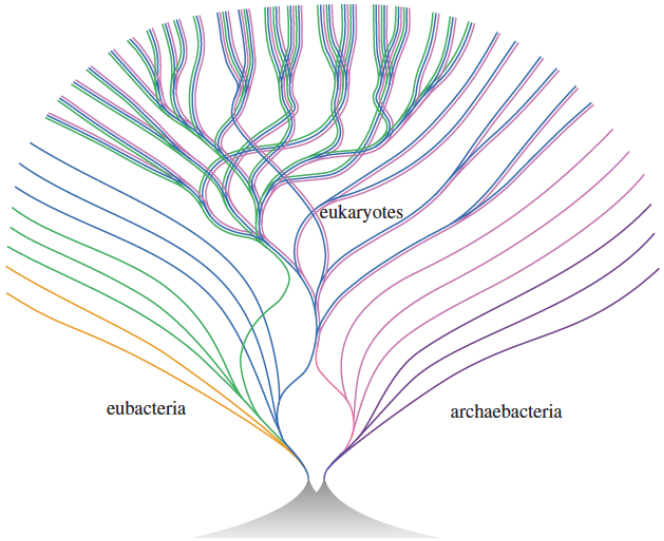
Throughout the late 19th century there were many attempts to portray evolutionary relationships with tree-like diagrams. These were based on overall appearances — shared similarities in the form and structure of organisms.

The tree of life image that appeared in Darwin's *On the Origin of Species*, 1859. It was the book's only illustration



Paradigm change ?





Margulis L. "Origin of Eukaryotic Cells," 1970

Martin W. Bioassays. 1999:21:99-104

nature microbiology

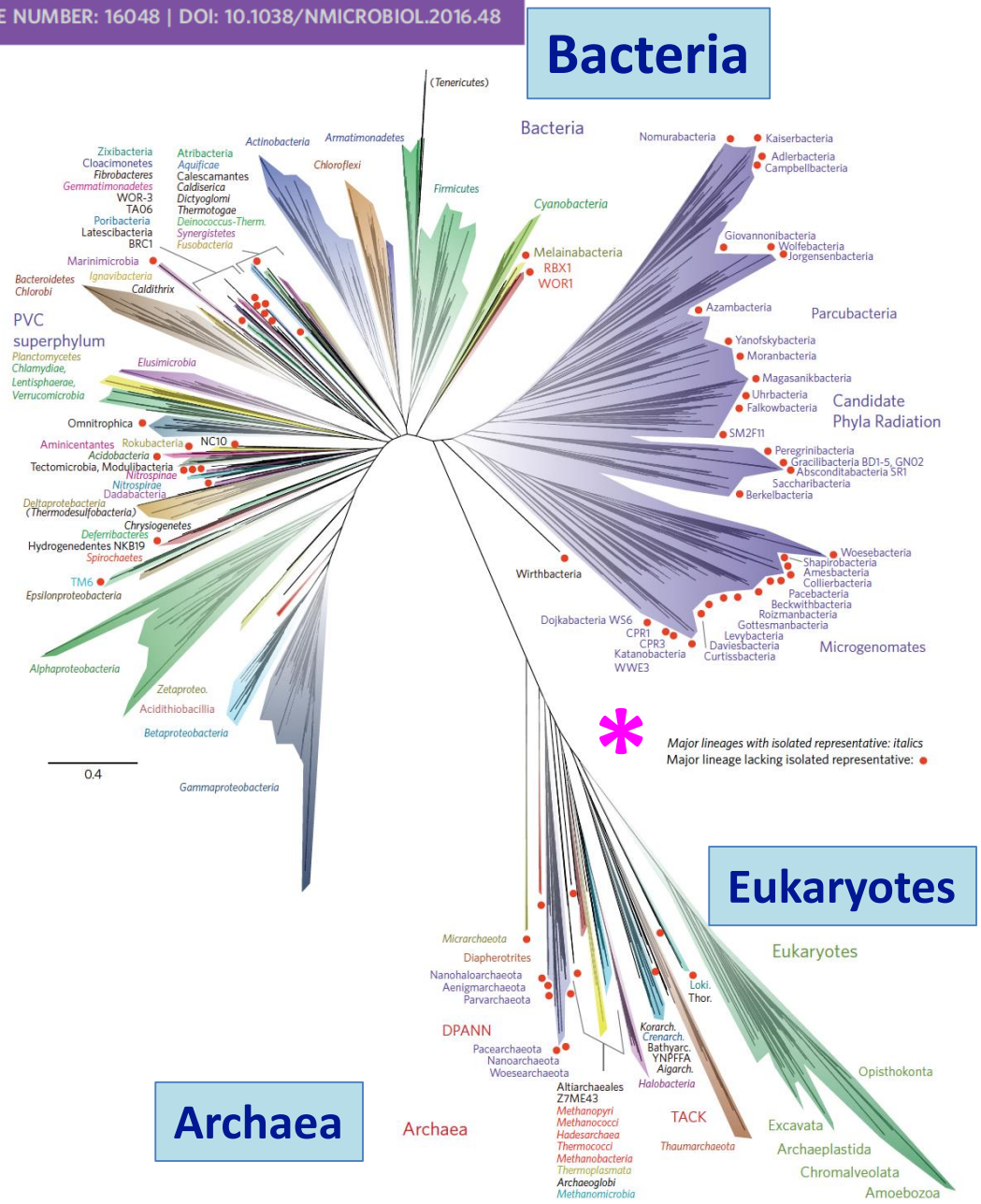
LETTERS

PUBLISHED: 11 APRIL 2016 | ARTICLE NUMBER: 16048 | DOI: 10.1038/NMICROBIOL.2016.48

A new view of the tree of life

Mitochondria define Eukaryotes!

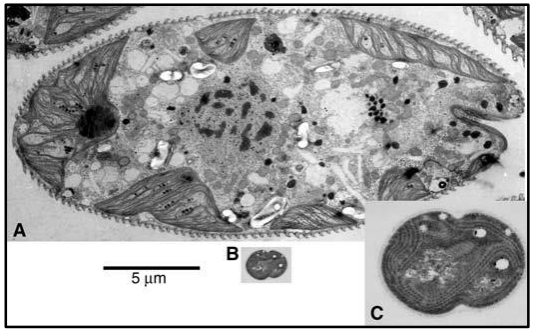
* Endosymbiosis



Bioenergetic Constrains on the Evolution of Complex Life

➢ **운명 공동체: Hidden Meaning of Endosymbiosis?**

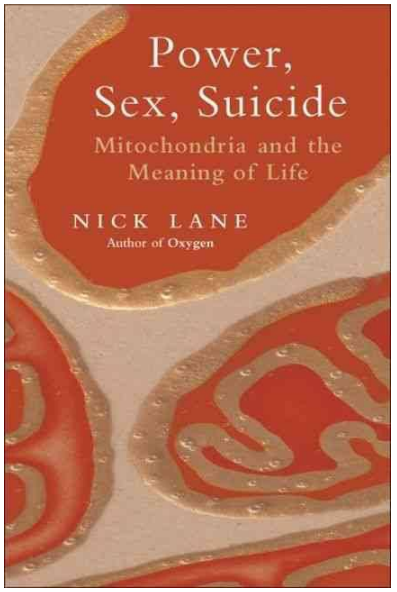
- All complex life on earth is eukaryotic.
- Eukaryotes arose in a rare endosymbiosis, which broke the energetic constrains on prokaryotes.
- The endosymbiosis radically altered selection on eukaryotes, potentially explaining the evolution of unique traits, including the nucleus, sex, two sexes, speciation, and aging.

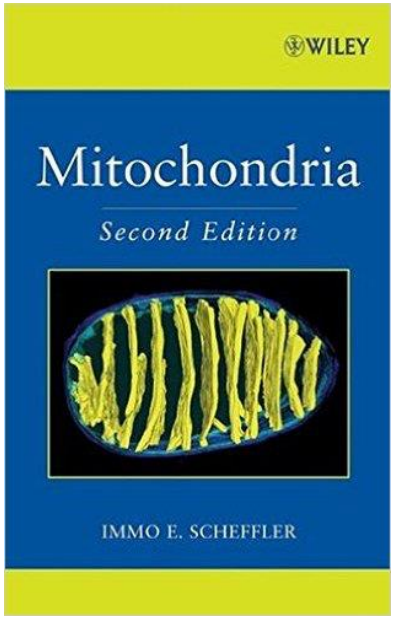


Lane N. Cold Spring Harb Perspect Biol. 2014;6:a015982

Mitochondria – Meaning of the Life

- Endosymbiosis is the key event which enabled the origin of eukaryotes and all of the complex life beyond prokaryotes… We will never understand what's going wrong in diseases unless we understand why the cell is the way it is...(Lane N. "*Power, Sex Suicide*" / J Cell Biol. 2015. People & Idea, Unearthing the first cellular innovations...)
- …Thus, mitochondria occupy a central position in our understanding of the cell, the "basic unit of life," and the study of mitochondria has, from the very beginning, revealed not only details, but also fundamental insights covering the entire spectrum from biophysics to cell biology and genetics… (Scheffler E. "*Mitochondria*", Chapter 1.)





Conclusion

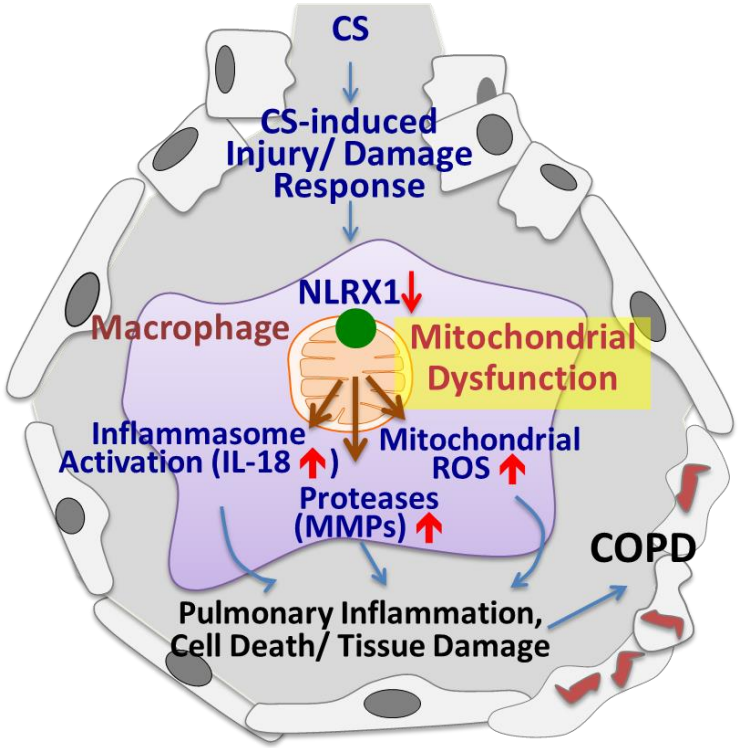
REVIEW
http://dx.doi.org/10.4046/trd.2016.79.4.207
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2016;79:207-213

A Mitochondrial Perspective of Chronic Obstructive Pulmonary Disease Pathogenesis

trd
Tuberculosis & Respiratory Diseases

A Mitochondrial Perspective on the Pathogenesis of Airway Disorders

Mitochondria-targeted Novel therapeutics



Acknowledgment

- Chang Min Yoon, Ph.D.
- Sang-Hun Kim, Ph.D.
- Tie-Zhong Cui, Ph.D.
- Hyeon-Jun Shin, Ph.D.
- Jung Yeon Lee, M.D.
- Yeon-Mok Oh, M.D., Ph.D.
- Woo Jin Kim, M.D., Ph.D.
- Naftali Kaminski, M.D.
- Patty J. Lee, M.D.
- Charles Dela Cruz, M.D., Ph.D.
- Gerald S. Shadel Ph.D.

DPH Keeping Connecticut Healthy

Flight Attendant Medical Research Institute

NIH National Heart, Lung, and Blood Institute

NIH National Institute on Aging
Turning Discovery Into Health

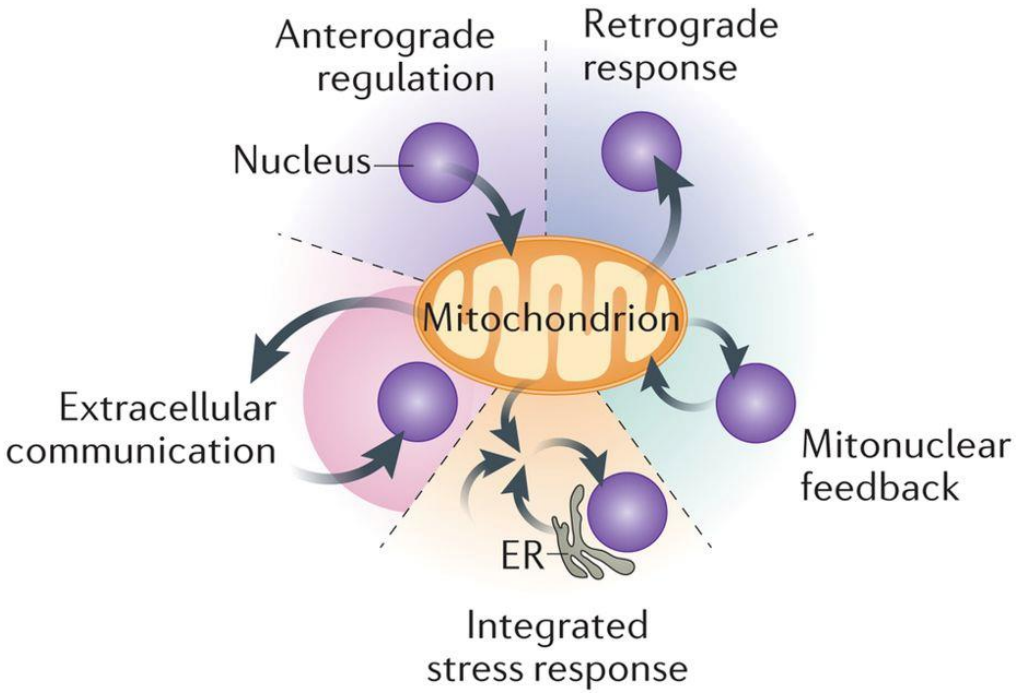
What is Life?

(Life = Energy + Information ?)

Life= Mitochondria (Bioenergetics) + Nucleus (Genetic Information)

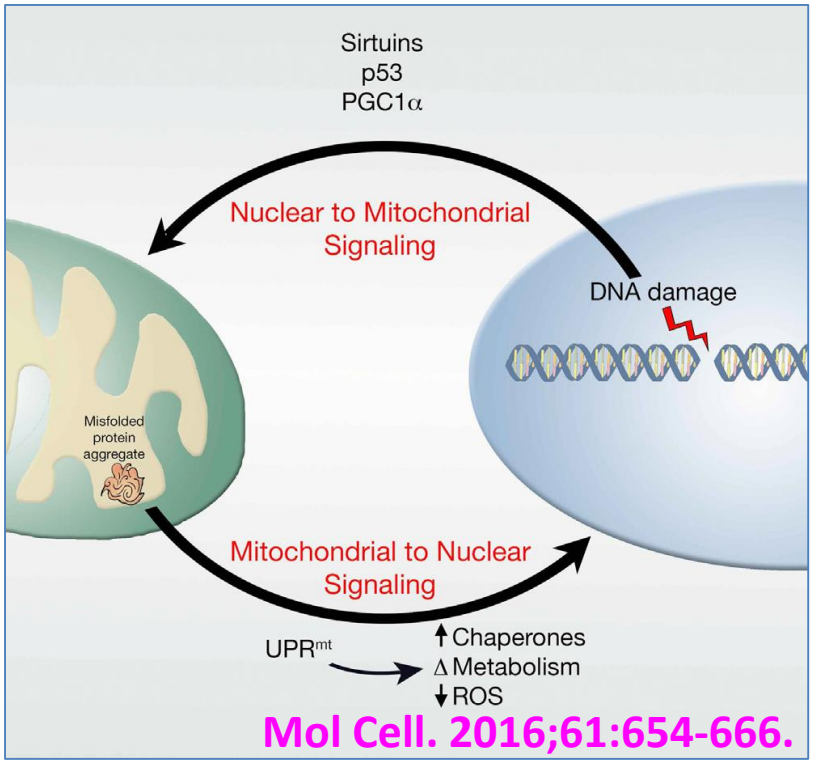
.. 이 둘의 결합에 의해 벌어지는 다양한 합주, 그것이 바로 생명현상.

Mitonuclear communication in homeostasis and stress.



Nat Rev Mol Cell Biol. 2016;17(4):213-26.

The mitochondrial basis of Aging.



Mol Cell. 2016;61:654-666.