

# Chapter 4: The innate immunity

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- An evolutionary view
- Features & Components of Innate Immunity
- The discovery of PRR and PAMP (theory)
- TLR, RLR, cGAS related immune signalings
- Antiviral defense (IFN based defense system, IFN, ISGs)
- Inflammation, pyroptosis and related diseases

# Life style risk factors

High fat diet

Tobacco

Env. Pollution

Stress

Radiation

Infections

Turmeric  
Red chilli  
Ginger  
Black pepper  
Cardamum  
Cumin

**NF- $\kappa$ B  
Activation**

Curcumin  
Capsaicin  
Gingerol  
Piperine  
Cardamomin  
Thymoquinone

## Major Pro-inflammatory biomarkers

IL-1

IL-6

IL-8

IL-17

TNF- $\alpha$

COX2

5LOX

CRP

PSA

环氧化酶

**STAT3 Activation**

## Major Chronic diseases

Cancer

Diabetes

Obesity

Cardiovascular  
diseases

Pulmonary  
diseases

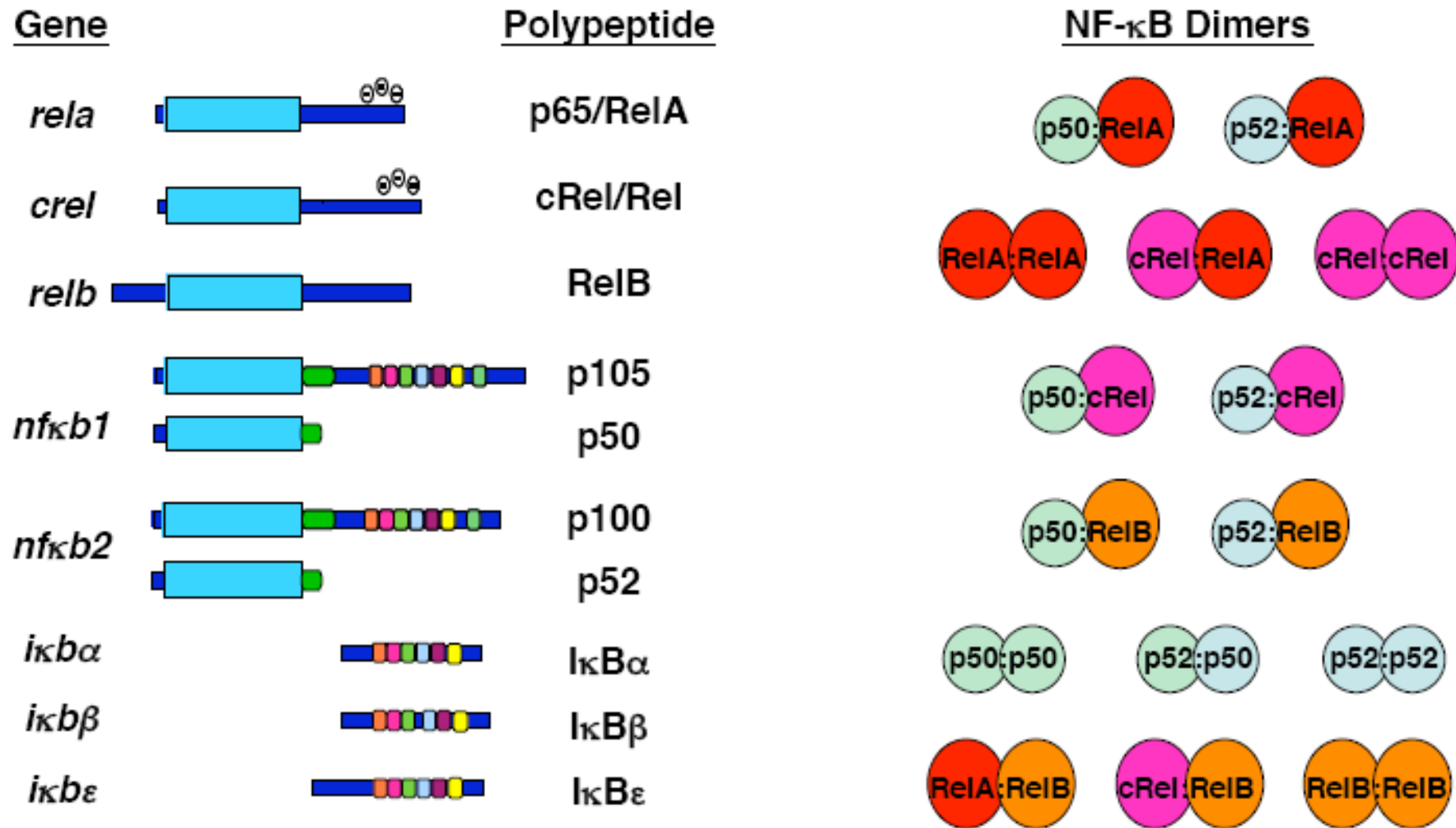
Neurological  
diseases

# Inflammation, pyroptosis and related diseases

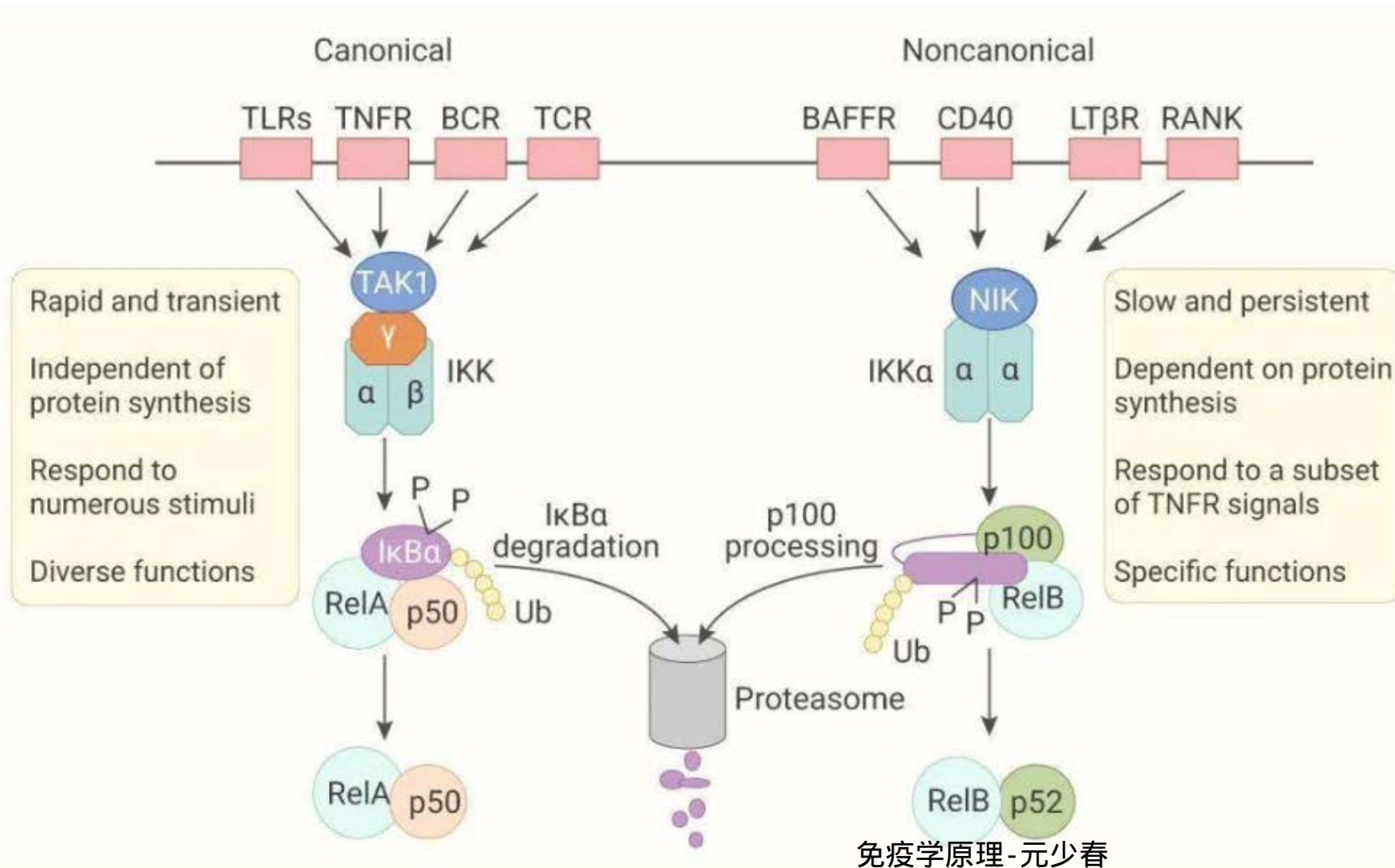
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- The NF- $\kappa$ B members and related pathways
- Inflammation
- The inflammasome
- The GSDM mediated pyroptosis (LPS sensing)
- Mast cell mediated inflammation

# The NF- $\kappa$ B and I $\kappa$ B families



# The NF- $\kappa$ B related signaling



- Canonical (TAK1)
- Noncanonical (NIK)
- Autoinhibition or inhibited by I $\kappa$ B
- Be phosphorylated
- Translocation

# NF- $\kappa$ B targeted Genes

## Genes under the control of NF- $\kappa$ B

### Inflammatory cytokines

TNF

IL-1

IL-6

IL-12

Lymphotoxin  $\alpha/\beta$

GM-CSF

IFN- $\beta$

### Chemokines

IL-8

MIP-1 $\alpha$

MCP

RANTES

Eotaxin

## Adhesion molecules

ICAM-1

VCAM-1

E-selectin

## Immune effector molecules

FasL

iNOS

COX-2

$\beta$ -defensins

## Pro-survival molecules

Bcl-XL

A1

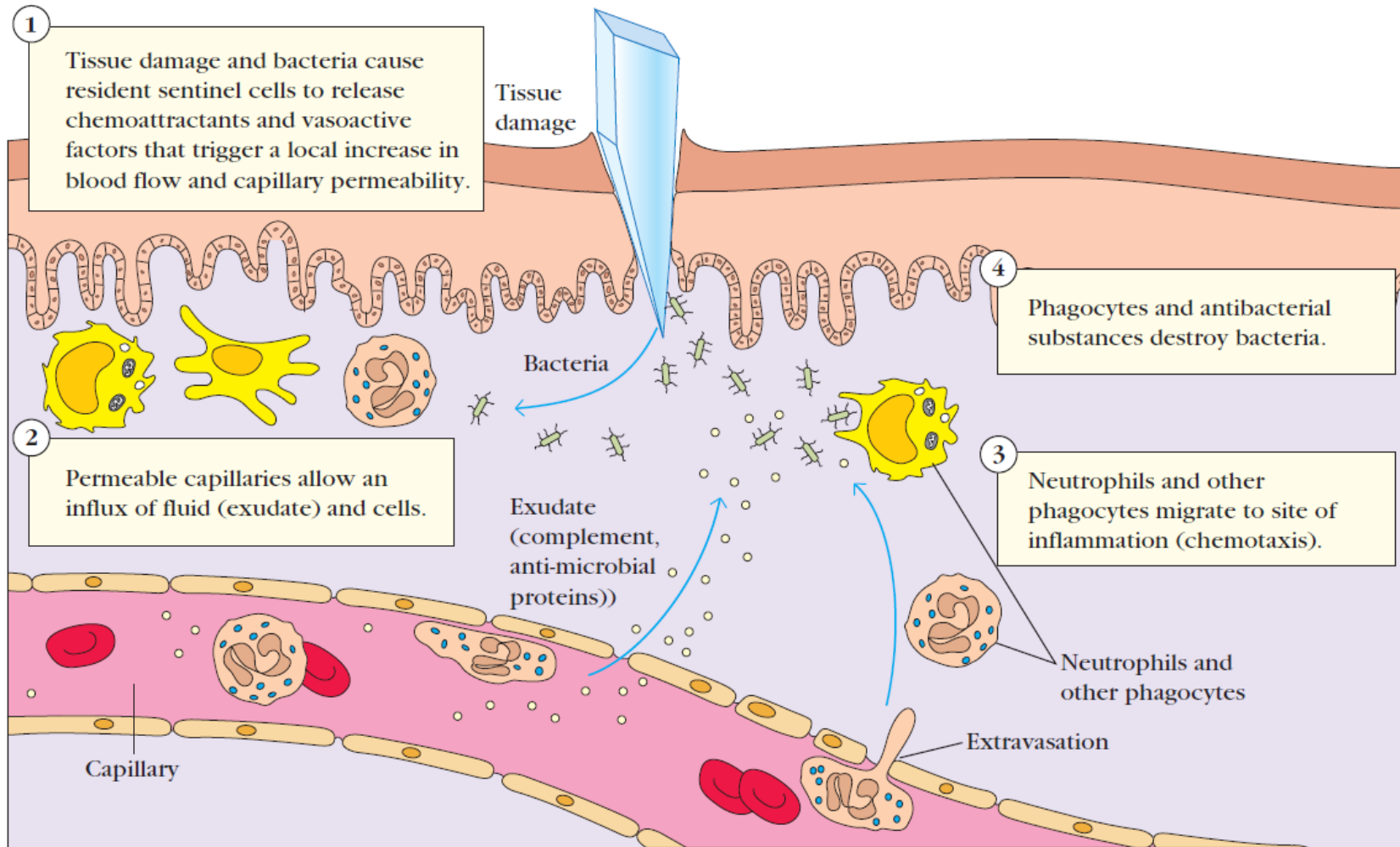
c-IAP1, 2

# Inflammation, pyroptosis and related diseases

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- The NF- $\kappa$ B members and related pathways
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# Inflammation



- Dilation of local arterioles (局部动脉扩张)
- Increased local blood flow and pressure
- Increase in vascular permeability (血管通透性增强)
- Leakage of protein
- Viscosity of local blood increases (局部血液粘稠度增加)
- Blood flow slows down
- Allows white blood cells to enter the site of injury

# Inflammation

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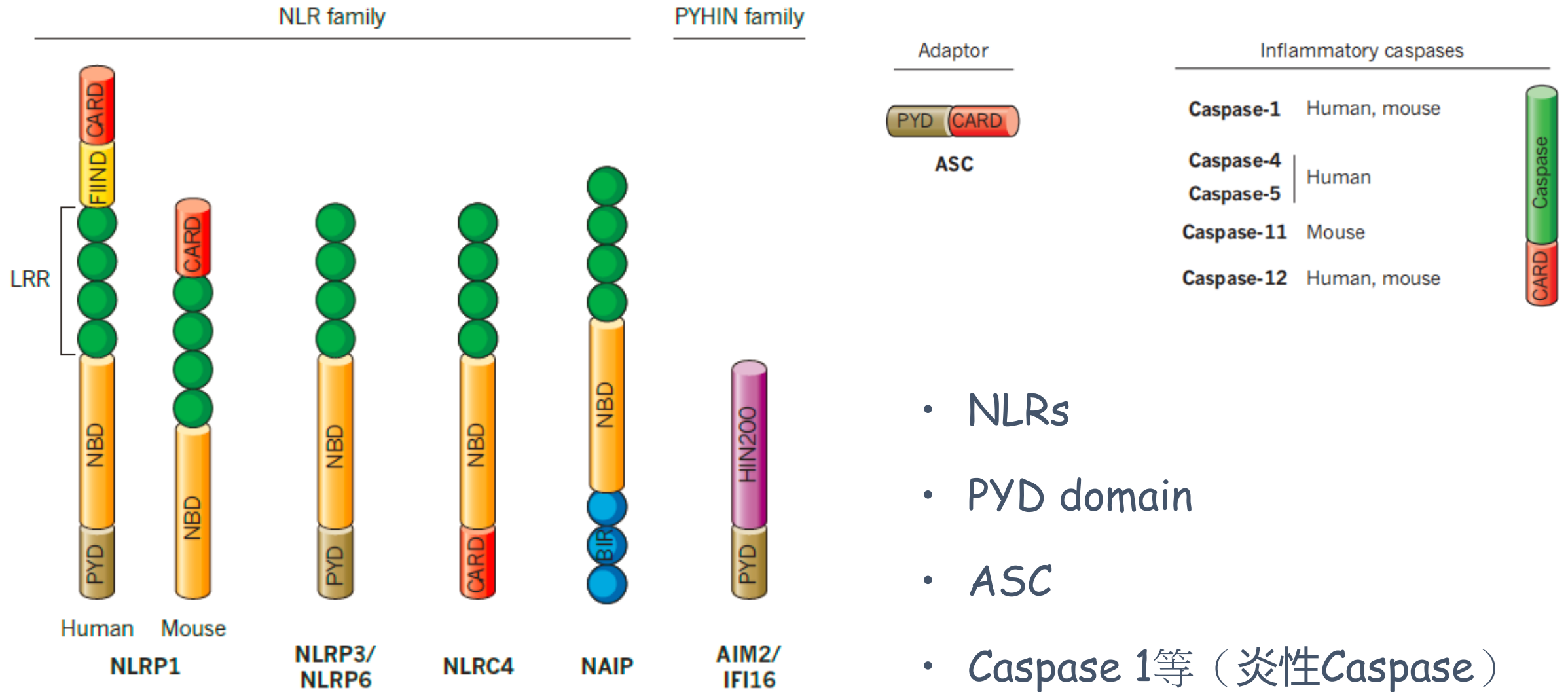
- Response of surrounding tissue to injury
- Allows substances in blood to enter the tissue (due to increased capillary permeability)
  - Antibodies, Complement, Clotting factors
- Purpose
  - Neutralize and eliminate offending agents
  - Destroy necrosed tissue
  - Prepare tissue for repair

# Features of Acute Inflammation

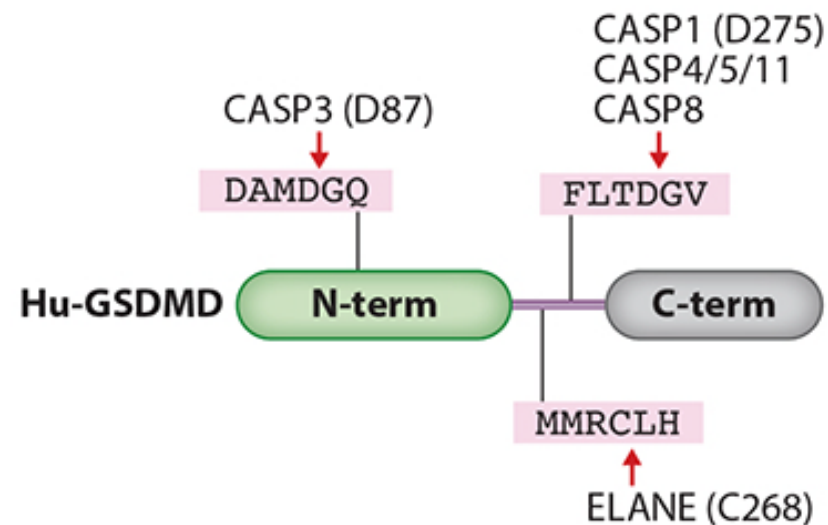
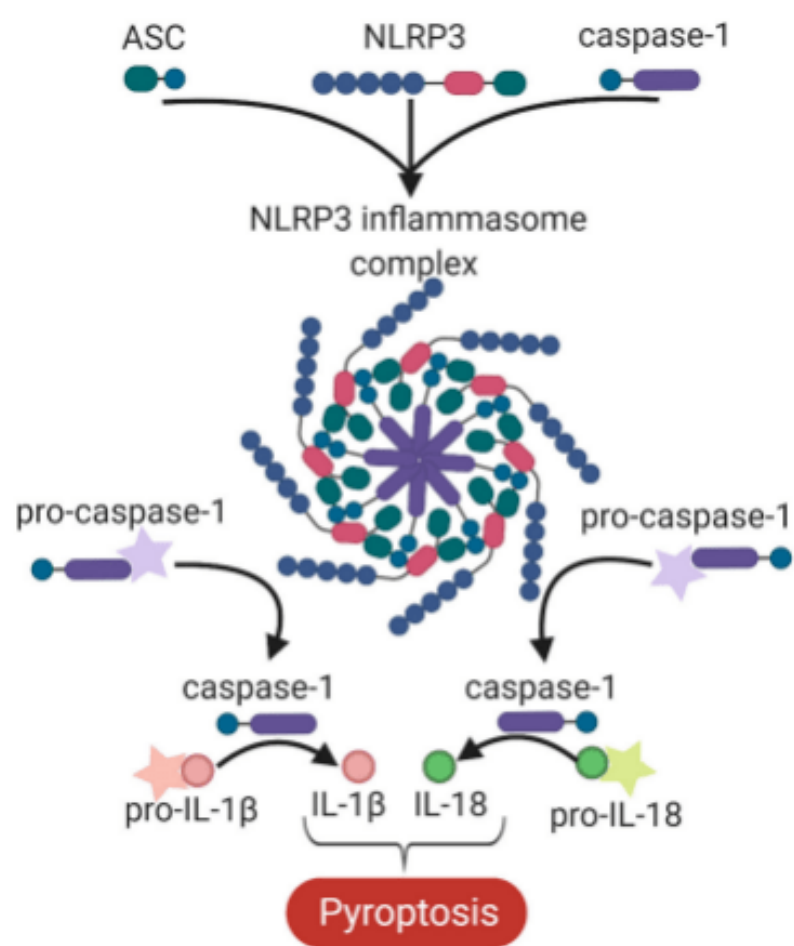
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- Redness
- Swelling
- Heat
- Pain
- Altered Function

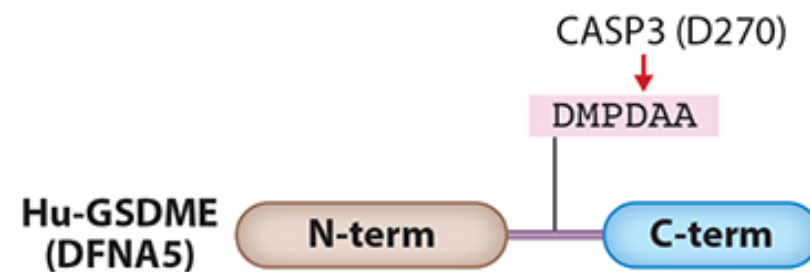
# The formation of Inflammasomes



- NLRs
- PYD domain
- ASC
- Caspase 1等（炎性Caspase）



Annu Rev Immunol. 2020 Apr 26;38:567-595.



2015年发现其功能

- Feng Shao (NIBS)
- Jiahuai Han (Xiamen U)
- Dixit VM (USA)

2017年发现其功能

- Shao Feng (NIBS)

Cleavage of **GSDMD** by inflammatory caspases determines pyroptotic cell death.

Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, Zhuang Y, Cai T, Wang F, **Shao F**.

Nature. 2015 Oct 29;526(7575):660-5. doi: 10.1038/nature15514. Epub 2015 Sep 16.

Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin.

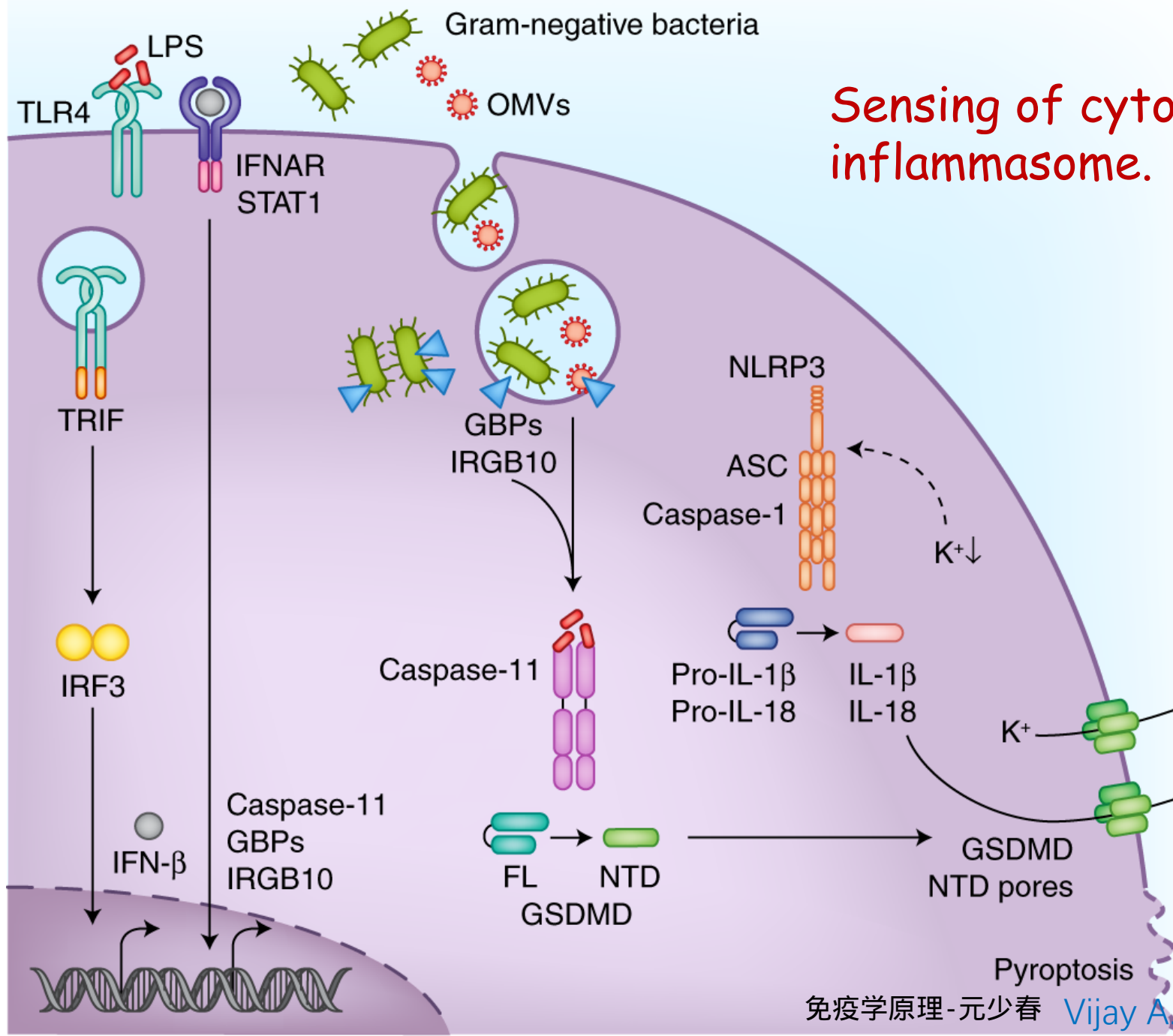
Wang Y, Gao W, Shi X, Ding J, Liu W, He H, Wang K, **Shao F**.

Nature. 2017 Jul 6;547(7661):99-103. doi: 10.1038/nature22393. Epub 2017 May 1.

Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling.

Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, Cuellar T, Haley B, Roose-Girma M, Phung QT, Liu PS, Lill JR, Li H, Wu J, Kummerfeld S, Zhang J, Lee WP, Snipas SJ, Salvesen GS, Morris LX, Fitzgerald L, Zhang Y, Bertram EM, Goodnow CC, **Dixit VM**.

Nature. 2015 Oct 29;526(7575):666-71. doi: 10.1038/nature15541. Epub 2015 Sep 16.



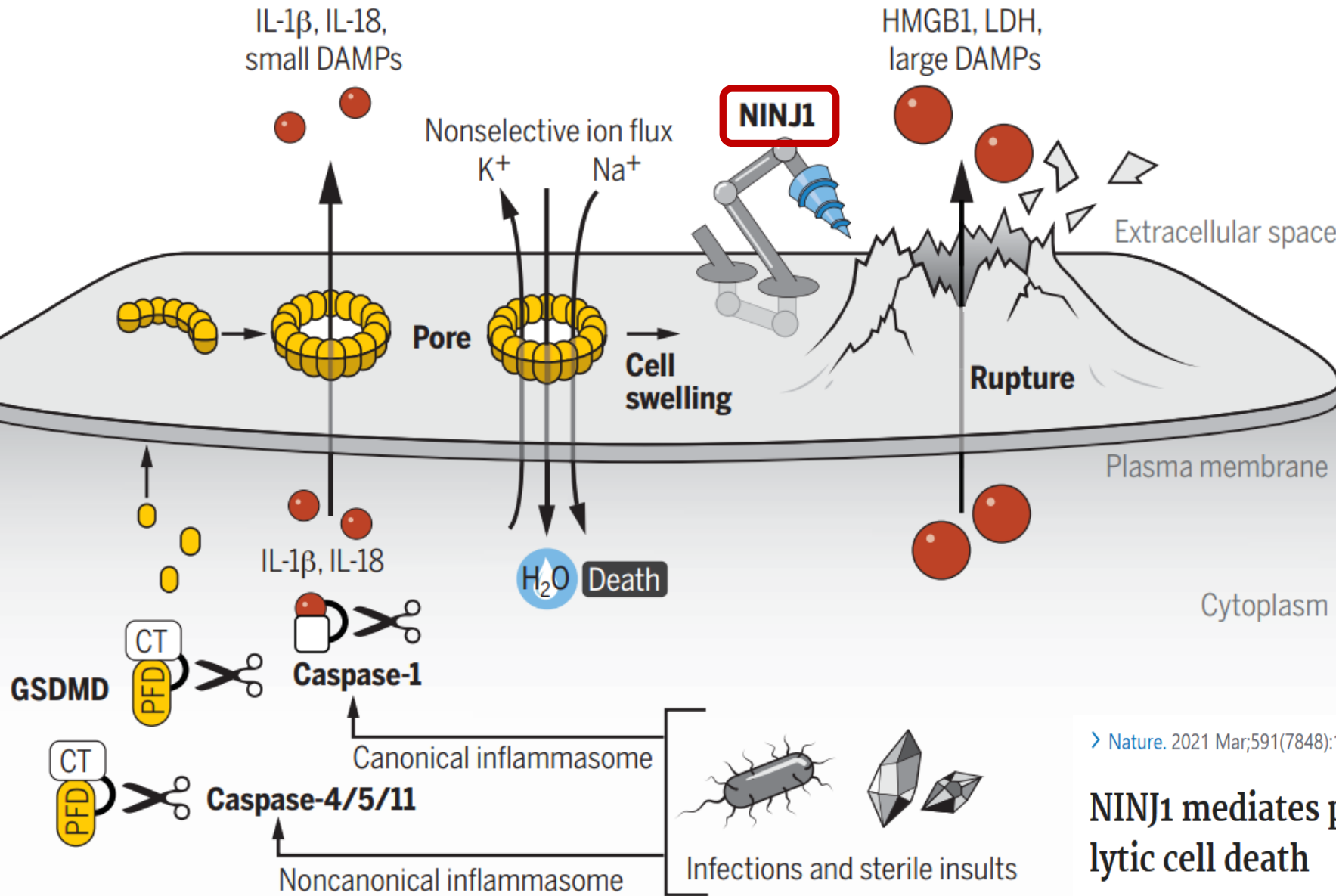
Sensing of cytosolic LPS by the non-canonical inflammasome.

LPS  
↓  
Caspase 11  
↓  
GSDMD  
↓  
pyroptosis

- GBPs (guanylate-binding proteins)
- IRGB10 (immunity-related GTPase family member b10)

## NINJ1 discovery

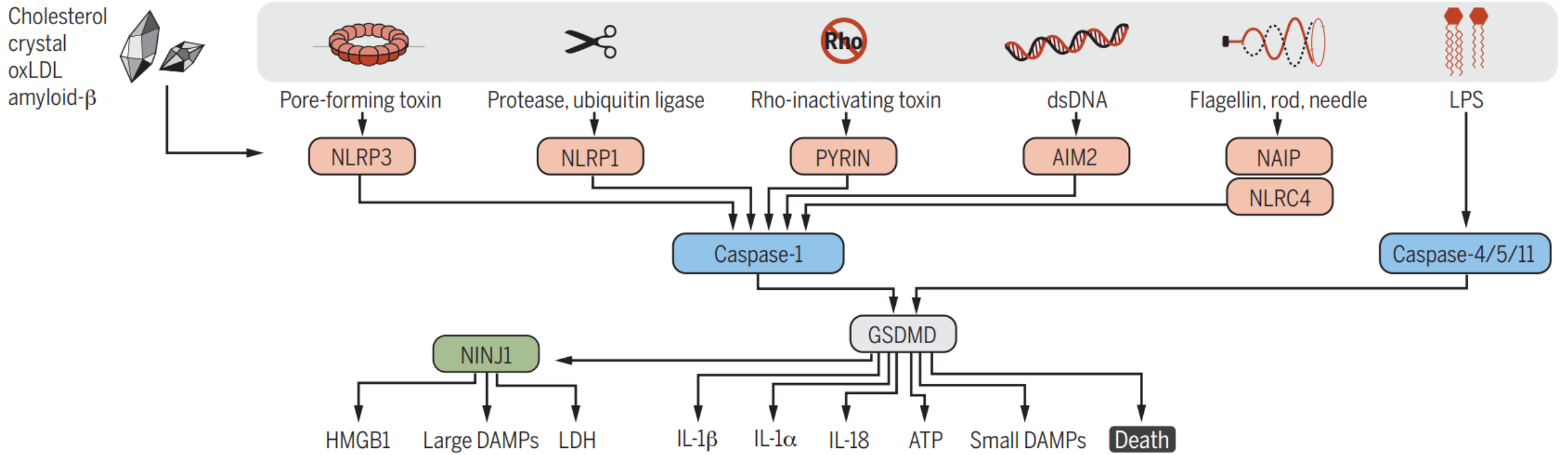
- A mediator of plasma membrane rupture.
- Overturns the long-held idea that cell death-related PMR is a passive event.



> [Nature](#). 2021 Mar;591(7848):131-136. doi: 10.1038/s41586-021-03218-7. Epub 2021 Jan 20.

**NINJ1 mediates plasma membrane rupture during lytic cell death**

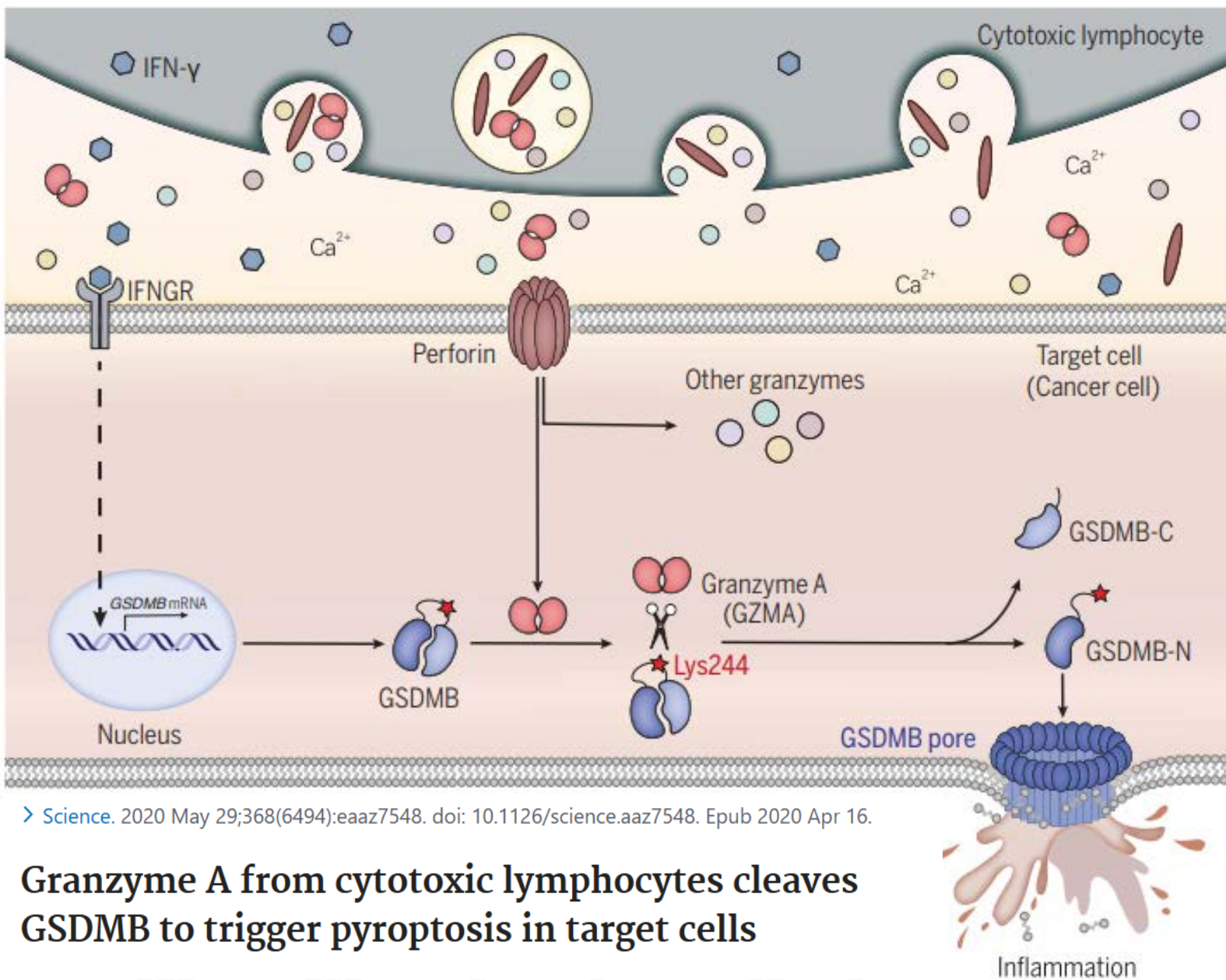
The roles of GSDMD and NINJ1 in pyroptosis and rupture of the plasma membrane



Kim Newton et al., Science. 2021

## An atlas of pyroptosis

Precisely how NINJ1 becomes activated is still unclear.



> Science. 2020 May 29;368(6494):eaaz7548. doi: 10.1126/science.aaz7548. Epub 2020 Apr 16.

## Granzyme A from cytotoxic lymphocytes cleaves GSDME to trigger pyroptosis in target cells

Zhiwei Zhou<sup># 1 2</sup>, Huabin He<sup># 3 2</sup>, Kun Wang<sup>2</sup>, Xuyan Shi<sup>2</sup>, Yupeng Wang<sup>1 2</sup>, Ya Su<sup>2</sup>, Yao Wang<sup>4</sup>, Da Li<sup>2</sup>, Wang Liu<sup>1 2</sup>, Yongliang Zhang<sup>5</sup>, Lianjun Shen<sup>5</sup>, Weidong Han<sup>4</sup>, Lin Shen<sup>6</sup>, Jingjin Ding<sup>2 7</sup>, Feng Shao<sup>8 2 7 9</sup>

免疫学原理-元少春

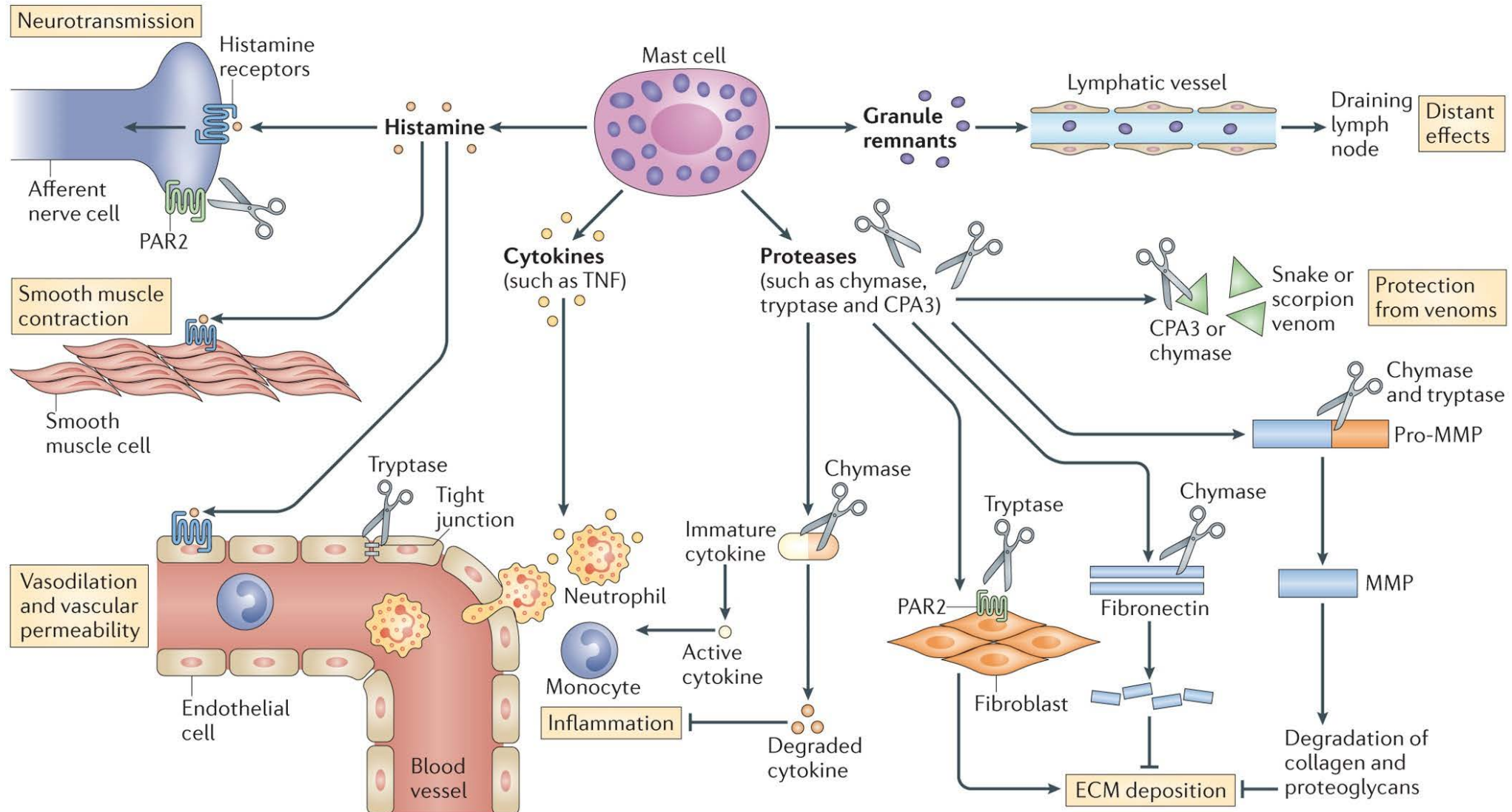
> Nature. 2020 Mar;579(7799):415-420. doi: 10.1038/s41586-020-2071-9. Epub 2020 Mar 11.

## Gasdermin E suppresses tumour growth by activating anti-tumour immunity

Zhibin Zhang<sup># 1 2</sup>, Ying Zhang<sup># 3 4</sup>, Shiyu Xia<sup>3 5</sup>, Qing Kong<sup>6 7</sup>, Shunying Li<sup>8</sup>, Xing Liu<sup>3 4 9</sup>, Caroline Junqueira<sup>3 4 10</sup>, Karla F Meza-Sosa<sup>3 4 11</sup>, Temy Mo Yin Mok<sup>3 4 12</sup>, James Ansara<sup>3 4</sup>, Satyaki Sengupta<sup>4 13</sup>, Yandan Yao<sup>8</sup>, Hao Wu<sup>3 5</sup>, Judy Lieberman<sup>14 15</sup>

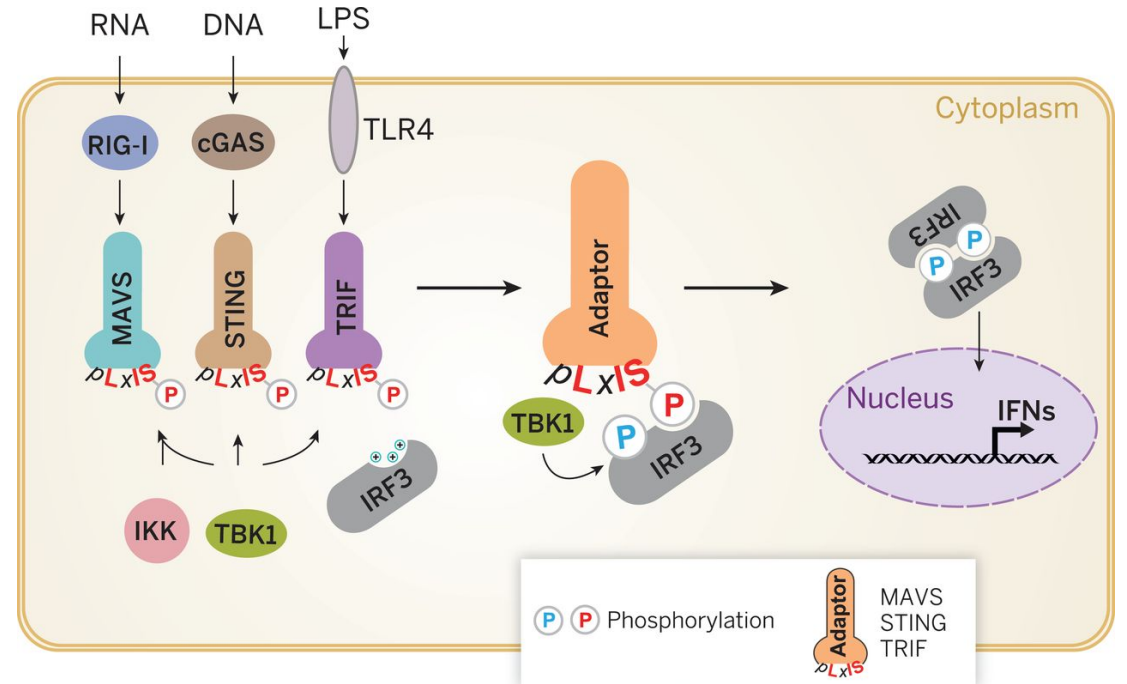
- **Granzyme A-cleavable GSDME** into mouse cancer cells promotes tumor clearance in mice.
- **Granzyme B** from Killer cytotoxic lymphocytes activates pyroptosis in target cells by directly cleaving **GSDME**.

# Mast Cell mediated inflammation



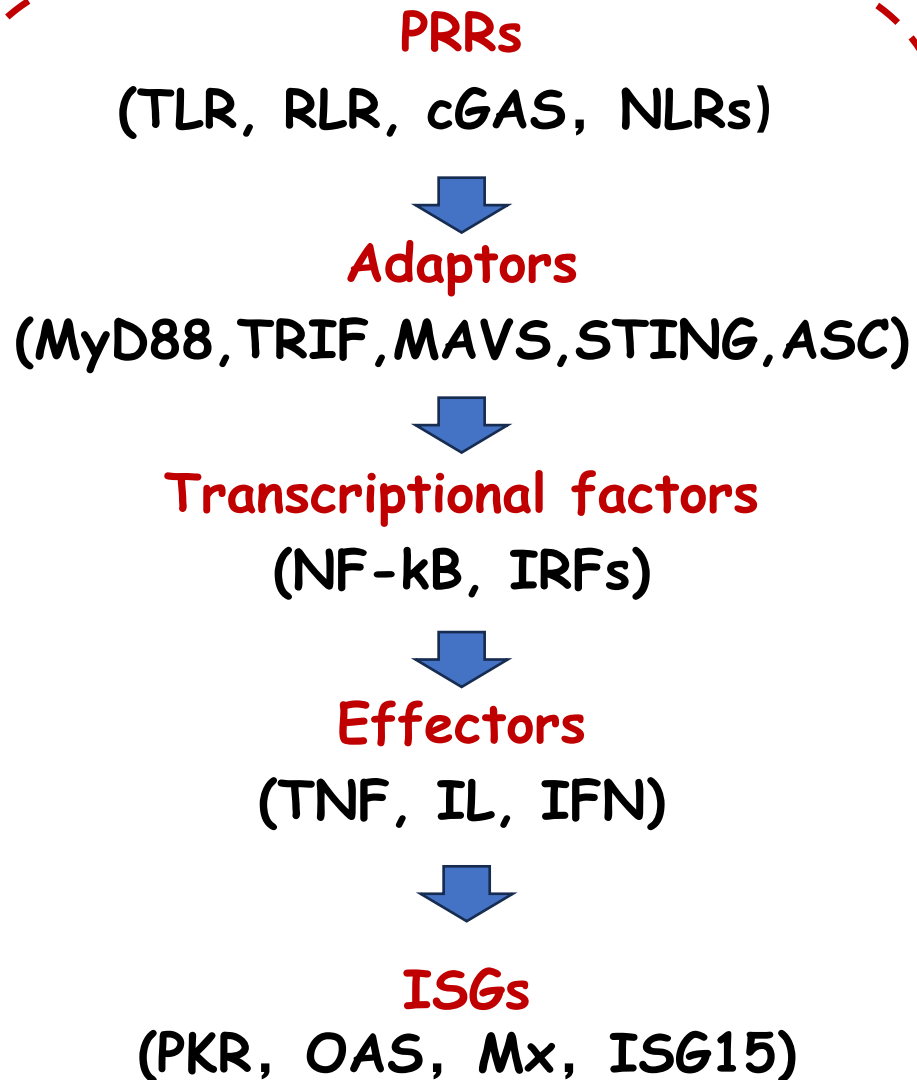
# Innate Immunity: PRR and PAMP

- Toll like receptors (细胞膜, endosomes)
  - TLRs
  - MyD88, TRIF
- RIG-I family receptors (胞质, mitochondria)
  - RIG-I, MDA-5
  - MAVS
- DAI receptors (胞质, ER)
  - cGAS
  - STING
- Inflammasome formation (胞质, TGN)
  - NLRP3, ASC
  - Gasdermin (胞膜成孔)



- Signaling transduction
- Essential motifs
- Essential domains

# Innate Immunity: PRR signaling and Inflammatory response



- Inflammation
  - ✓ Recover leads to **Tissue homeostasis**
  - ✓ Over-response leads to **Chronic inflammation and inflammatory diseases**
- 自身免疫性疾病（复杂多样）
  - ✓ 器官特异性自身免疫性疾病（原发性肝炎，胆管炎等）
  - ✓ 全身性自身免疫性疾病（抗原抗体复合物广泛沉积于血管壁，比如SLE，RA，系统性血管炎）

## 思考题（请于10月15日之前提交）

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- 请你系统地比较Pattern recognition receptor与Antigen recognition receptor的异同（[建议用图表](#)）。
- 针对GSDM 介导的Pyroptosis，你认为可以从哪些角度进行负调控？