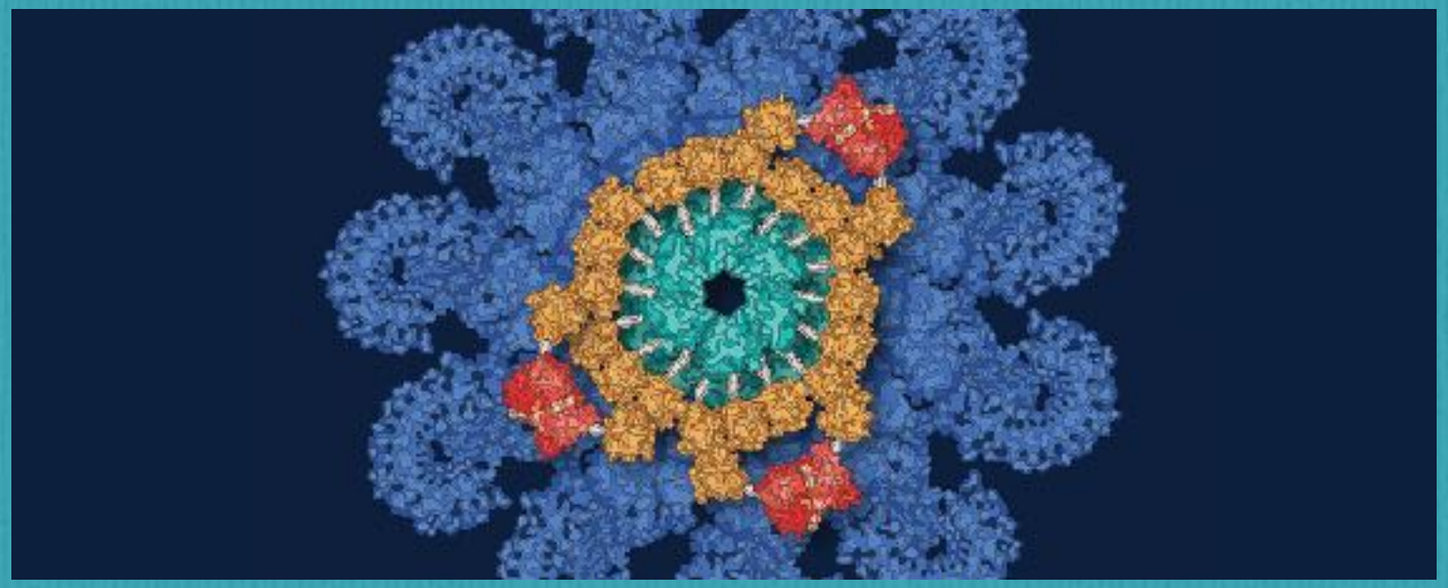
Programa de Pôs-graduação em Imunologia ICB/USP
Disciplina BMI 5904 – Reconhecimento no Sistema Imune

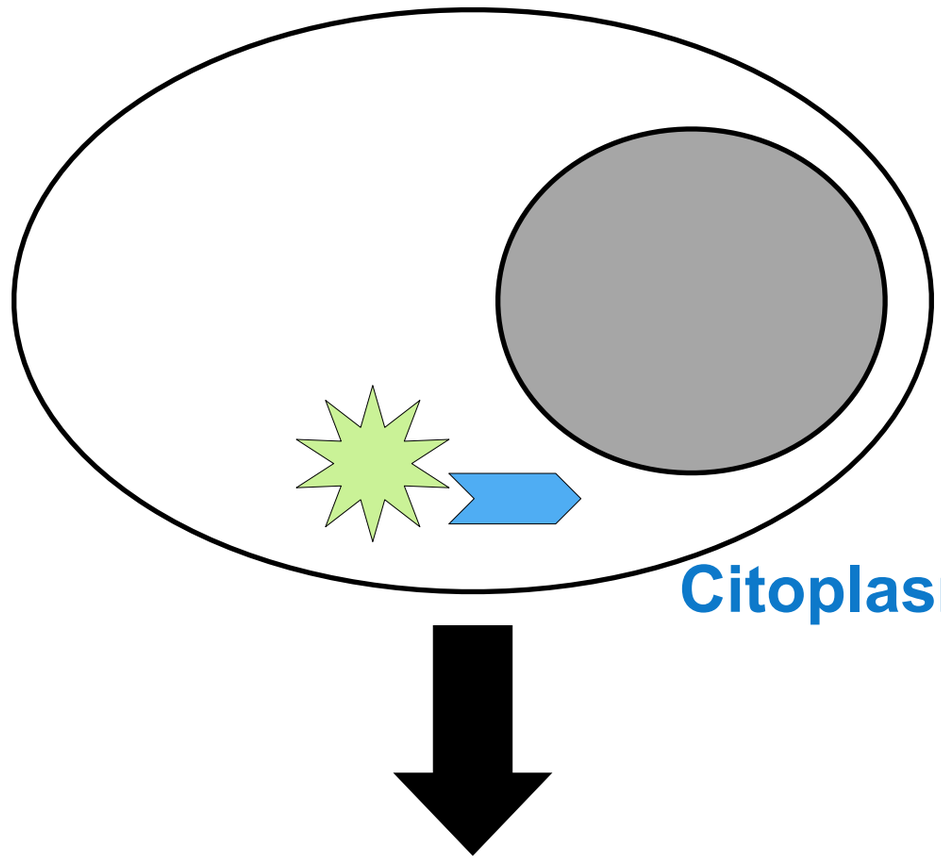


Aula 5

Alessandra Pontillo

Lab. Imunogenetica/Dep.Imunologia/ICB/USP

Cytosolic PRRs



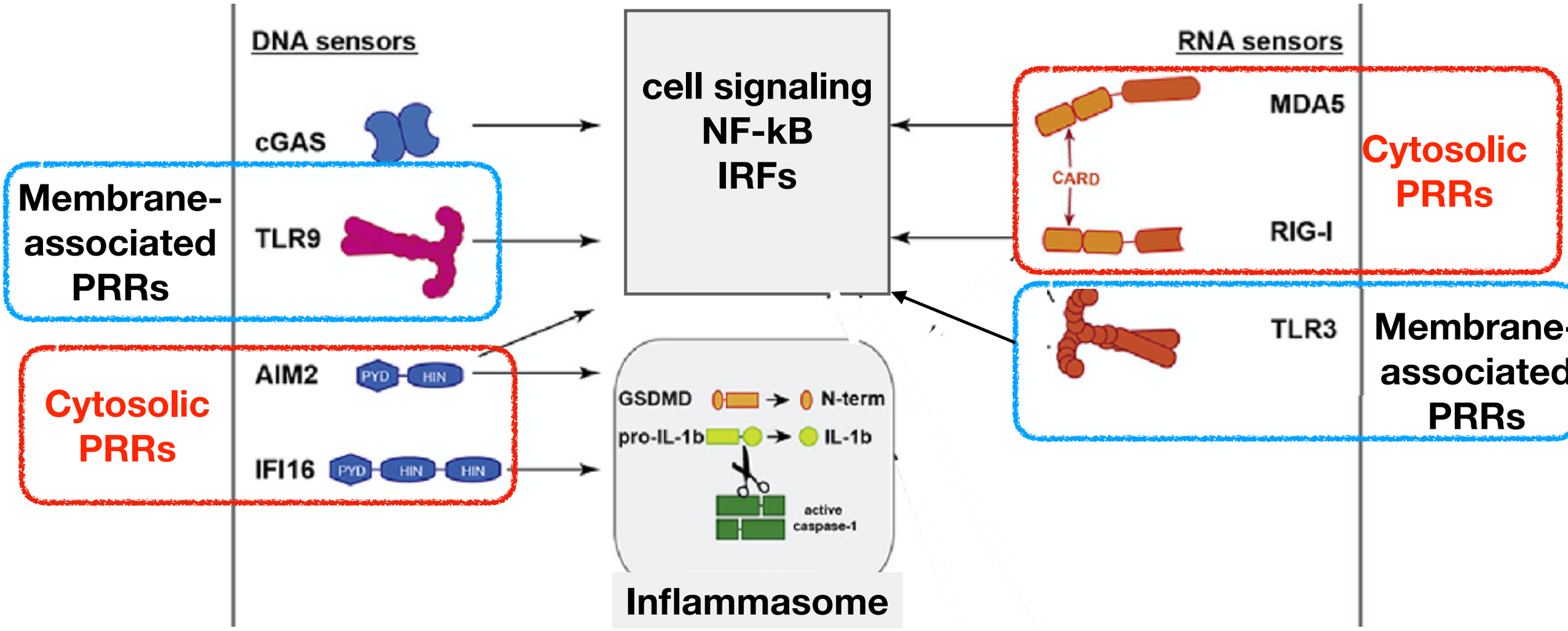
Citoplasmaticos

RECEPTORES DE SINALIZACAO

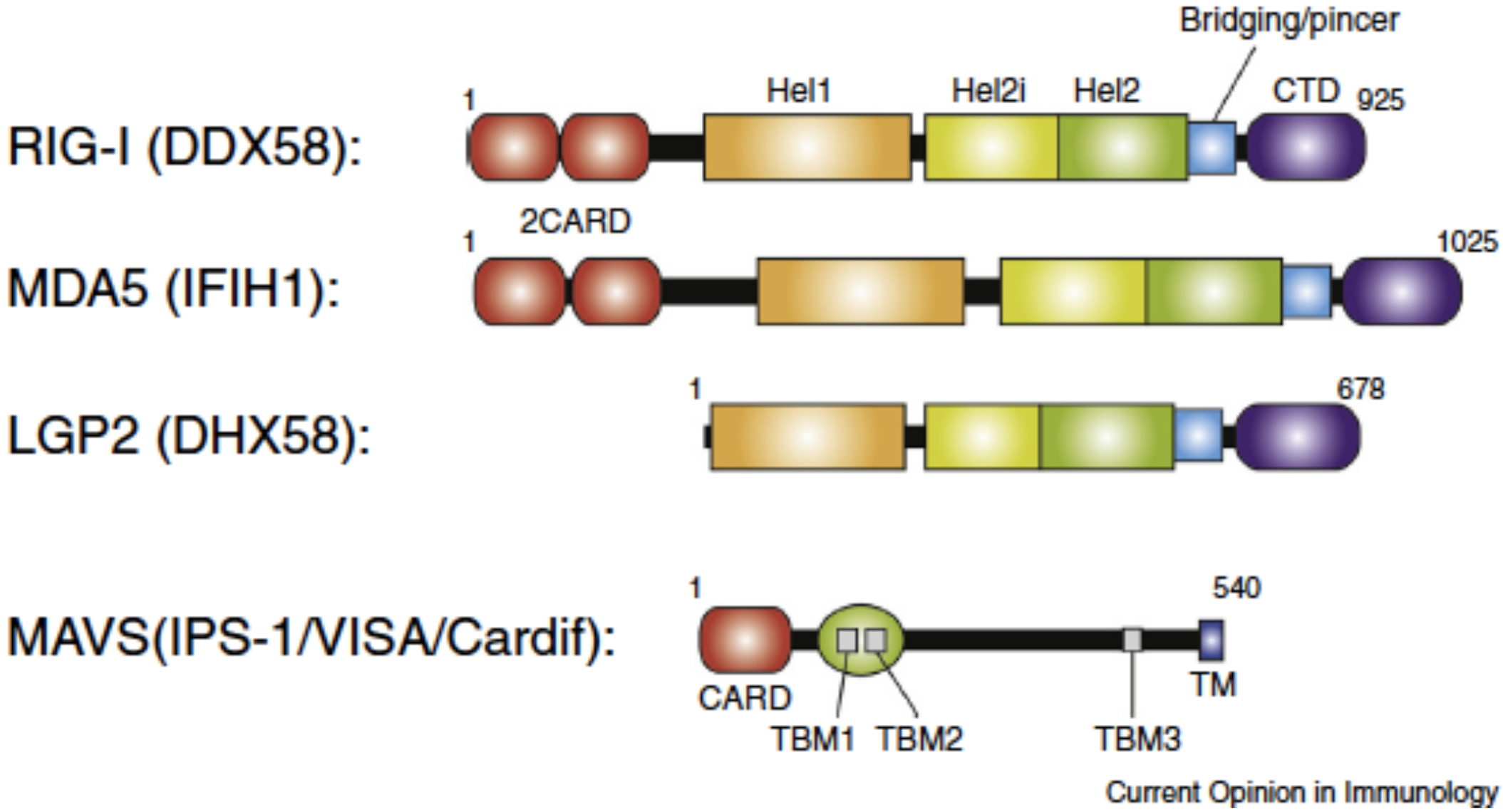
NACHT and LRRs containing receptors (NLRs)
PYD and HIN containing receptors (PYHIN)
RIG-like receptors (RLRs)

morte (da célula infectada)

Receptors for DNA, RNA



RIG-like Receptors (RLRs)



Familia de receptores citoplasmaticos para RNA viral

- ✓ RIG-I reconhece dsRNA (Newcastle disease, Sendai, Influenza, Vesicular stomatitis, Japanese encephalitis, measles, Rabies, Hepatitis C, Dengue)
- ✓ MDA-5 reconhece dsRNA (Picornavirus, Encephalomyocarditis, Rabies, Sendai, Dengue, Rotavirus, murine hepaitis, murine norovirus I)

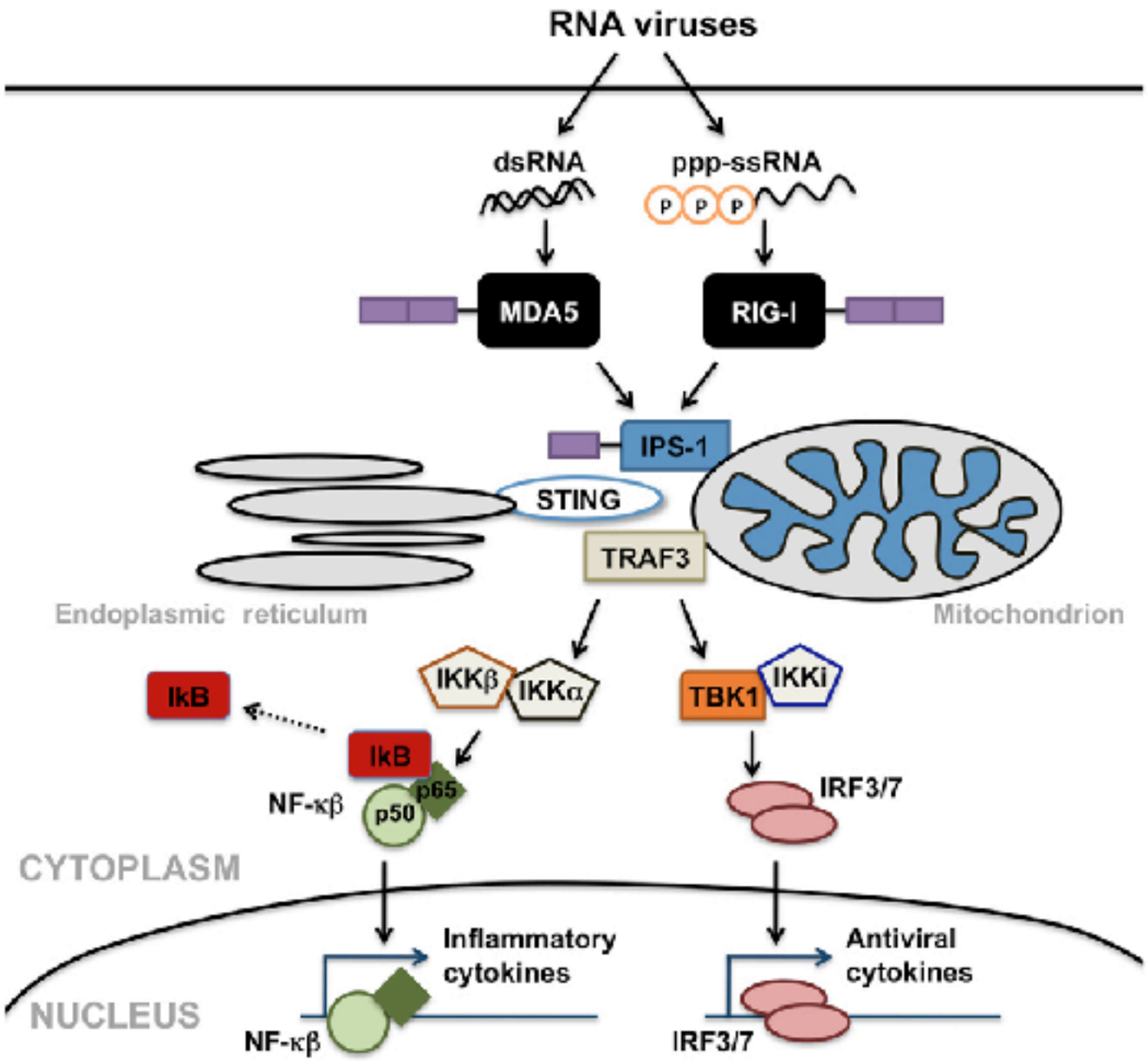
RIG-like receptors (RLRs)

Familia de receptores citoplasmaticos para RNA

- ✓ RIG-I reconhece ssRNA (Newcastle disease, Sendai, Influenza, Vesicular stomatitis, Japanese encephalitis, measles, Rabies, Hepatitis C, Dengue)
- ✓ MDA-5 reconhece dsRNA (Picornavirus, Encephalomyocarditis, Rabies, Sendai, Dengue, Rotavirus, murine hepaitis, murine norovirus I)

Importantes na resposta anti-viral

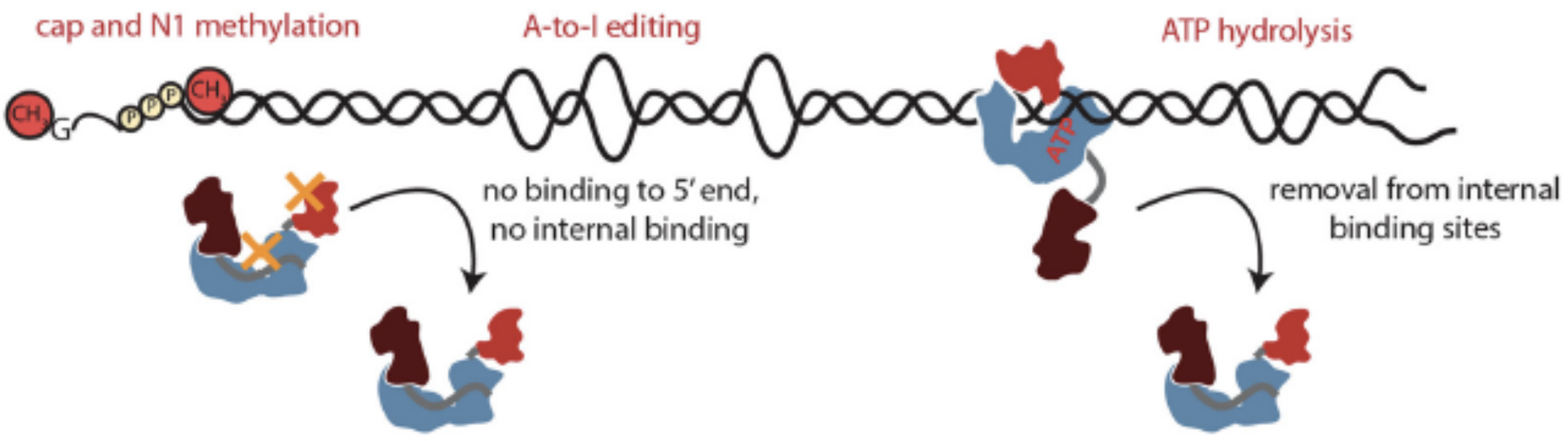
- Ativam NF-kB e inflamação
- Ativam IRF3/7 e produção de IFN-tipo I



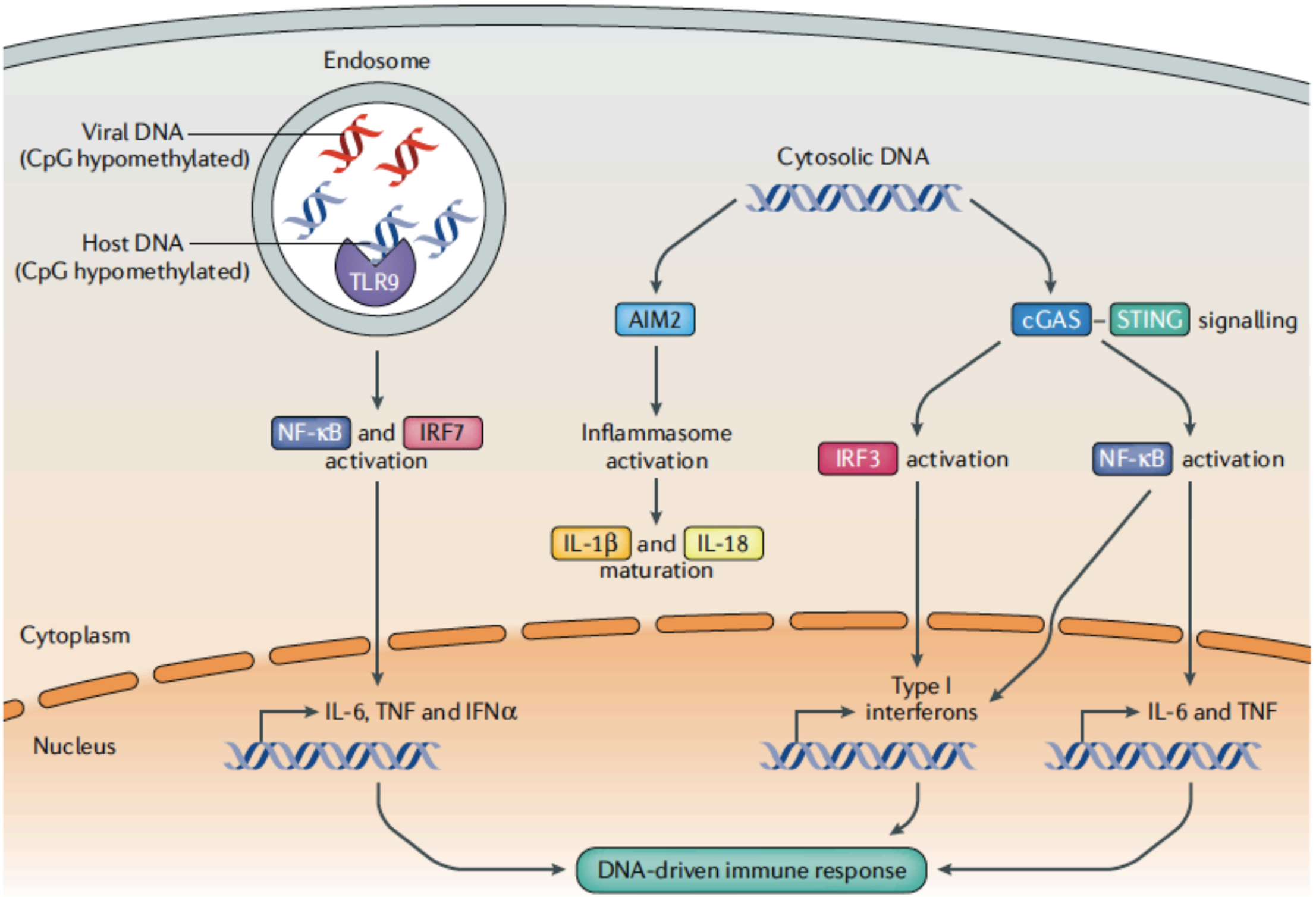
RLRs

O reconhecimento de RNA “self” pelos RLRs é evitado pelas modificações pós-traducionais:

- mutilação do “5’guanine-cap”
- mutilação do primeiro ribonucleotideo



DNA sensing

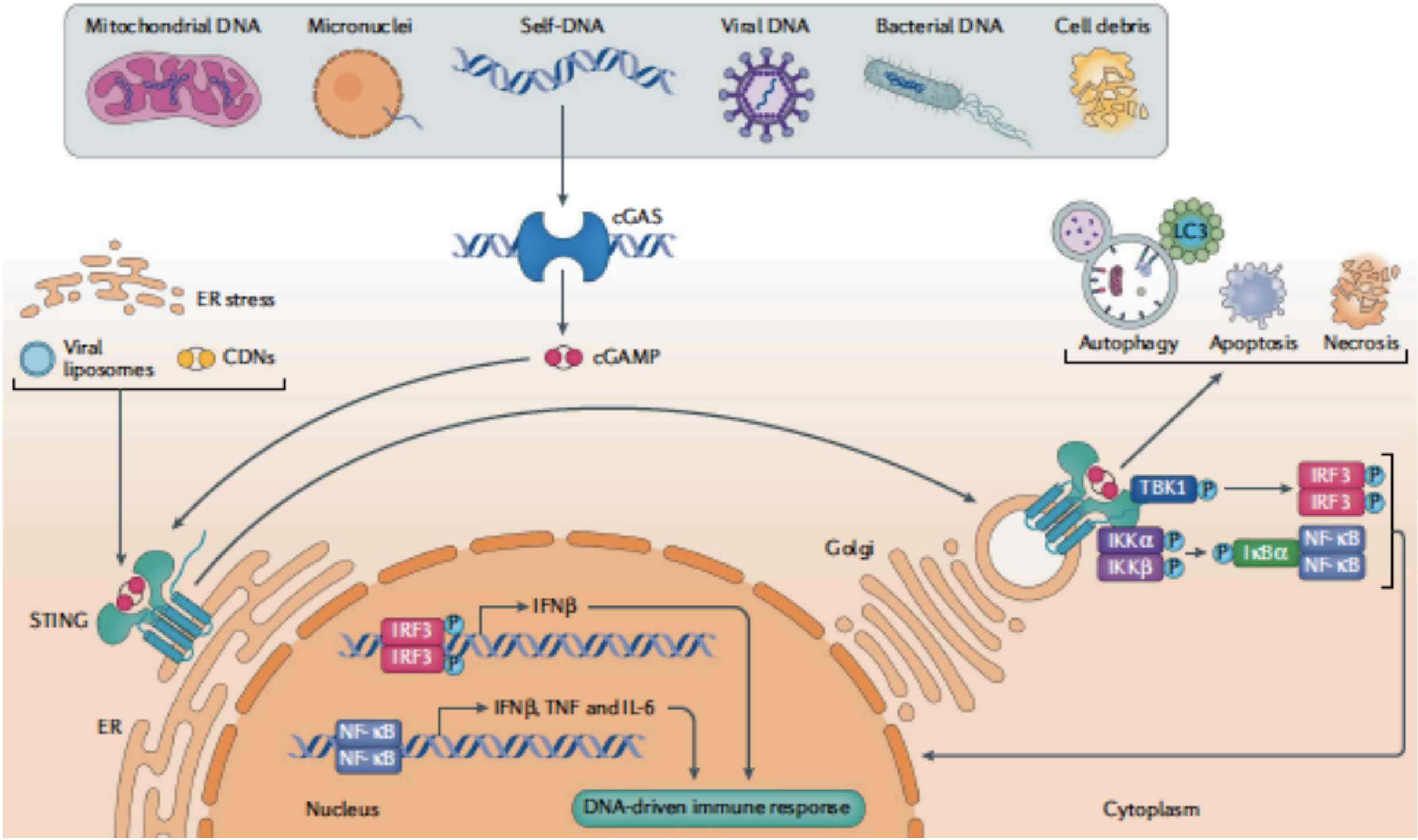


From Motwani et al. 2019

c-GAS STING pathway

- Um dos maiores mecanismos de deteção de DNA citosólico
- Importante em infecções por bacterias intracelulares e alguns virus a DNA
- O reconhecimento do DNA è direto
- O tamanho do DNA è crucial (>45 bp interação mais estavel)
- O reconhecimento resulta na ativação do adaptador STING
- Resulta na produção de IFN-I e ativação do NF-kB

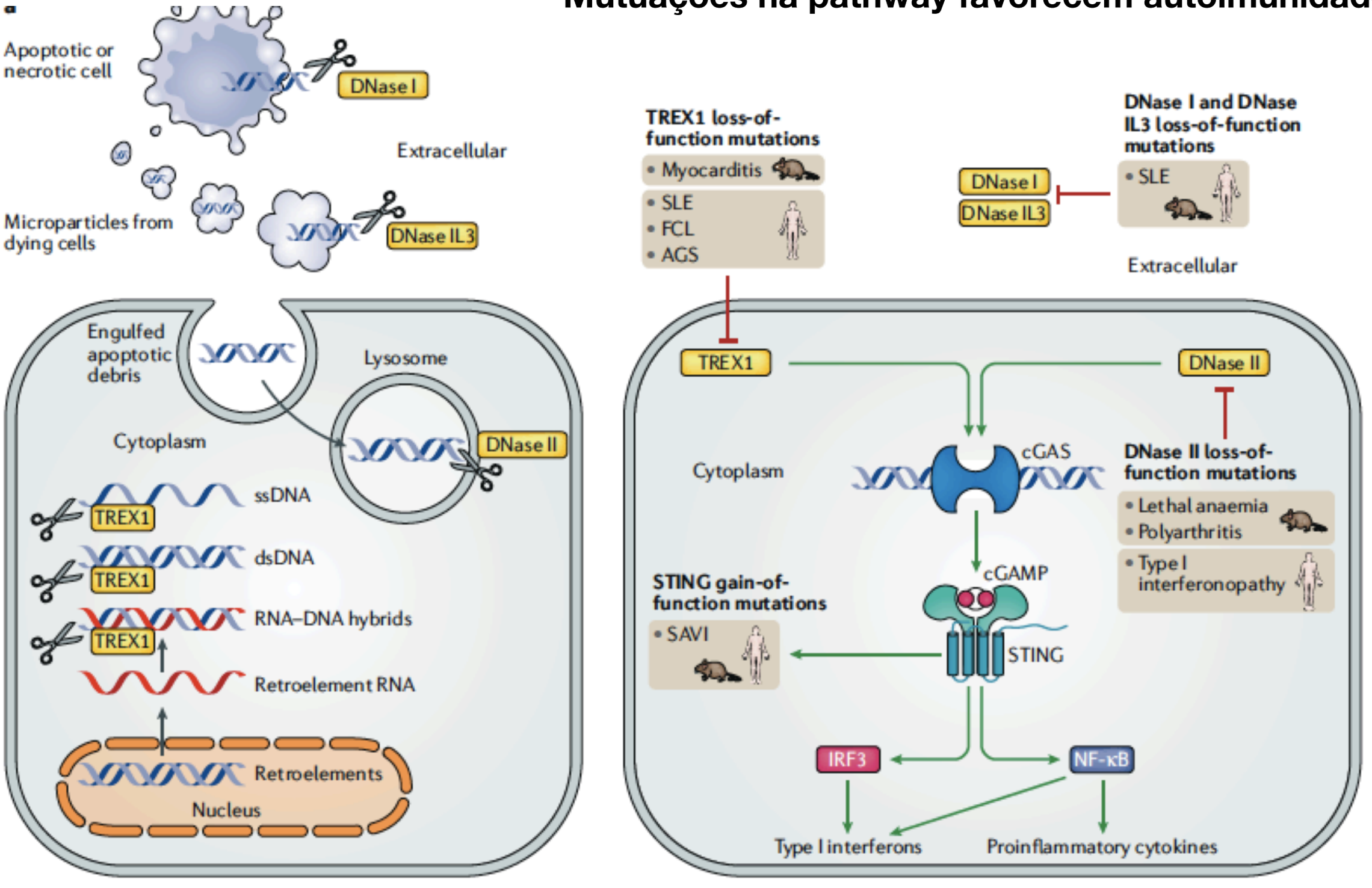
c-GAS STING pathway



From Motwani et al. 2019

c-GAS STING pathway

Mutuações na pathway favorecem autoimunidade



From Motwani et al. 2019

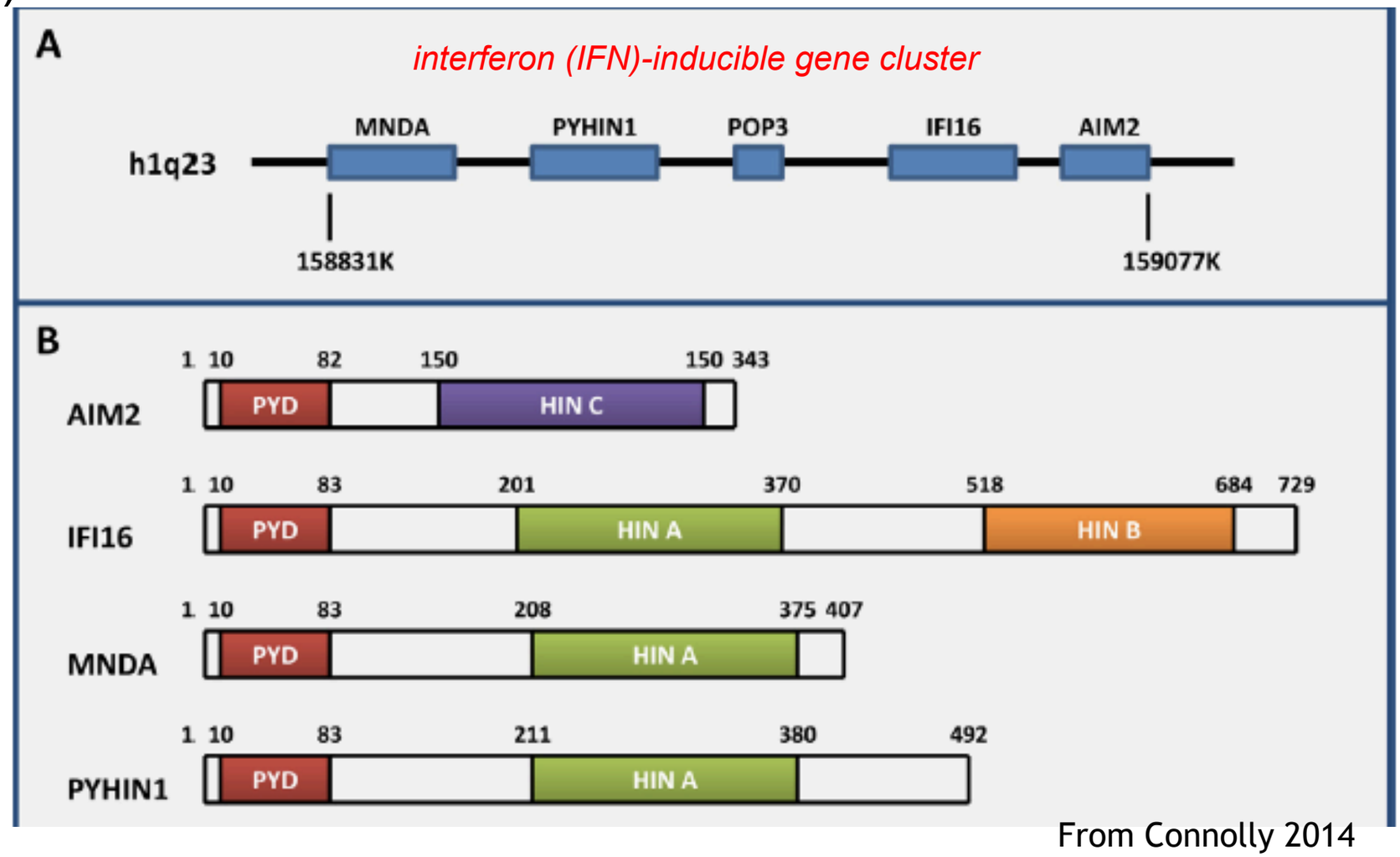
Receptores PYHIN

✓ Receptores de DNA (PAMP ou DAMP) que contem os dominios
- (N terminal) PYD
- (C-terminal) Hematopoietic IFN inducible Nuclear protein with 200-aminoacids (HIN-200)

4 homologos in humanos (13 in camundongo)

1. MNDA (1986, cell growth)
2. **AIM2**
3. **IFI16**
4. IFIX

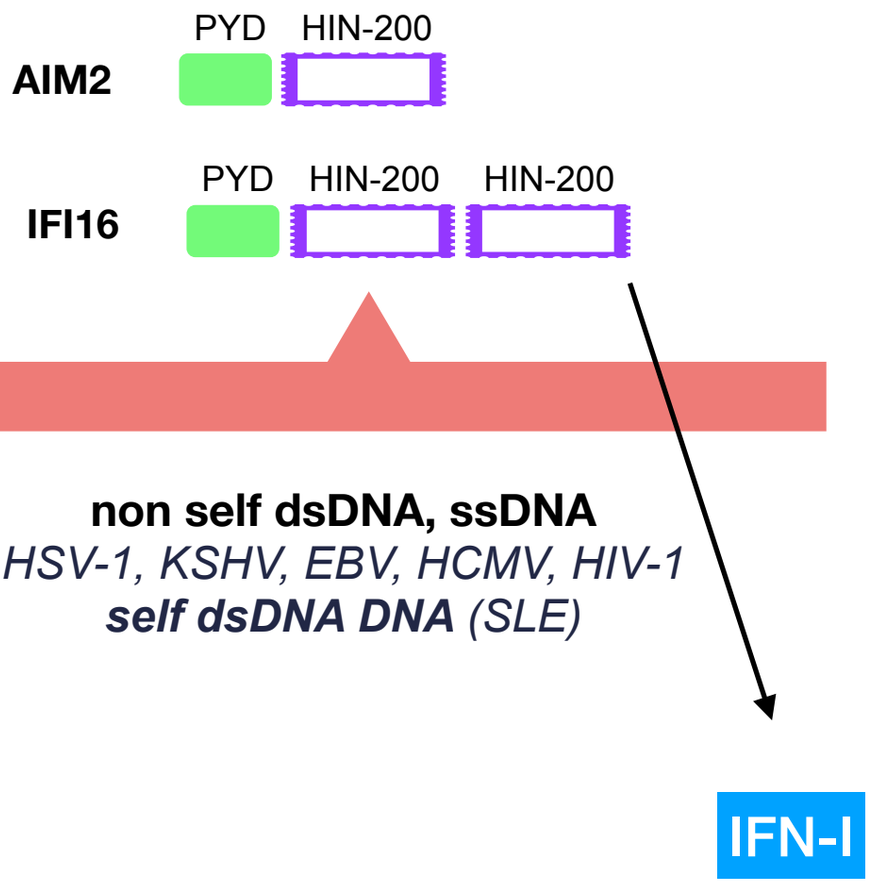
Localizaçao
- Nucleo (**IFI16***, MNDA*, IFIX)
- Citosol (**AIM2**)



From Connolly 2014

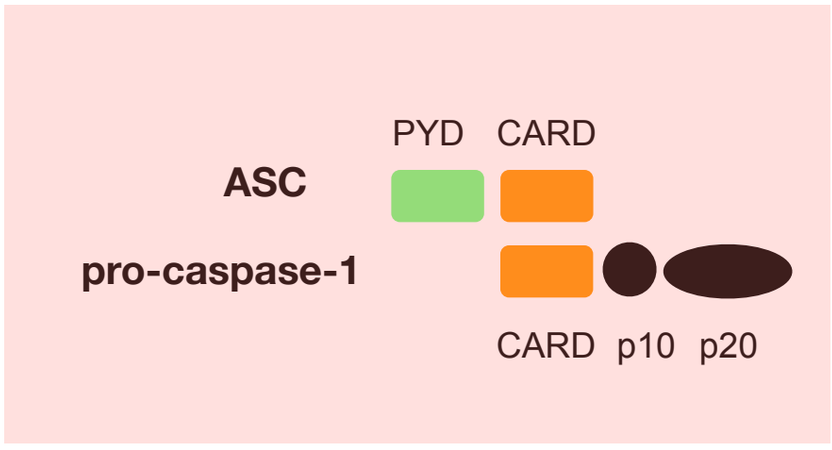
PYHIN Receptors

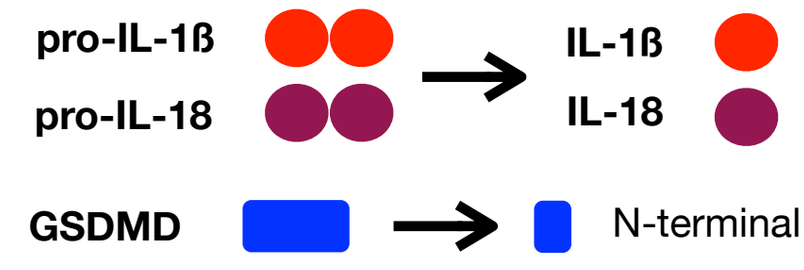
non self dsDNA
L.*monocytogenes, M. tuberculosis, Plasmodium spp*, *F. tularensis, S pneumoniae, M. tuberculosis, S. aureus, A. fumigatus, vaccinia virus,CMV, HPV*
self dsDNA DNA *(SLE, acute pancreatitis)*



non self dsDNA, ssDNA
HSV-1, KSHV, EBV, HCMV, HIV-1
self dsDNA DNA *(SLE)*

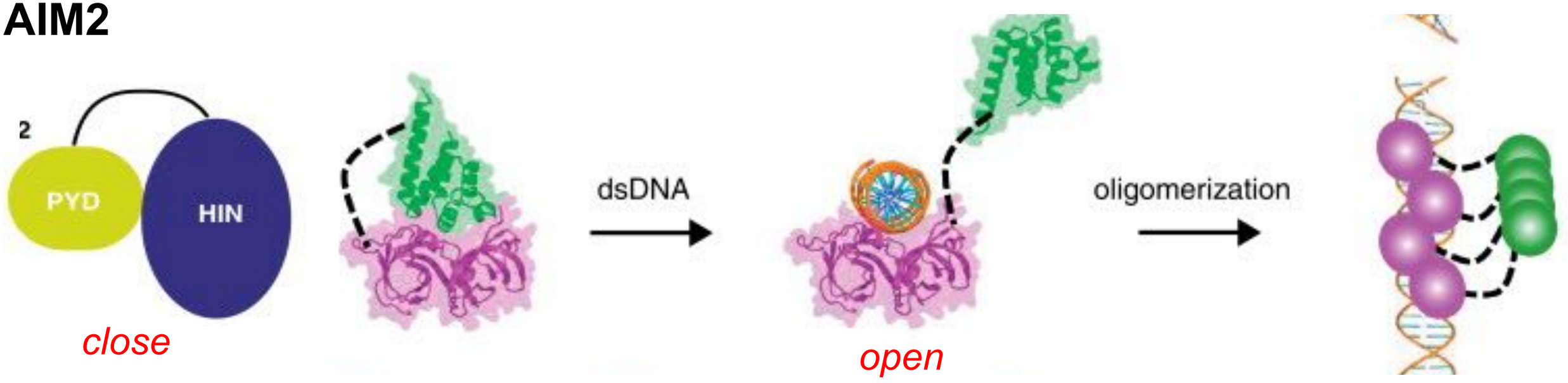
IFN-I



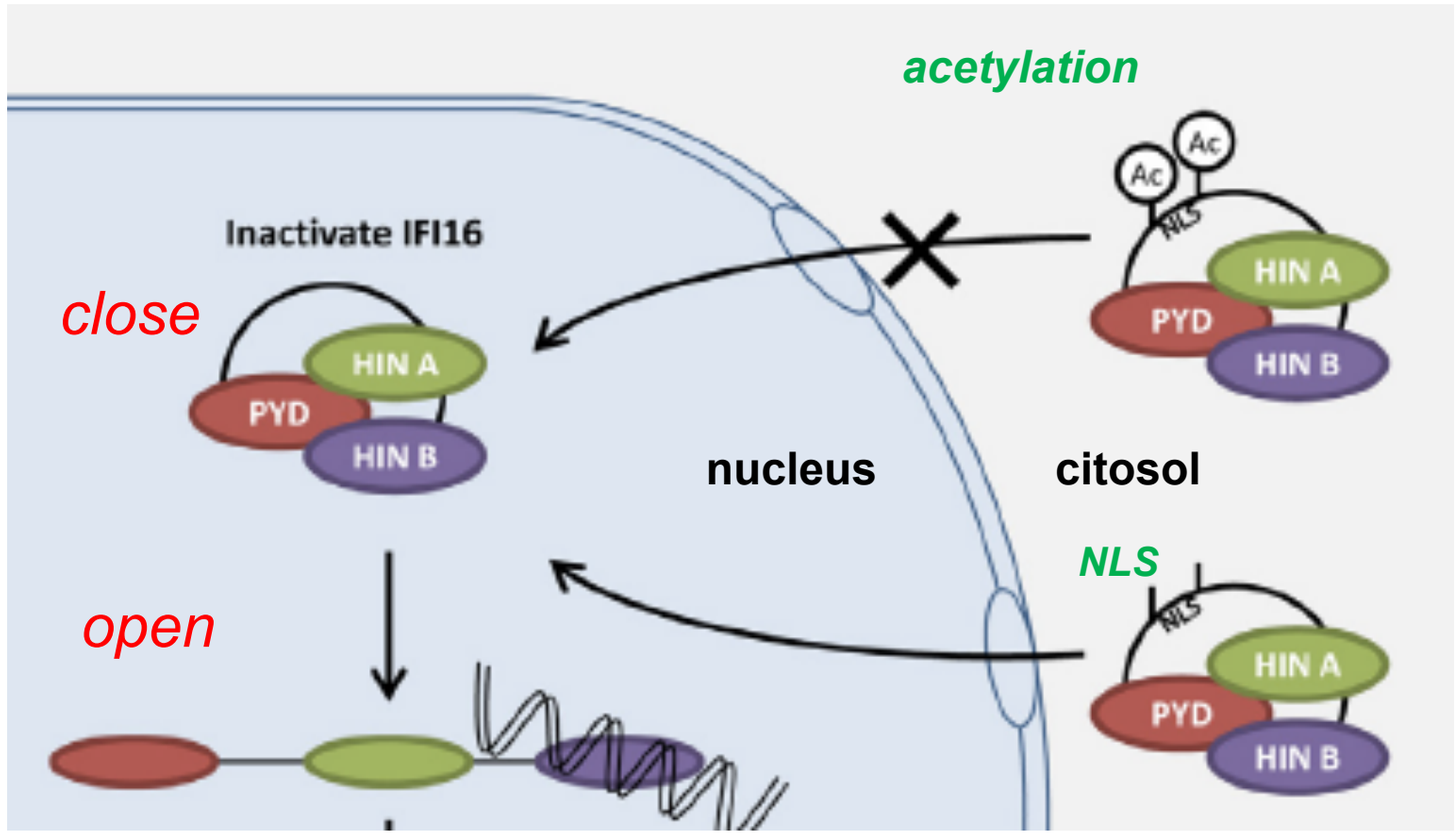


Receptores PYHIN

AIM2

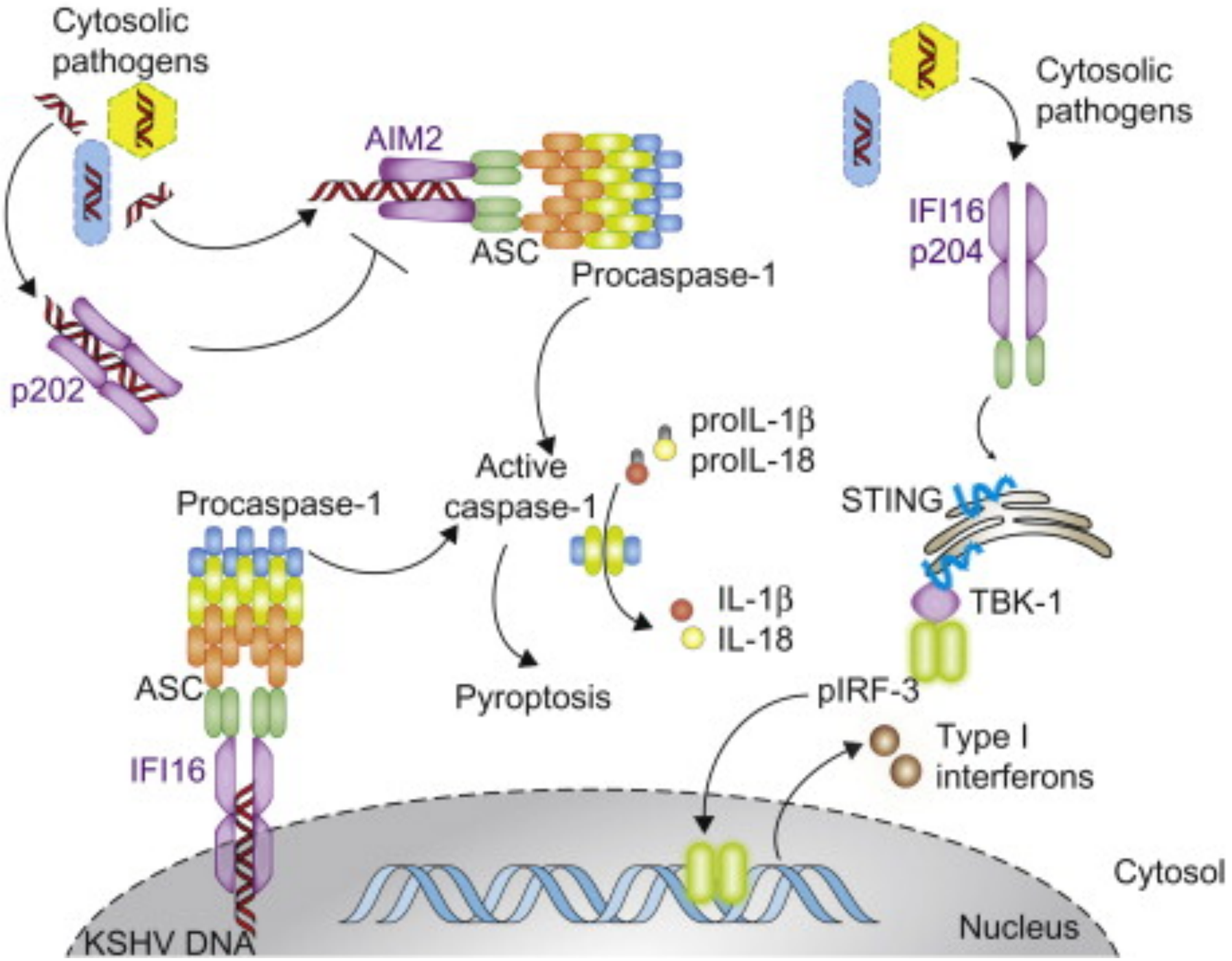


IFI16



Connolly 2014

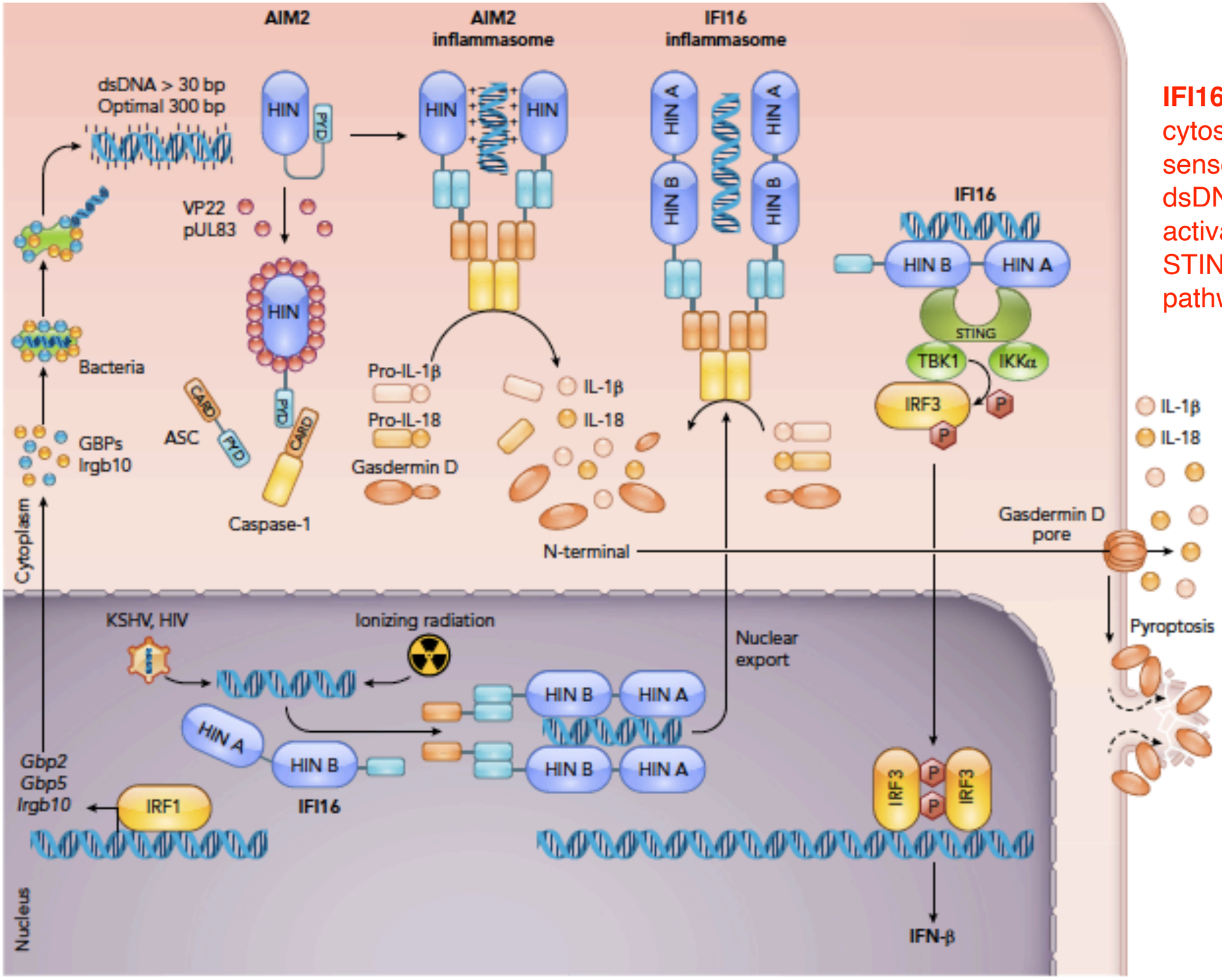
PYHIN Receptors



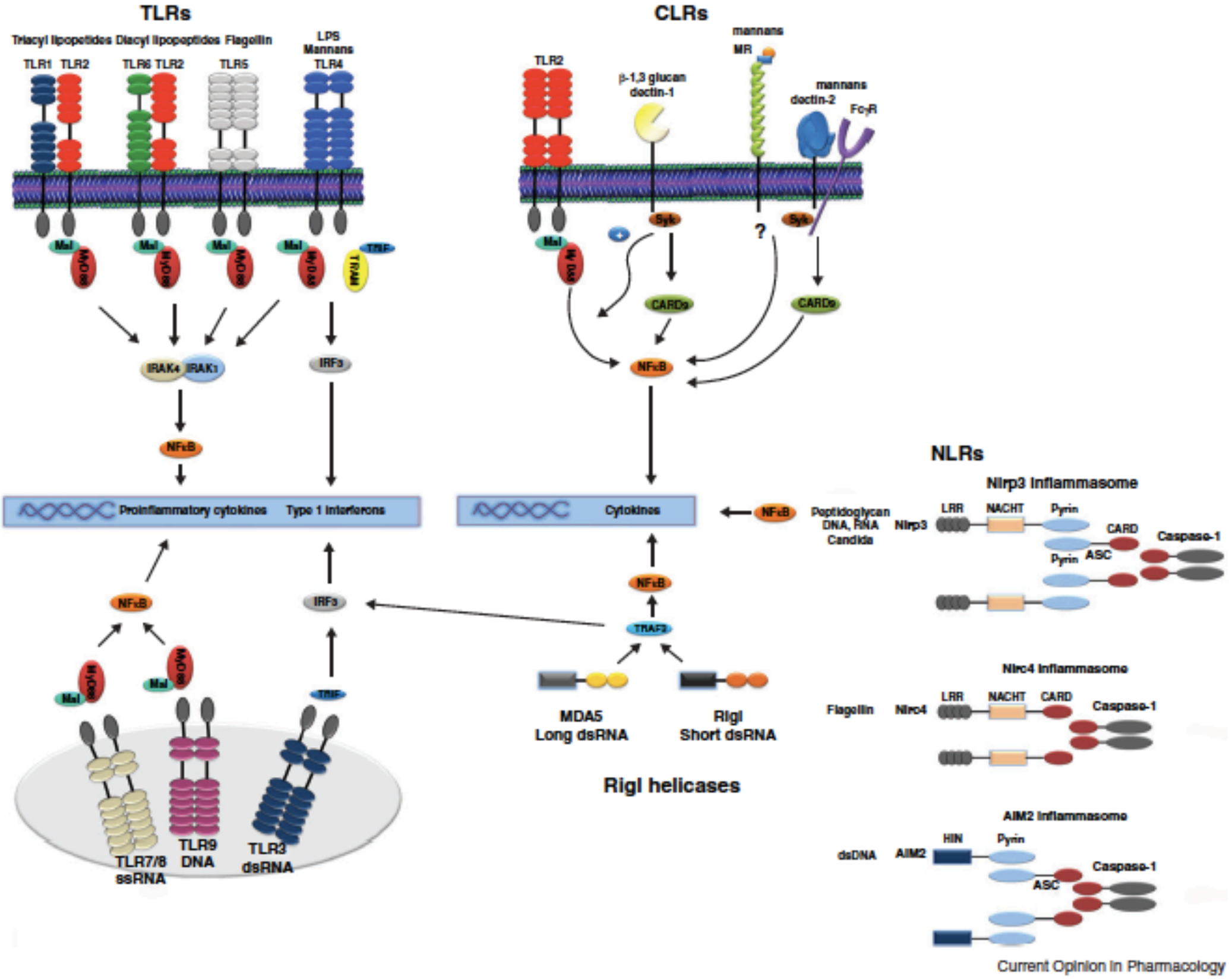
PYHIN Receptors

IRF1-dependent **GBPs** and **IRGB10** facilitate the release of bacterial DNA into the cytosol for **AIM2** detection

IFI16 is localized in the nucleus and senses dsDNA directly from there.



Resumindo PRRs



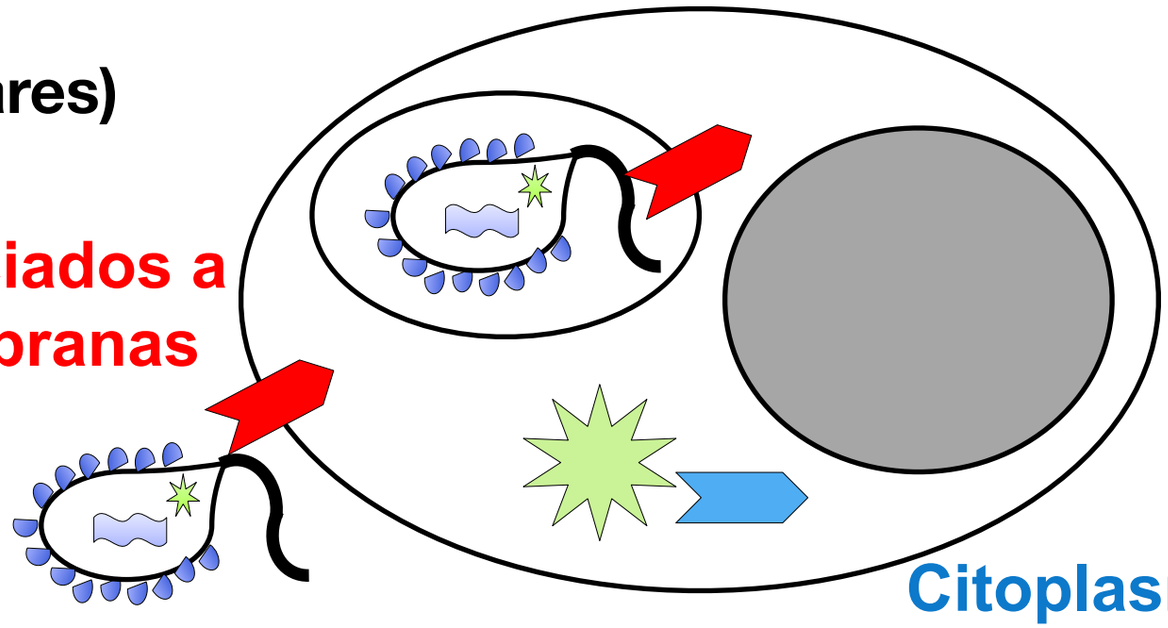
Nettea 2011

Resumindo…

PRRs
(padrões moleculares)

TLRs
CLRs
Scavangers

Associados a membranas



Citoplasmaticos

NLRs
PYHIN
RLRs

Receptores de Opsoninas (PRMs, AC, S. complemento)

Ativação do sistema imune inato

Sinalização intracelular
- NF-kB (mediadores pro-inflamatorios, moléculas antimicrobianas)
- IRFs (IFN-I, fatores anti-virais)
- inflamassoma (IL-1ß/18, pyroptose)

Fagocitose & killing
Desgranulaçao
Citotoxicidade
ADCC

Morte celular