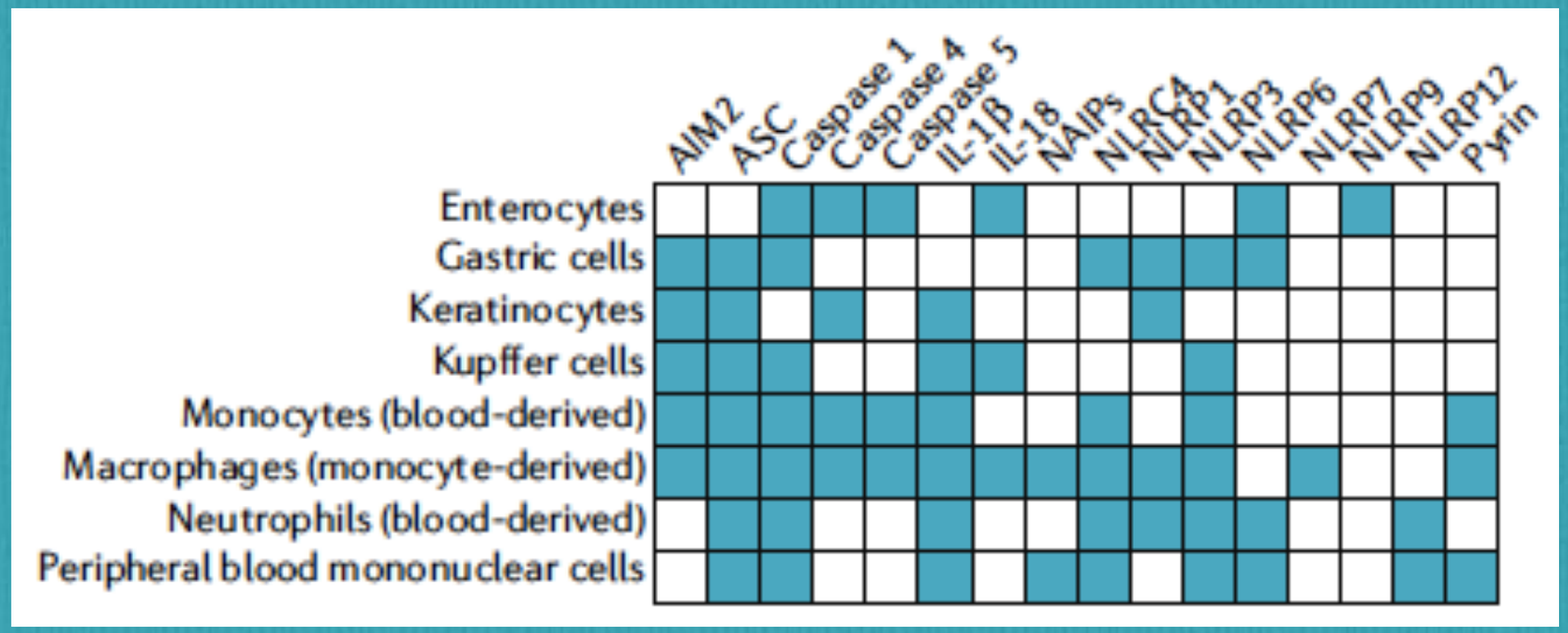
# Programa de Pôs-graduação em Imunologia ICB/USP

# Disciplina BMI 5904
# Reconhecimento no Sistema Imune




# Aula 6

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# Tópicos de hoje

✓ Alguns receptores da imunidade inata que não são PRRs

✓ Onde estão expressos e em qual nível os PRRs

# Ainda Rec de Fagocitose

| Receptor type on phagocytes | Examples | LIgands |
|---|---|---|
| **Reconhecimento direto do patogeno** | | |
| C-type lectin receptors (CLRs) | Mannose receptor | Mannans (bacteria, fungi, parasites) |
| | Dectin 1 | β-glucans (fungi, some bacteria) |
| | DC-SIGN | Mannans (bacteria, fungi, parasites) |
| Scavenger receptors | SR-A | Lipopolysaccharide (LPS), lipoteichoic acid (LTA) (bacteria) |
| | SR-B | LTA, lipopeptides, diacylglycerides (bacteria), β-glucans (fungi) |
| **Reconhecimento indireto (das OPSONINAS)** | | |
| Collagen-domain receptor | CD91/calreticulin | **PRMs** Collectins SP-A, SP-D, MBL; L-ficolin; C1q |
| Complement receptors | CR1, CR3, CR4, CRIg, C1qRp | Complement components and fragments* |
| Immunoglobulin Fc receptors | FcαR | **ACs** Specific IgA antibodies bound to antigen# |
| | FcγRs | Specific IgG antibodies bound to antigen;# C-reactive protein |

→ ***Produção de mediadores***

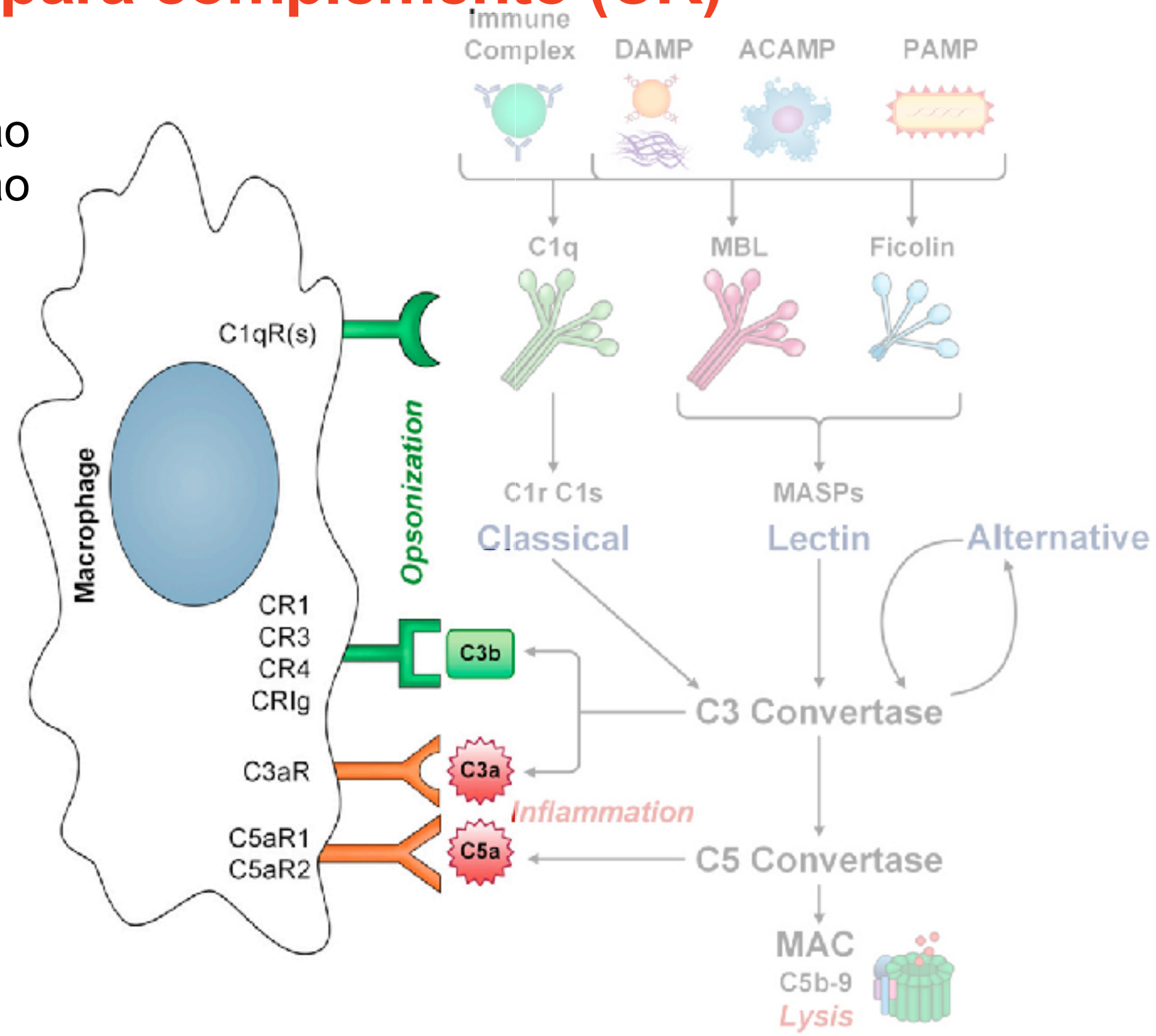
- ***Recrutar e ativar leucocitos***
- ***Inflamaçao***

**Help!!!!**

# Reconhecimento indireto

## Receptores para complemento (CR)

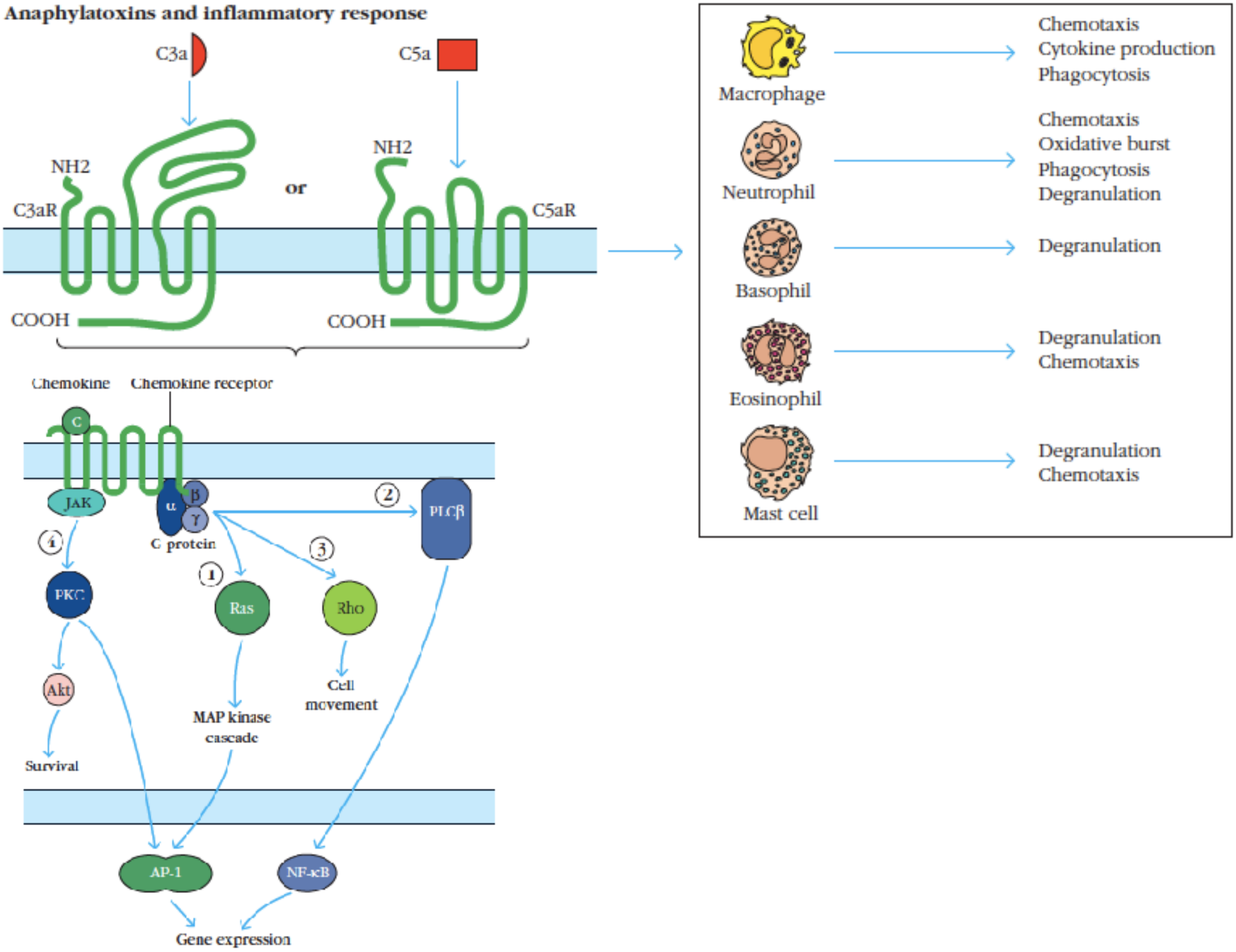
- Fagocitose
- Desgranulaçao
- Pro-inflamaçao



# CRs

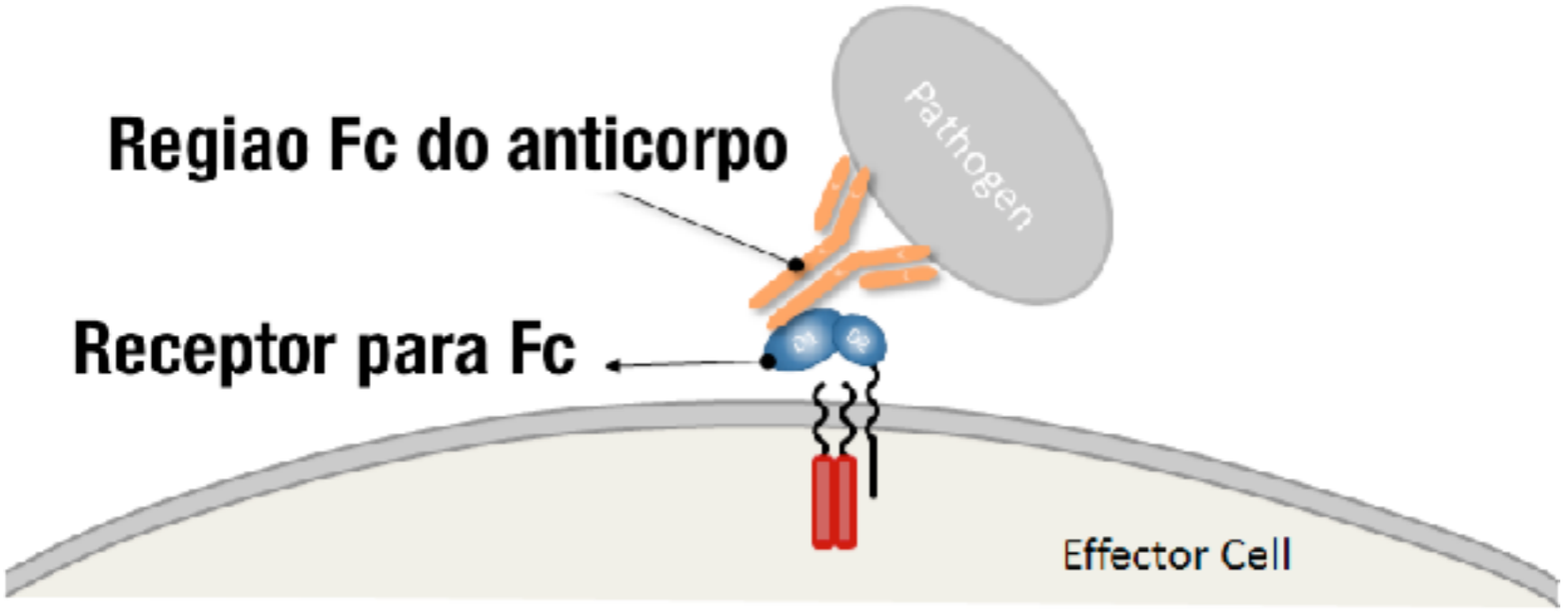
| Receptor | Alternative name(s) | Ligand | Cell surface binding or expression | Function |
|---|---|---|---|---|
| CR1 | CD35 | C3b, C4b, C1q, iC3b | Erythrocytes, neutrophils, monocytes, macrophages, eosinophils, FDCs, B cells, and some T cells | Clearance of immune complexes, enhancement of phagocytosis, regulation of C3 breakdown |
| CR2 | CD21, Epstein-Barr virus receptor | C3d, C3dg (human), C3d (mouse) iC3b | B cells and FDCs | Enhancement of B-cell activation, B-cell coreceptor, and retention of C3d-tagged immune complexes |
| CR3 | CD11b/CD18, Mac-1 | iC3b and factor H | Monocytes, macrophages, neutrophils, NK cells, eosinophils, FDCs, T cells | Binding to adhesion molecules on leukocytes, facilitates extravasation; iC3b binding enhances opsonization of immune complexes |
| CR4 | CD11c/CD18 | iC3b | Monocytes, macrophages, neutrophils, dendritic cells, NK cells, T cells | iC3b-mediated phagocytosis |
| CRIg | VSIG4 | C3b, iC3b, and C3c | Fixed-tissue macrophages | iC3b-mediated phagocytosis and inhibition of alternative pathway |
| $C1qR_p$ | CD93 | C1q, MBL | Monocytes, neutrophils, endothelial cell, platelets, T cells | Induces T-cell activation; enhances phagocytosis |
| SIGN-R1 | CD209 | C1q | Marginal zone and lymph node macrophages | Enhances opsonization of bacteria by MZ macrophages |
| C3aR | None | C3a | Mast cells, basophils, granulocytes | Induces degranulation |
| C5aR | CD88 | C5a | Mast cells, basophils, granulocytes, monocytes, macrophages, platelets, endothelial cells, T cells | Induces degranulation; chemoattraction; acts with IL-1β and/or TNF-α to induce acute phase response; induces respiratory burst in neutrophils |
| C5L2 | None | C5a | Mast cells, basophils, immature dendritic cells | Uncertain, but most probably down-regulates proinflammatory effects of C5a |

# Anaphylatoxins & inflammation

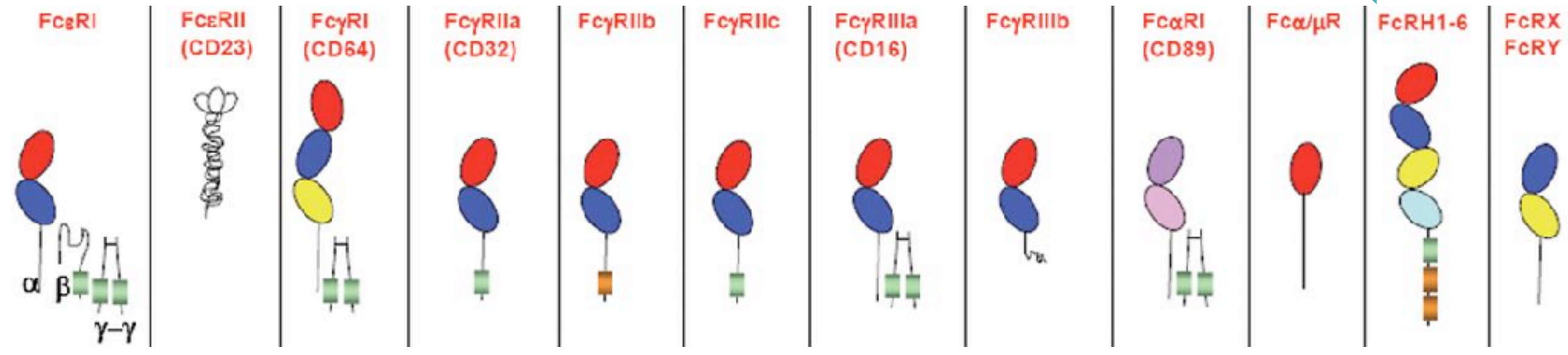


# Reconhecimento indireto

## Receptores para Fc dos AC (FcR)

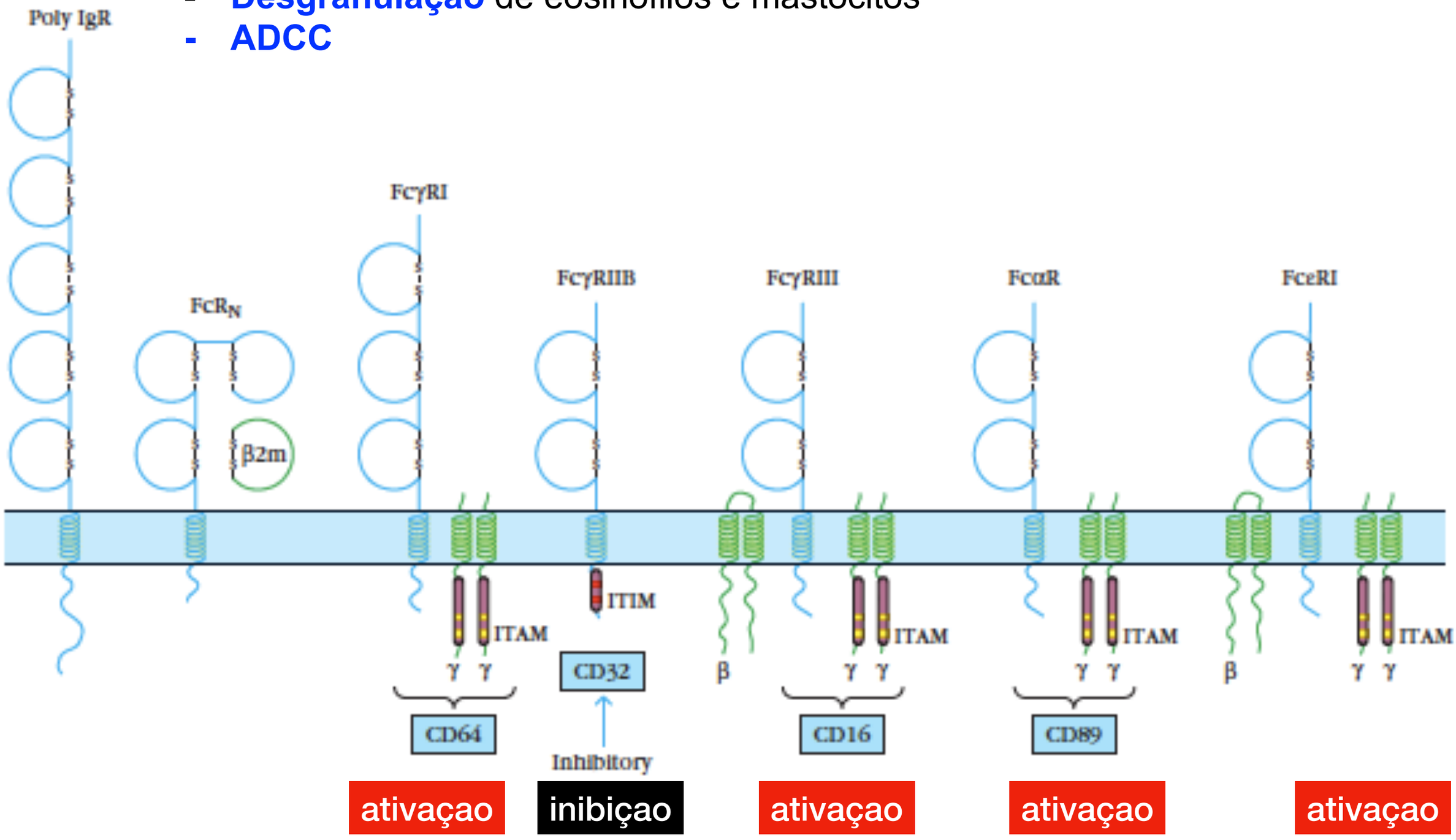



*IgM, IgG, IgA, IgE*

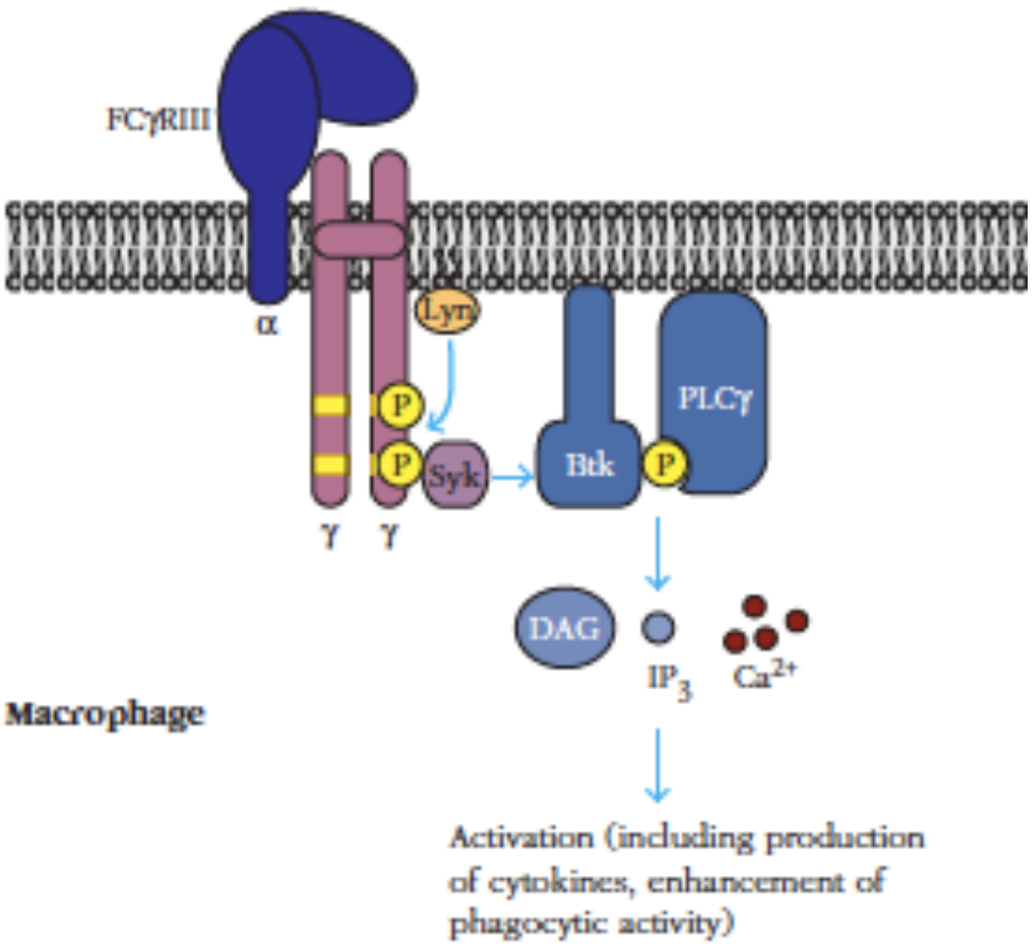


# FcRs

- ✓ na superficie de muitos leucocitos
- ✓ induzem
- - **Fagocitose** da célula opsonizada pelos AC e potenciamento do *Killing*
- - **Desgranulaçao** de eosinofilos e mastocitos
- - **ADCC**

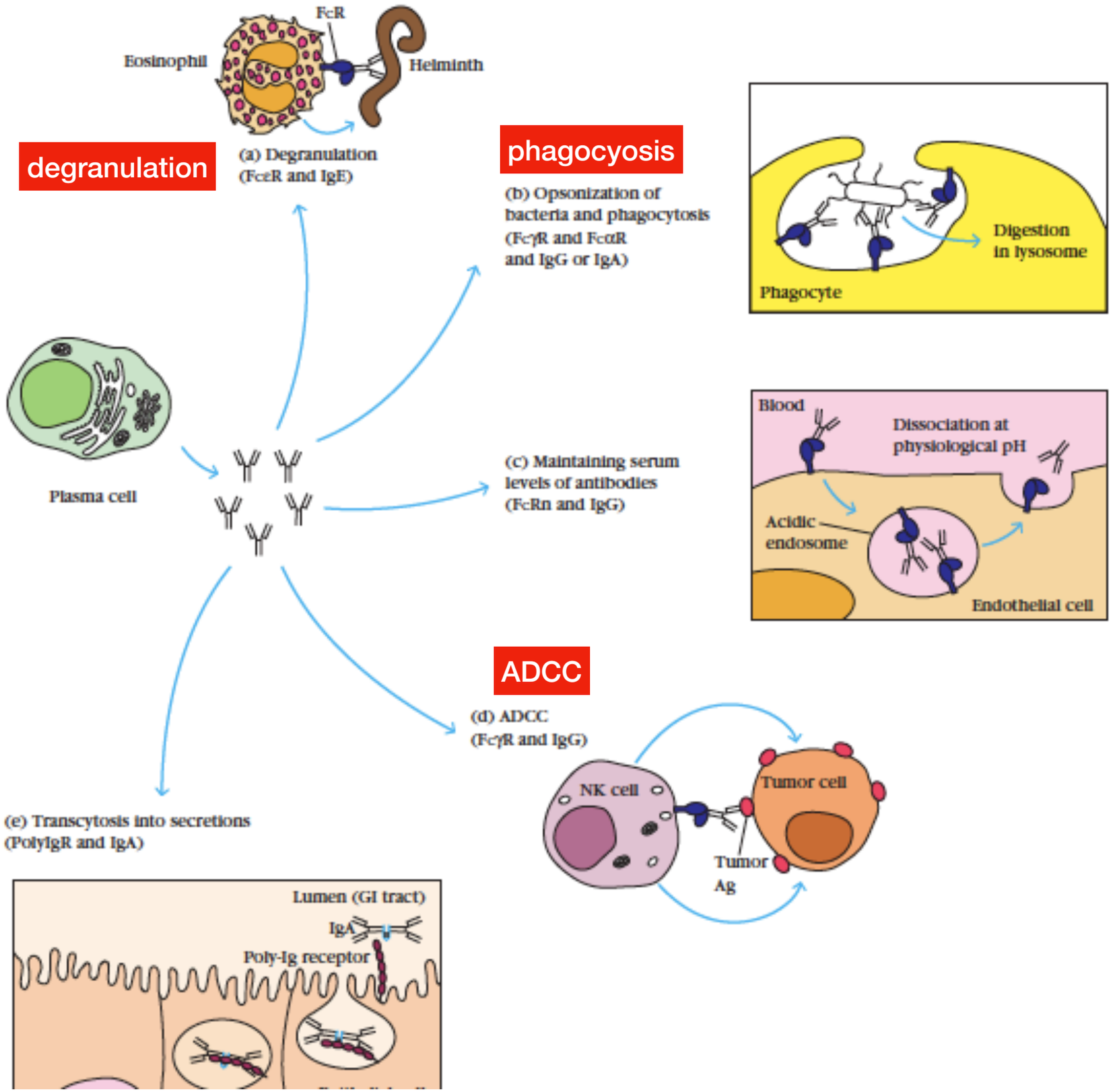


# FcRs

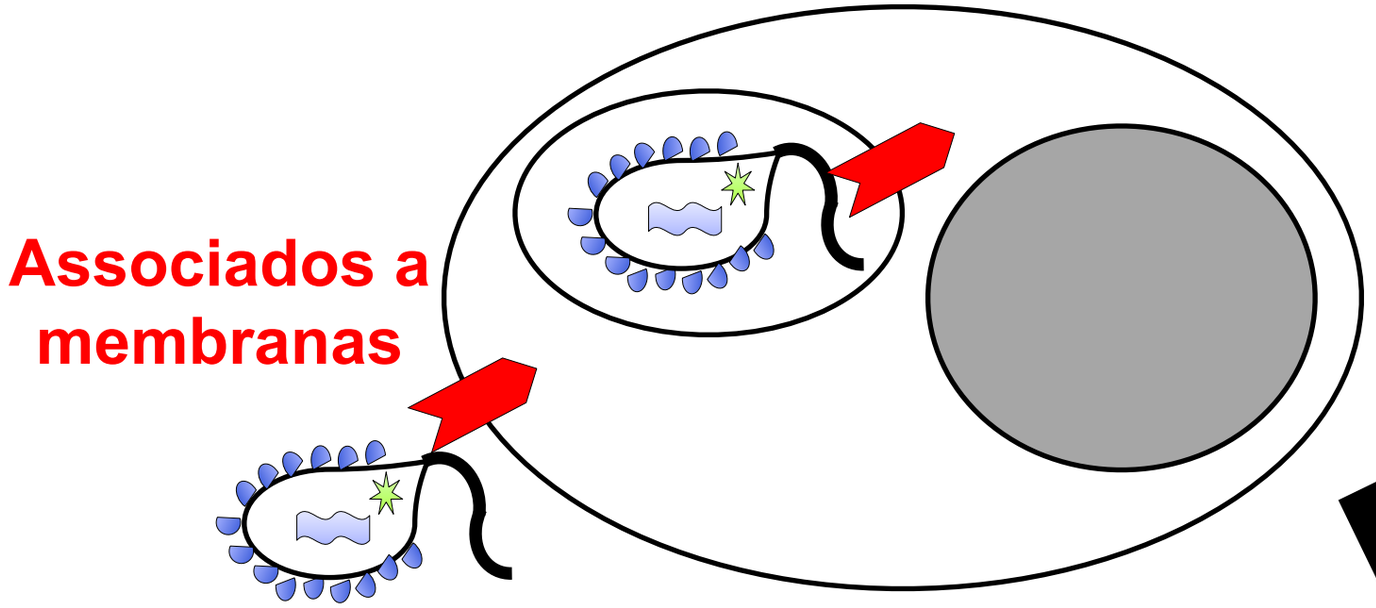



| FcR | Isotypes they bind | Cells that express them | Function |
|---|---|---|---|
| FcγRI (CD64) | IgG2a in mice, IgG1 and IgG3 in humans<br>High-affinity receptor | Dendritic cells, monocytes, macrophages, granulocytes, B lymphocytes | Phagocytosis<br>Cell activation |
| FcγRII (CD32) | IgG | Dendritic cells, monocytes, macrophages, granulocytes, B lymphocytes, some immature lymphocytes | Inhibitory receptor<br>Traps antigen-antibody complexes in germinal center<br>Abrogates B-cell activation |
| FcγRIII (CD16)<br>Humans generate two versions: FcγRIIIA (CD16a) and FcγRIIIB (CD16b) | IgG1, IgG2a, and IgG2b in mouse; IgG1 in human<br>Low -affinity receptor<br>Only FcR that binds mouse IgG1 | Dendritic cells, monocytes, macrophages, granulocytes, B lymphocytes<br>Only FcR expressed by NK cells | ADCC<br>Cell activation |
| FcγRIV (in mouse, with some similarity to human FcγRIIIA and/or human FcεRI) | IgG2a and IgG2b in mice; IgG1 in humans<br>Intermediate affinity receptor, although exhibits higher affinity for human IgG1 than FcgRIIA. | Monocytes, macrophages, granulocytes<br>Not on lymphocytes | ADCC<br>Cell activation |
| FcεRI | IgE | Eosinophils, basophils, mast cells | Degranulation of granulocytes, including eosinophils, basophils, mast cells |
| FcεRII (CD23) | IgE (low affinity) | B lymphocytes | Regulation of B-cell production of IgE<br>Transport of IgE-antigen complexes to B-cell follicles |
| FcαRI (CD89) | IgA | Dendritic cells, monocytes, macrophages, granulocytes, some liver cells | Phagocytosis<br>Cell activation<br>ADCC |
| pIgR | IgA and IgM | Multiple epithelial cells | Transport of antibody from blood to the lumens of GI, respiratory, and reproductive tracts (transcytosis) |
| FcRn (neonatal FcR) | IgG | Epithelial cells (including intestinal epithelium)<br>Endothelial cells of mature animals | Transport of antibodies from milk to blood (transcytosis)<br>Transport of antibody-pathogen complexes from gut to mucosal immune tissue<br>Phagocytosis<br>Maintenance of levels of serum IgG and albumin |

# FcRs & Functions



# Membrane-associated PRRs & non-PRRs




**non-PRRs**

CRs, FcRs, opsonin R

**Fagocitose, Endocitose, Desgranulação ADCC**

**PRRs**

Receptores de carboidratos (CLRs)
Receptores Scavenger

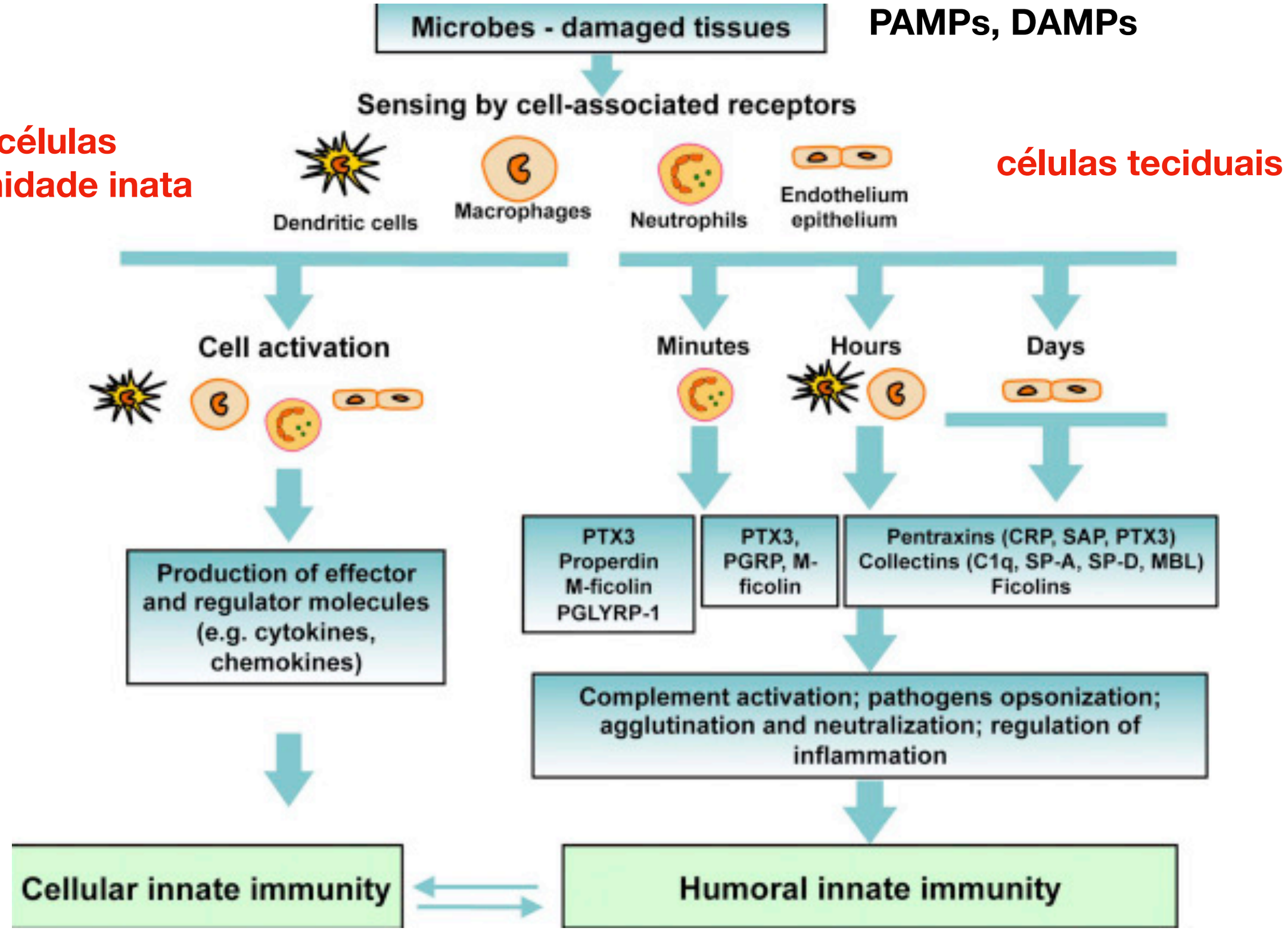
**Fagocitose, endocitose (Cytotoxicity in NK)**

**Sinalização intracelular**

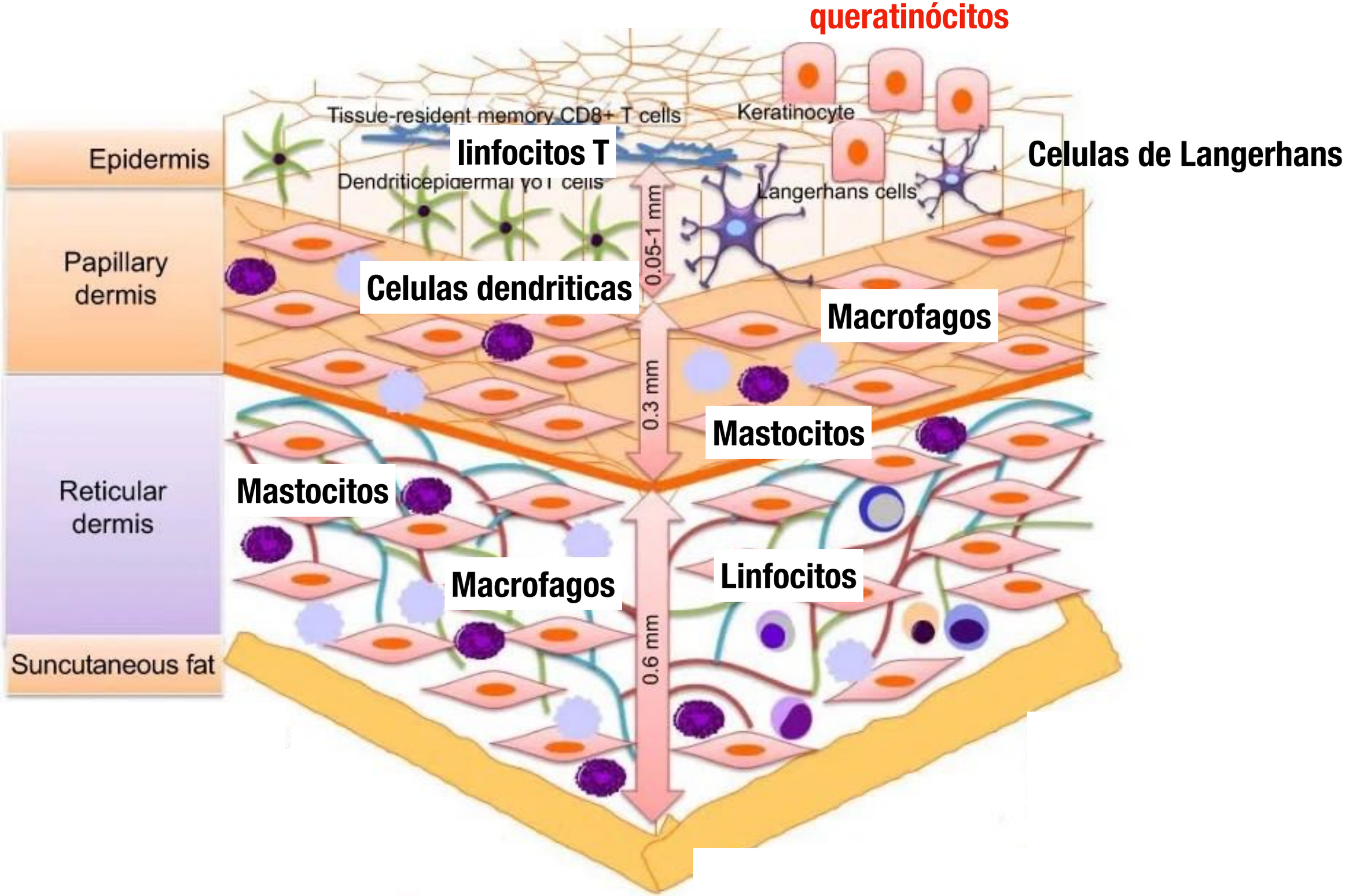
# PRRs e Cia: expressão celulo-especifica?

células imunidade inata

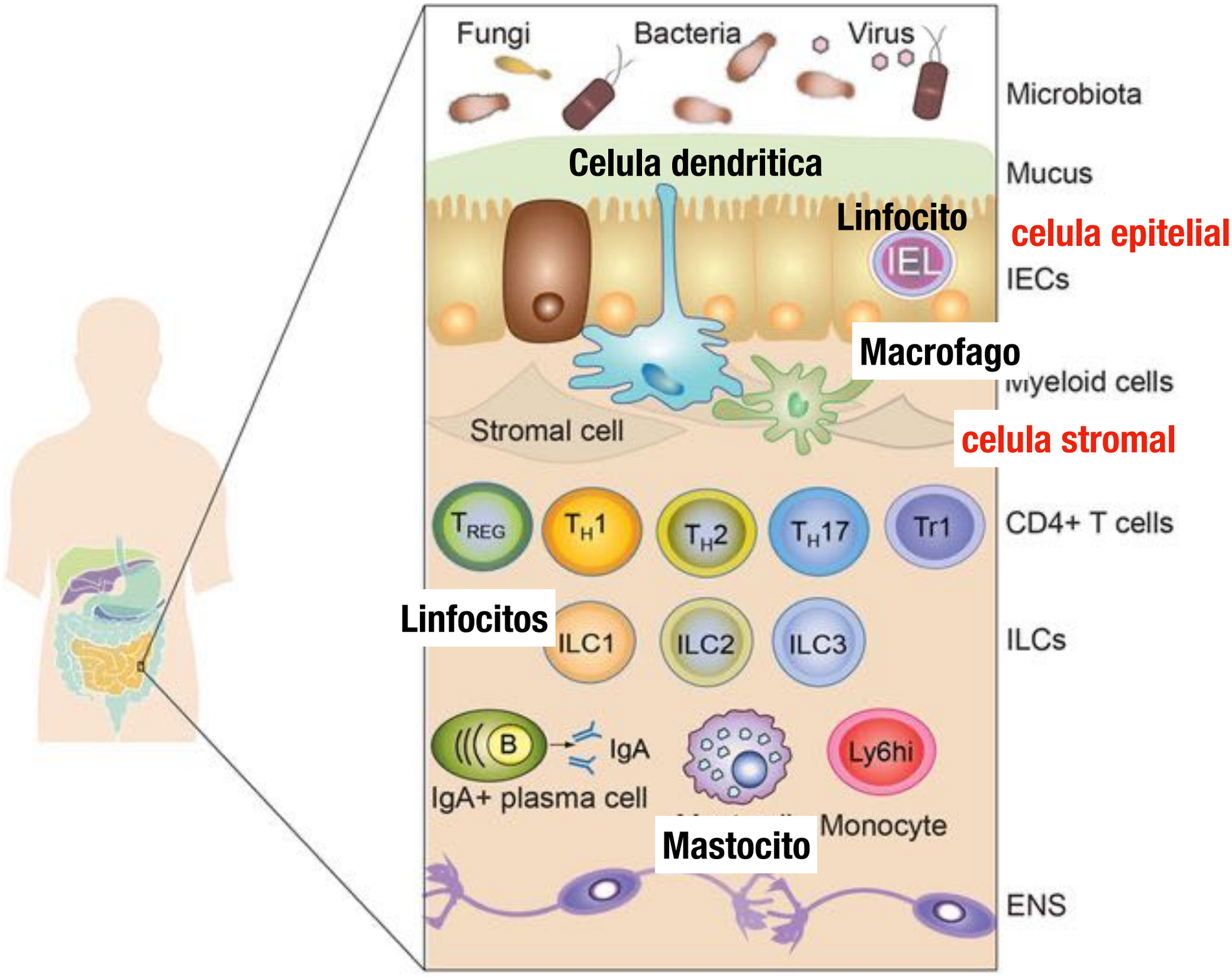
células teciduais



# Pele

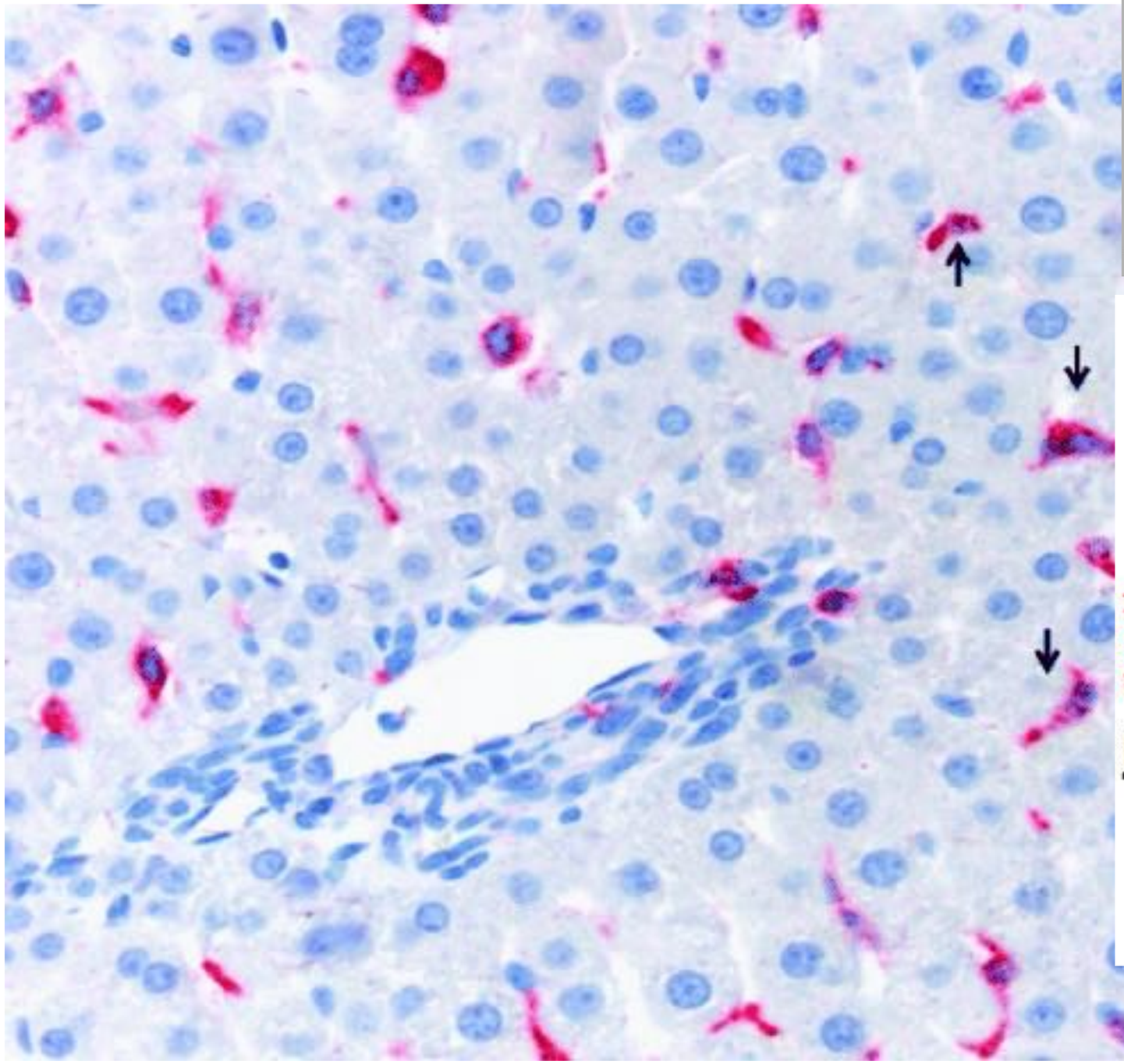

queratinócitos
Tissue-resident memory CD8+ T cells
linfocitos T
Keratinocyte
Celulas de Langerhans
Epidermis
Dendriticepidermal γδ T cells
Langerhans cells
0.05-1 mm
Papillary dermis
Celulas dendriticas
Macrofagos
0.3 mm
Mastocitos
Mastocitos
Reticular dermis
Macrofagos
Linfocitos
0.6 mm
Suncutaneous fat

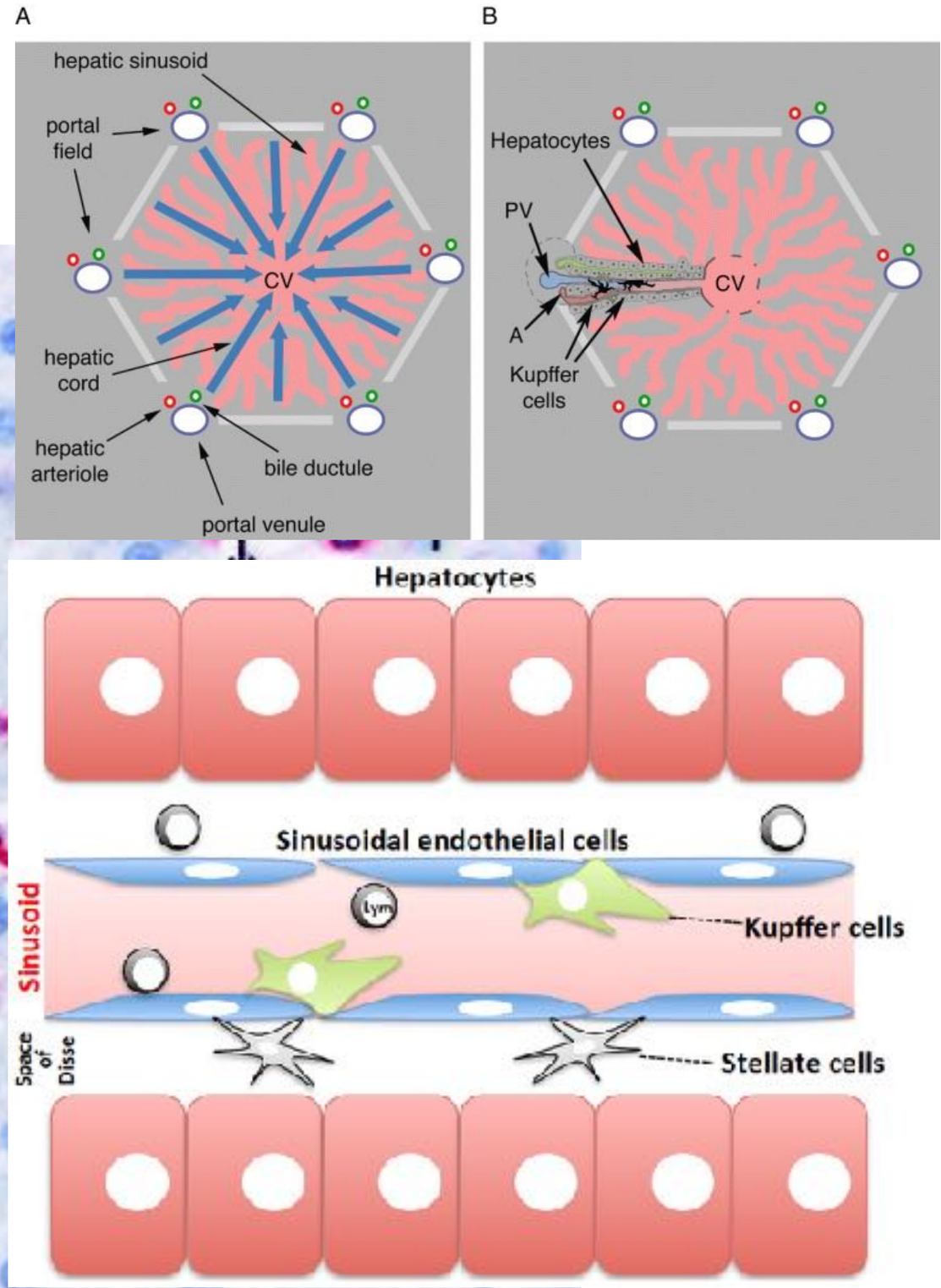
# Intestino


Fungi
Bacteria
Virus
Microbiota
Celula dendritica
Mucus
Linfocito
celula epitelial
IEL
IECs
Macrofago
Myeloid cells
Stromal cell
celula stromal
TREG
TH1
TH2
TH17
Tr1
CD4+ T cells
Linfocitos
ILC1
ILC2
ILC3
ILCs
B
IgA
IgA+ plasma cell
Ly6hi
Monocyte
Mastocito
ENS

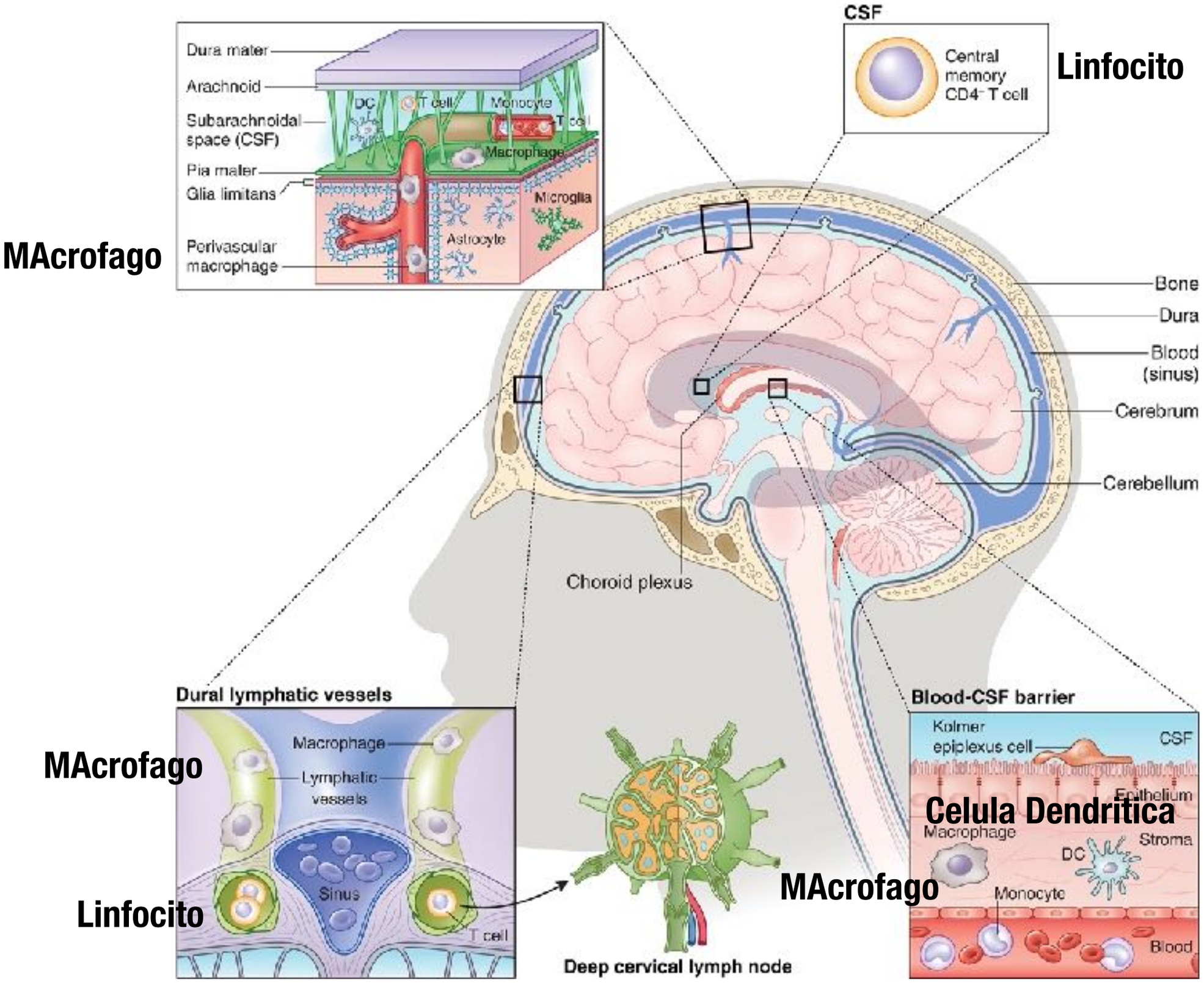
# Figado

## Celulas de Kupferr





# SNC




Nature Neuroscience (*Nat Neurosci*) ISSN 1546-1726

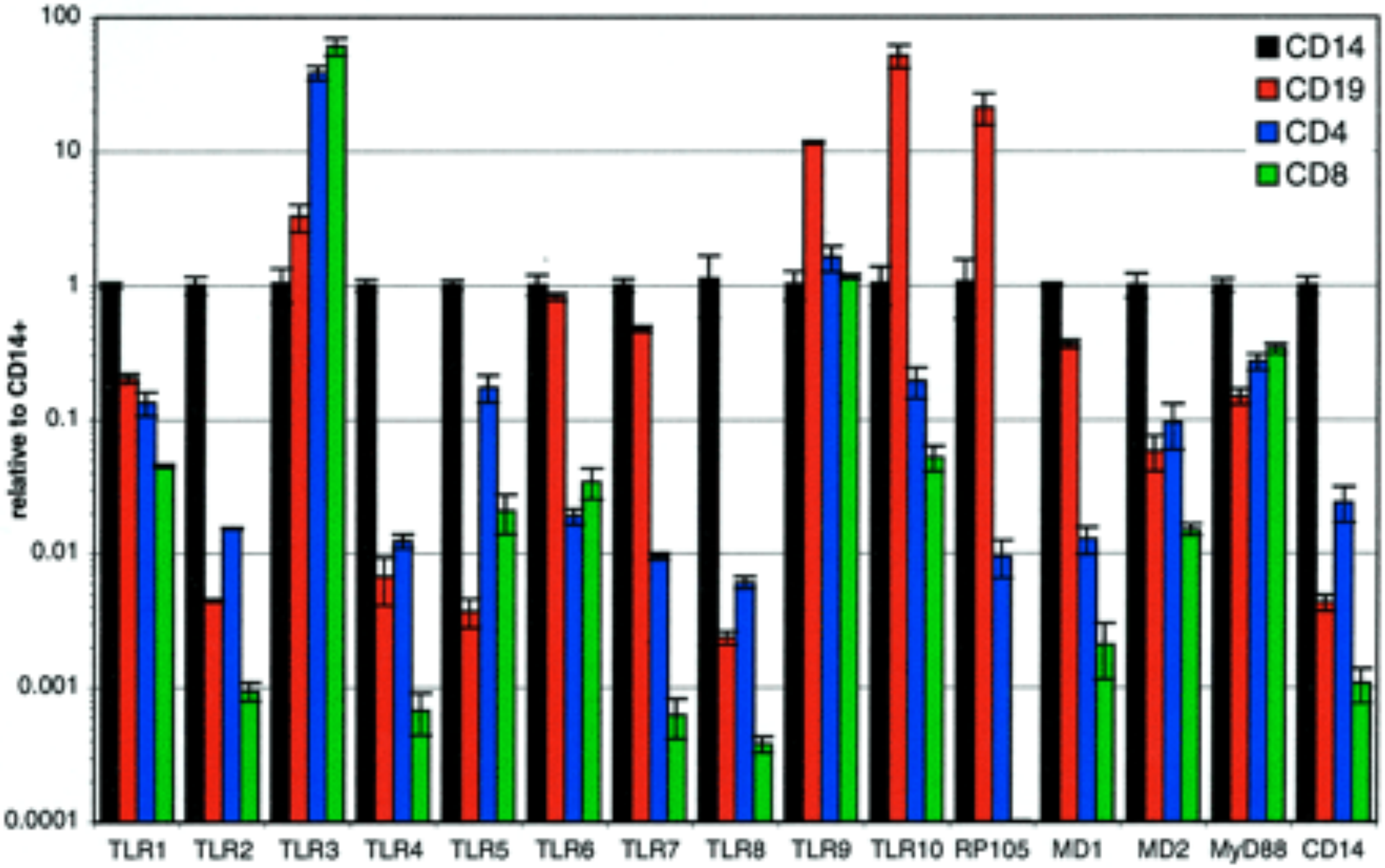
# Onde os PRRs sao expressos?

TLRs are differentially expressed in human tissues

| Tissue | Protein |
|---|---|
| 1. Blood | TLR1, TLR2, TLR4, TLR6, TLR8, TLR9, TLR10 |
| 2. Bone marrow | TLR2, TLR4 |
| 3. Vascular | TLR1, TLR4, TLR8 |
| 4. Heart | TLR2 |
| 5. Brain | TLR1, TLR2, TLR3, TLR4, TLR5, TLR7, TLR8, TLR10 |
| 6. Lymph nodes | TLR1, TLR6, TLR7, TLR9, TLR10 |
| 7. Pancreas | TLR3, TLR5, TLR7 |
| 8. Placenta | TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8 |
| 9. Spleen | TLR1, TLR3, TLR4, TLR8, TLR10 |
| 10. Thymus | TLR1, TLR2, TLR3, TLR4, TLR6, TLR8, TLR9 |
| 11. Trachea | TLR1, TLR2, TLR3, TLR4, TLR5, TLR8, TLR9, TLR10 |

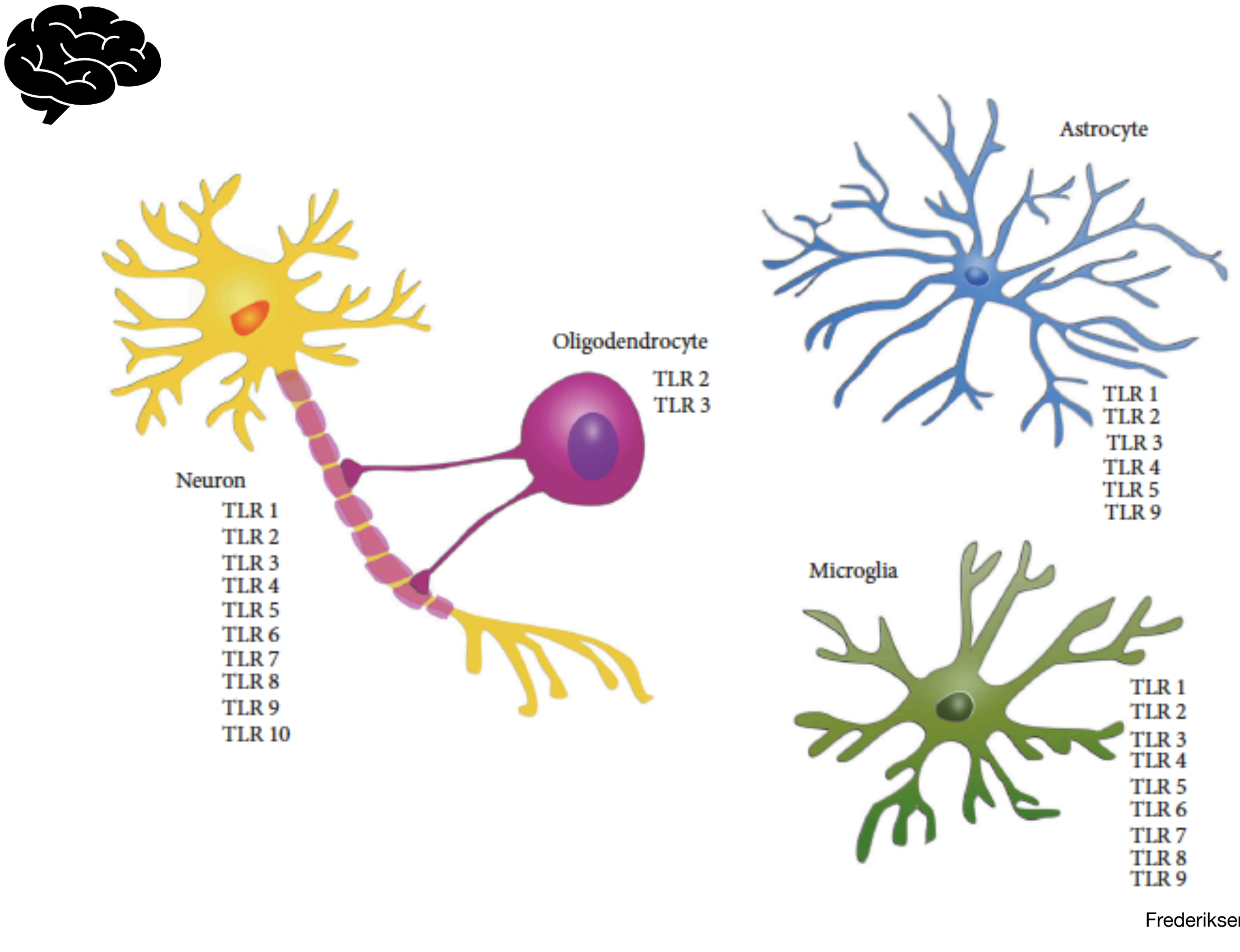
Yin et al 2010

# Onde os PRRs sao expressos?




Zarember and Godowski 2002

# Onde os PRRs sao expressos?




Frederiksen et al 2019

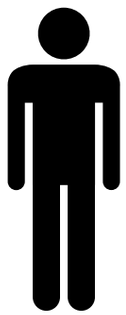
# Onde os PRRs sao expressos?

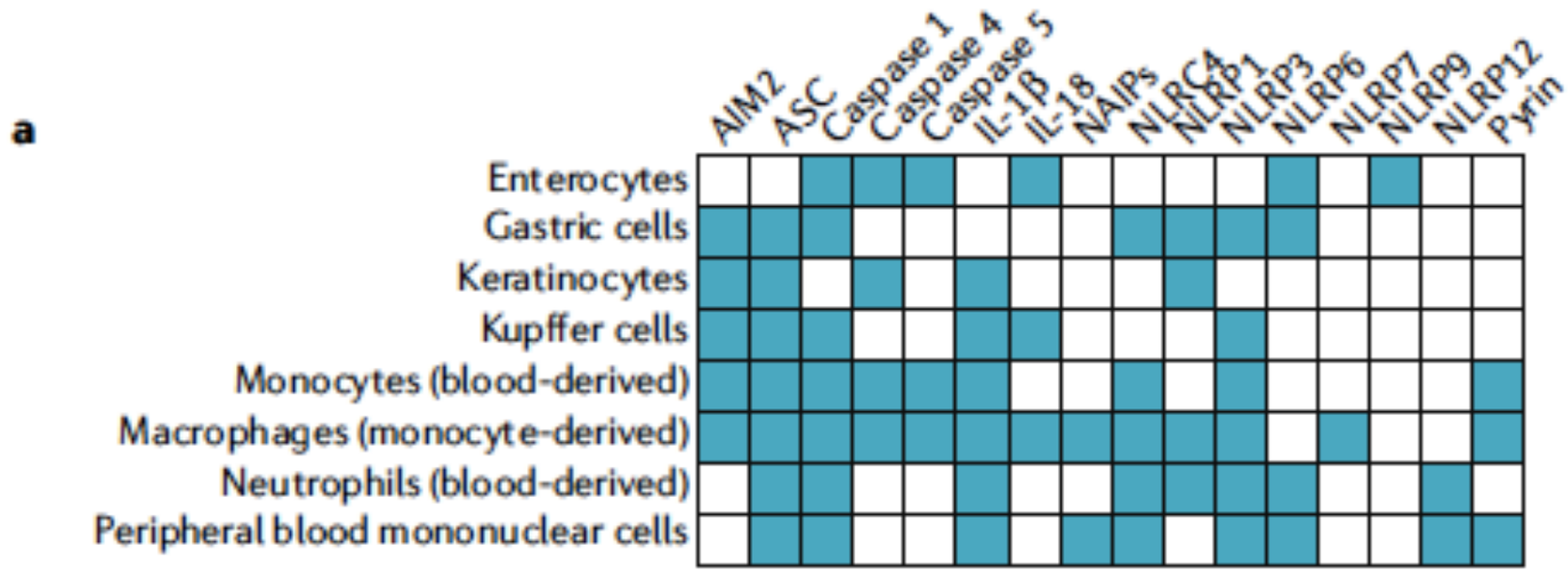
NLRs are differentially expressed in human tissues

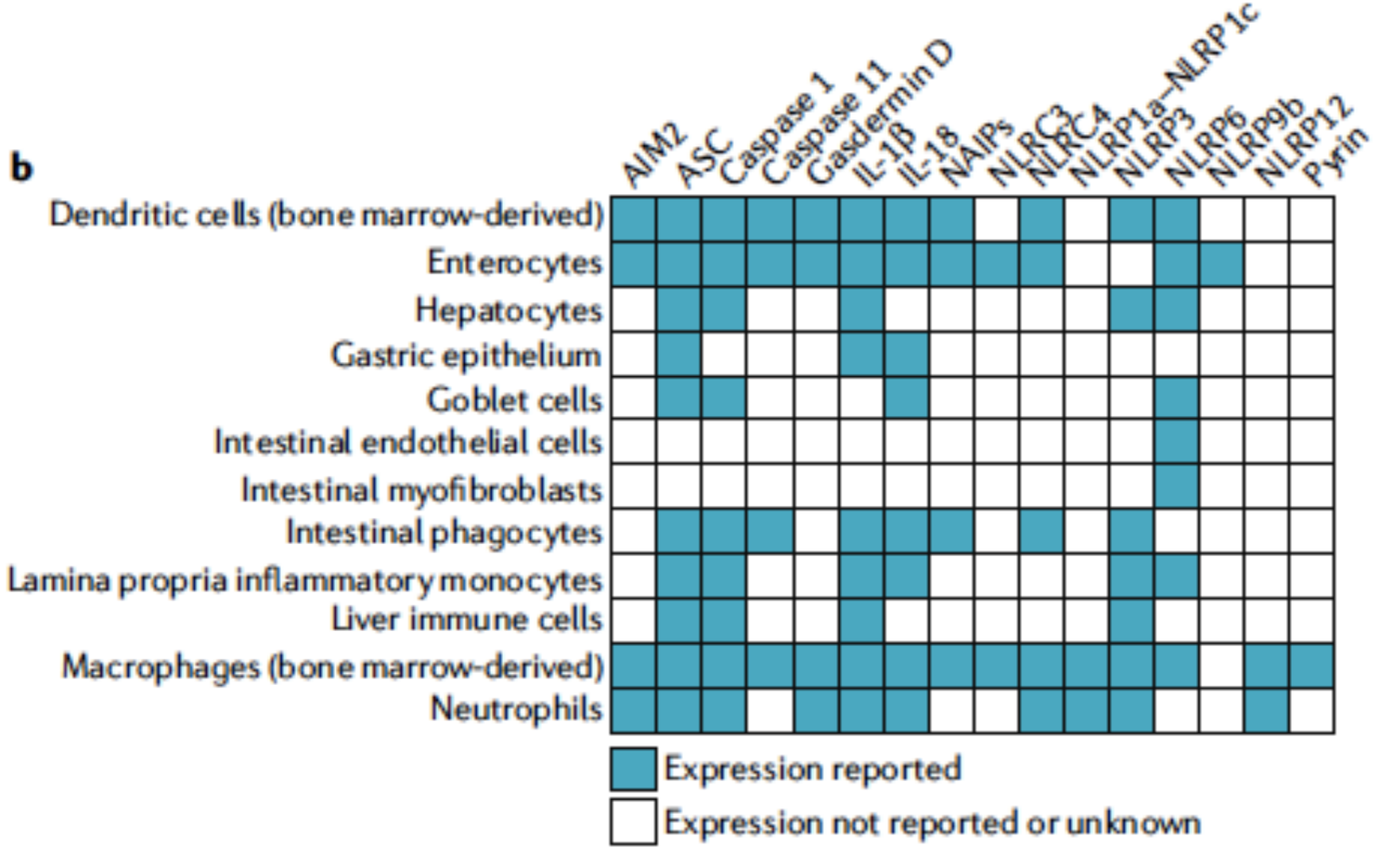
| Tissue | Protein |
|---|---|
| 1. Blood | NOD1, NOD2, NOD4, NALP1, NALP2, NALP3, NALP4, NALP6, NALP7, NALP12, NAIP, IPAF |
| 2. Bone marrow | NOD1, NOD4, NALP1, NALP3, NALP12, IPAF, NOD1, NALP14 |
| 3. Vascular | |
| 4. Heart | NOD2, NOD4, NALP2 |
| 5. Brain | NOD1, NOD3, NOD4, NALP1, NALP2, NALP3, NALP11, NALP14 , NAIP |
| 6. Lymph nodes | NOD1, NOD3, NOD4, NALP1, NALP2, NALP4, NALP9, NAIP |
| 7. Pancreas | NOD1, NOD4, NALP1, NALP2, NALP3 , IPAF , NAIP |
| 8. Placenta | NOD1, NOD2, NOD3, NOD4, NALP1, NALP2, NALP4, NALP7, NALP10, NALP12, NAIP |
| 9. Spleen | NOD1, NOD2, NOD3,NOD4, NALP1, NALP12, NAIP |
| 10. Thymus | NOD1, NOD3, NOD4, NALP1, NALP2, NALP3, NALP6, IPAF,NAIP |
| 11. Trachea | NOD4, NALP1, NALP2, NALP6, NALP14 |

Yin et al 2010

# Onde os PRRs sao expressos?






Man et al 2018

# Constitutivo vs Induzido

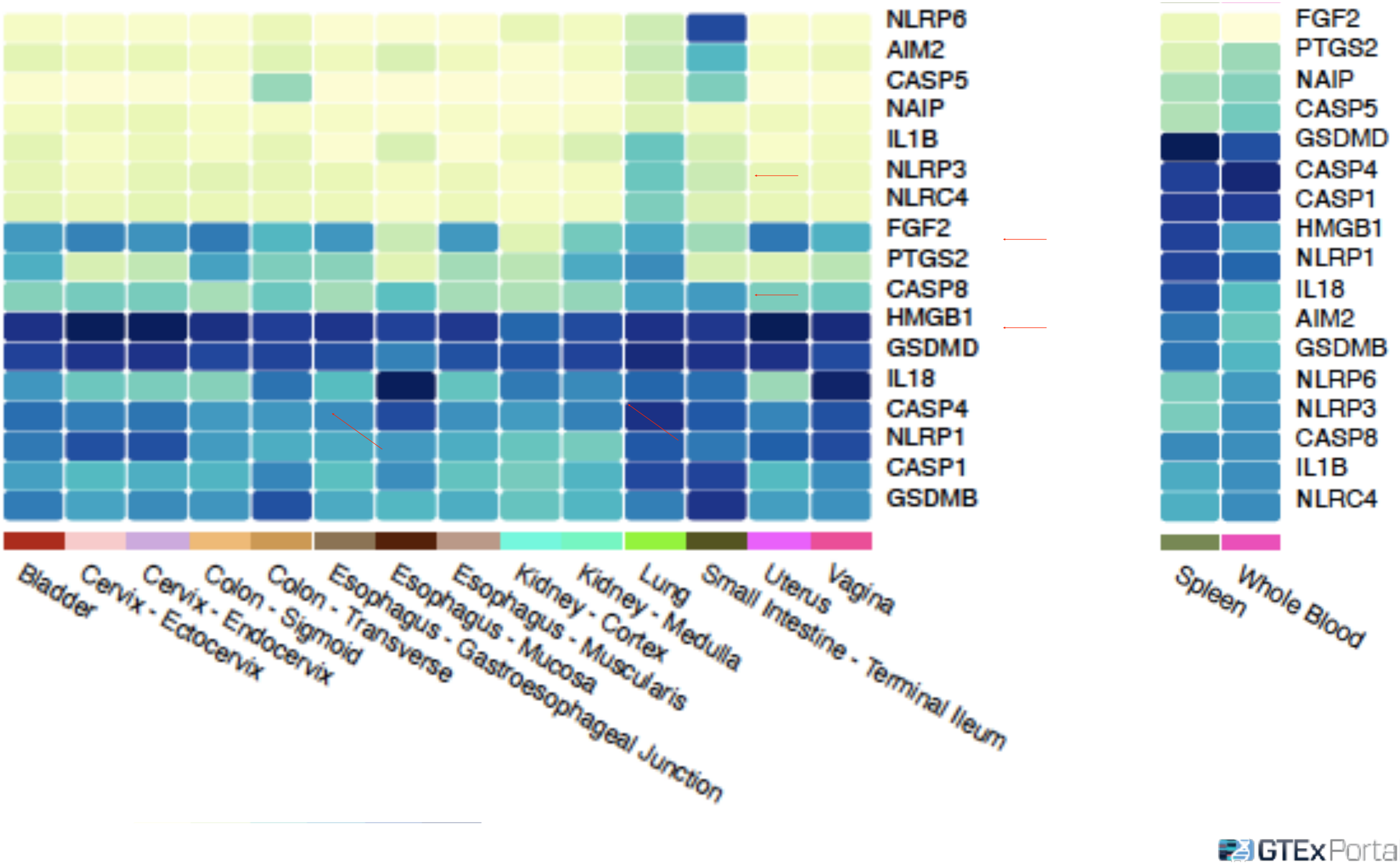
The three tier expression status of inflammasome types in tissues

| Inflammasome type | Tissue |
|---|---|
| First tier ("ready to go" expression status with all components) | |
| NALP1 inflammasome (NALP1, PYCARD, caspase-1 and caspase-5) | Brain, placenta |
| NALP3 inflammasome (NALP3, PYCARD and caspase-1, Cardinal ) | Blood, brain |
| IPAF inflammasome (IPAF, NAIP, caspase-1) | Blood, Thymus |
| Second tier (nearly-ready expression status that requires one component missing) | |
| NALP1 inflammasome | Blood, pancreas, placenta, trachea |
| NALP3 inflammasome | Vascular, lymph nodes, pancreas, placenta, thymus, trachea |
| IPAF inflammasome | Brain, lymph node, pancreas, placenta, spleen |
| Third tier (expression status that requires upregulation of more than one components) | |
| NALP1 inflammasome | Bone marrow, vascular, heart, spleen, thymus |
| NALP3 inflammasome | Bone marrow, heart, spleen, trachea |
| IPAF inflammasome | Bone marrow, vascular, heart, placenta, trachea |

Yin et al 2010

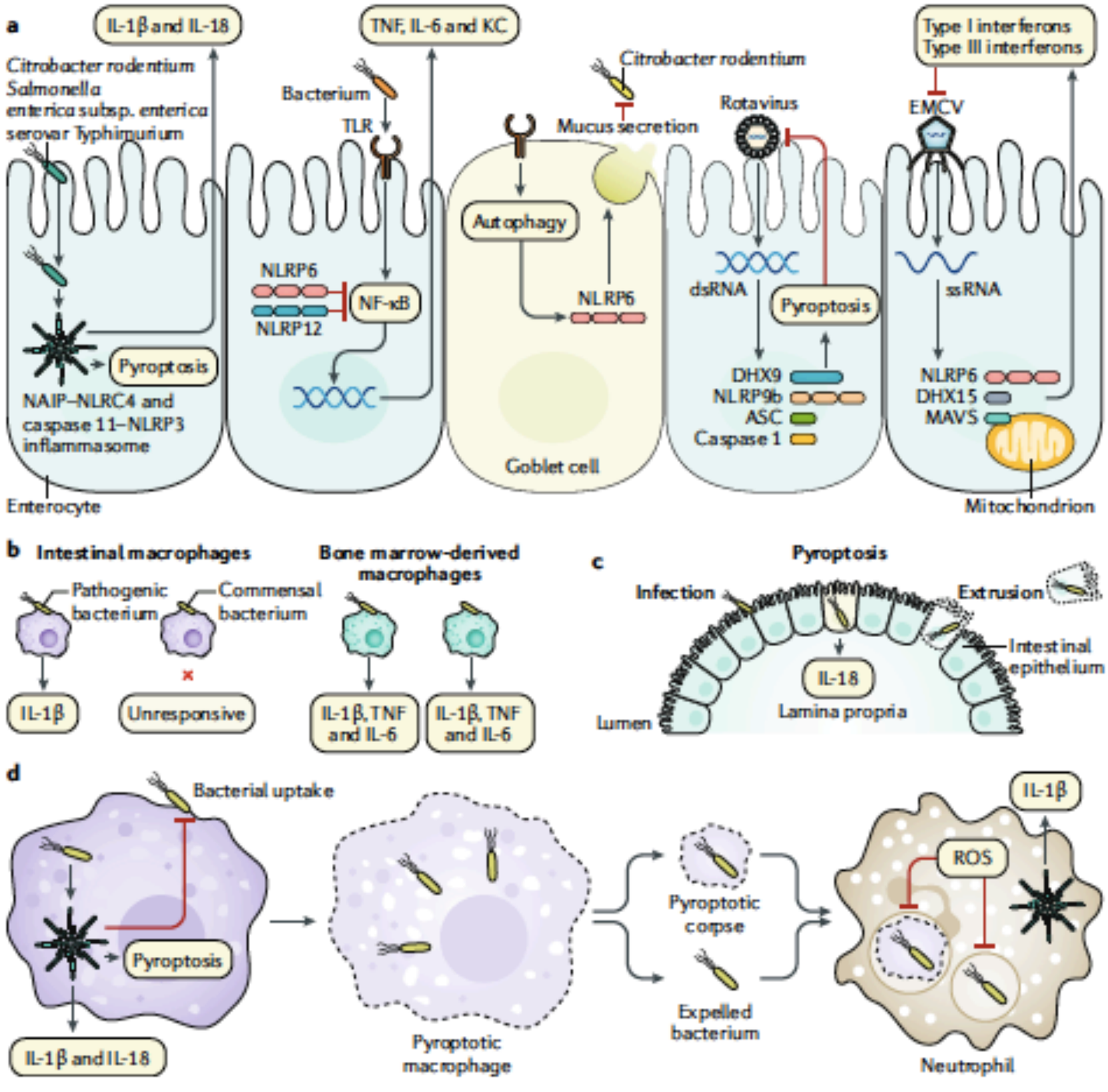
# Onde os PRRs sao expressos?

*epitelio*




GTExPortal

# Onde os PRRs sao expressos?




Man et al 2018

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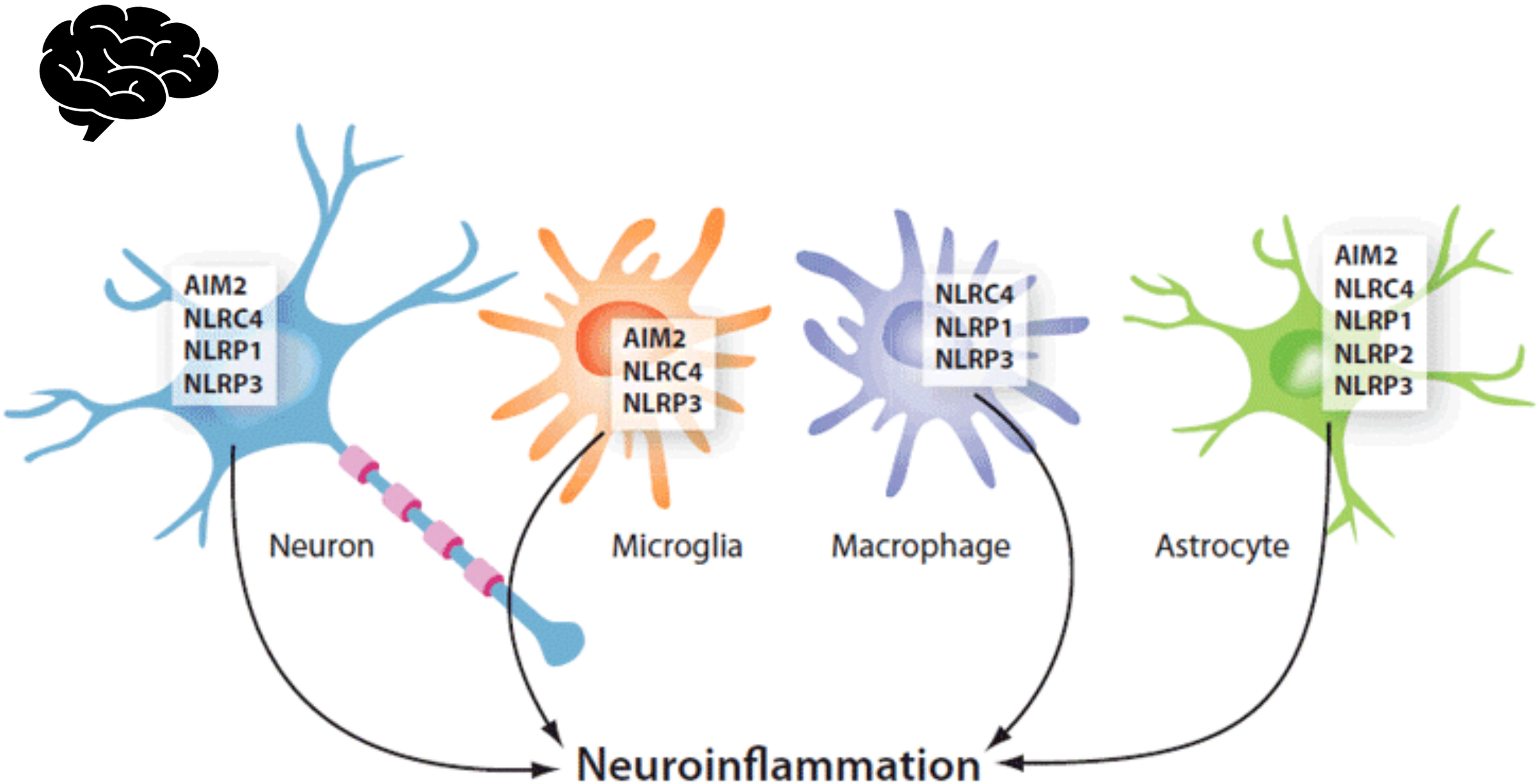

# e as respostas?

Todas as células: resposta IFN