Imunidade aos microrganismos: Malária

Disciplina integrada: Microbiologia, Imunologia e Parasitologia

Prof. Dr. Diego Luís Costa

Resposta imune à malária???

REVIEW

nature immunology

Immunity to malaria: more questions than answers

Jean Langhorne[1], Francis M Ndungu[1], Anne-Marit Sponaas[1] & Kevin Marsh[2]

frontiers | Frontiers in Immunology

TYPE Mini Review
PUBLISHED 19 August 2022
DOI 10.3389/fimmu.2022.914598

Innate immunity to malaria: The good, the bad and the unknown

Kai Pohl[1,2] and Ian A. Cockburn[2*]

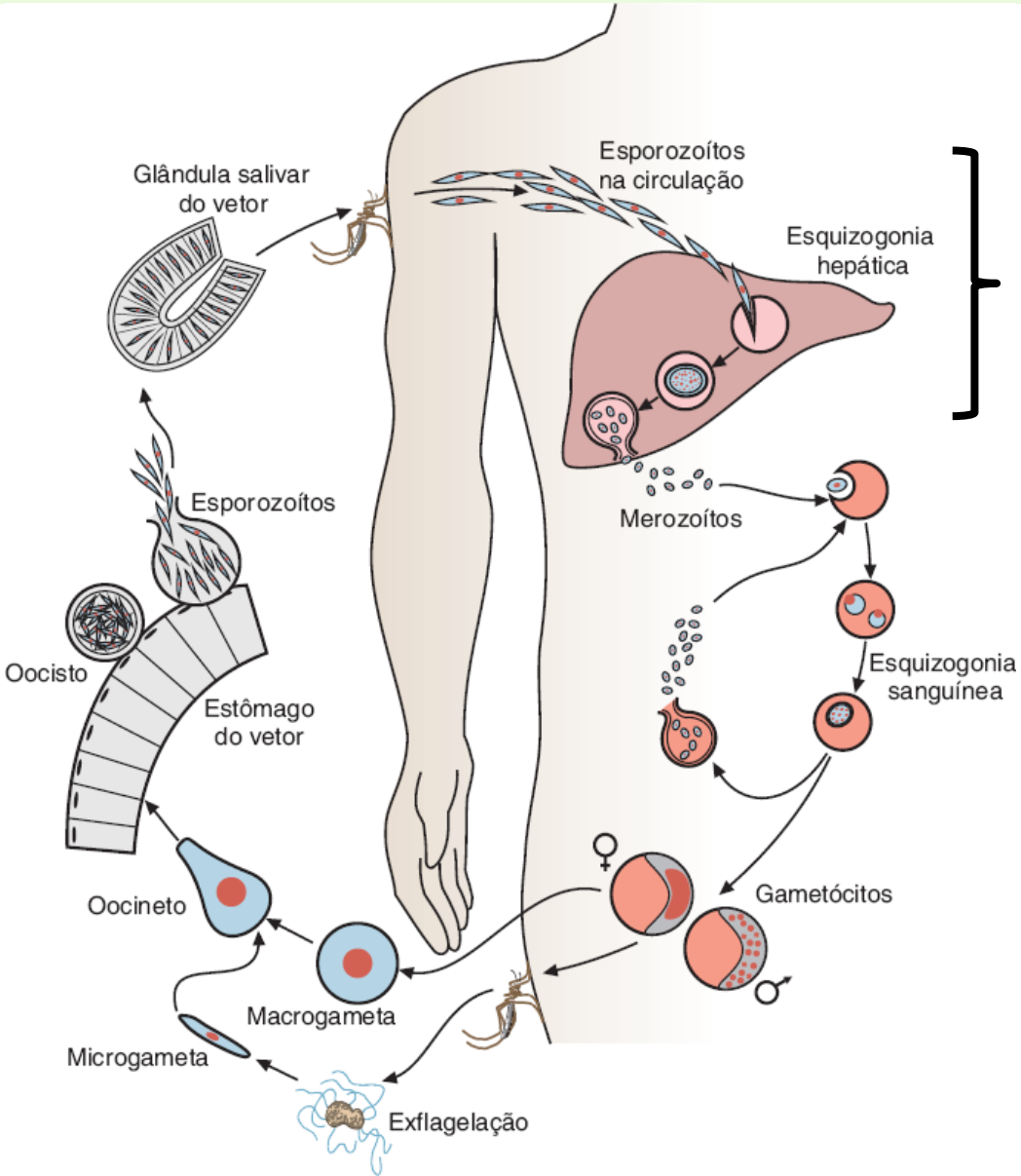
- Múltiplas espécies de *Plasmodium.*

- Diferentes formas do parasita.

- Diferentes manifestações da doença.

- Complexa relação de adaptabilidade entre patógeno e hospedeiro.

Ciclo do *Plasmodium* no hospedeiro vertebrado

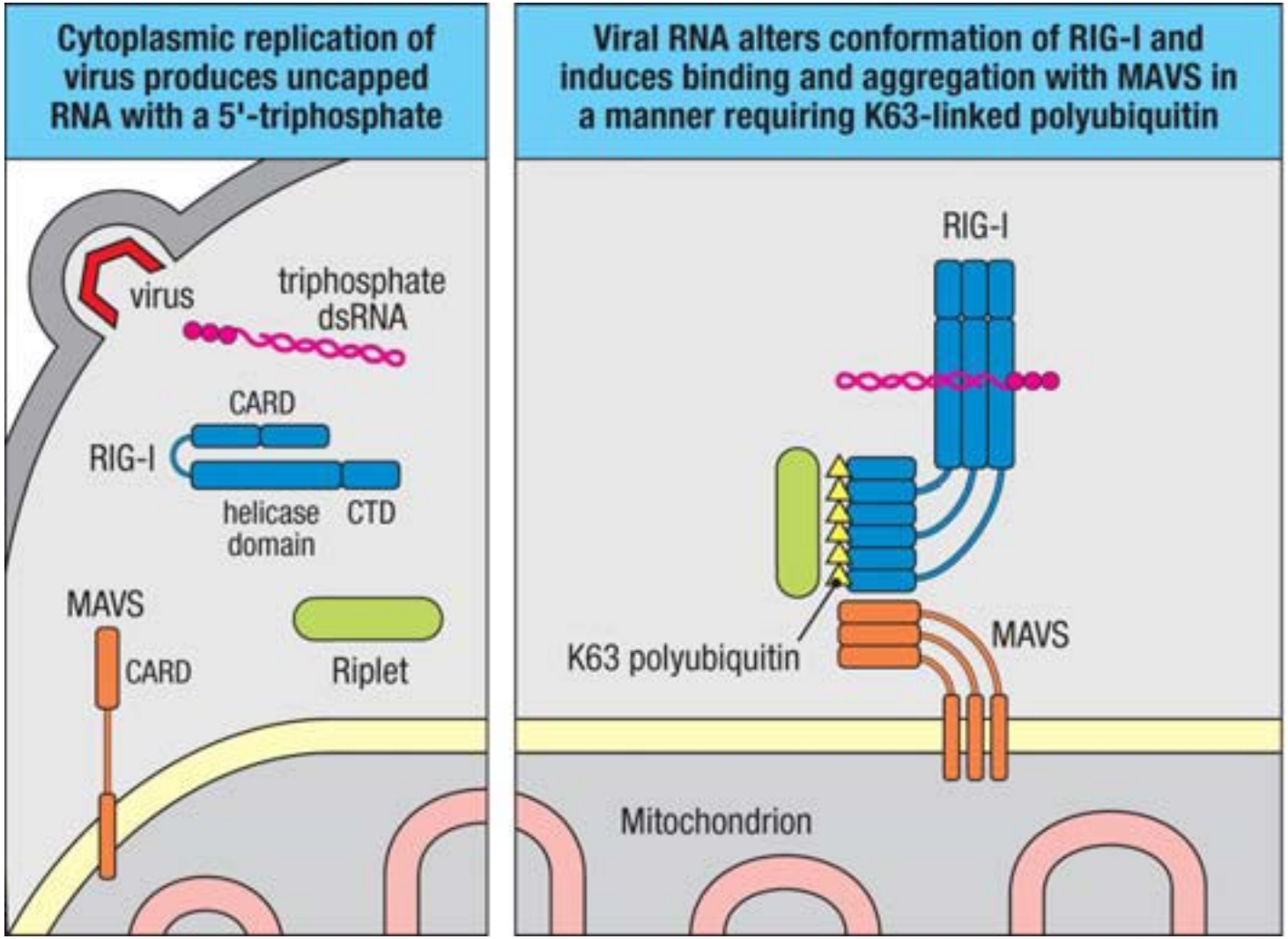


Ciclo pré-eritrocitário

Ciclo eritrocitário

Adaptado de: Ferreira, Parasitologia Contemporânea, 2a. Edição, 2021.

Receptores RIG-I (RIG-I like receptors - RLRs)

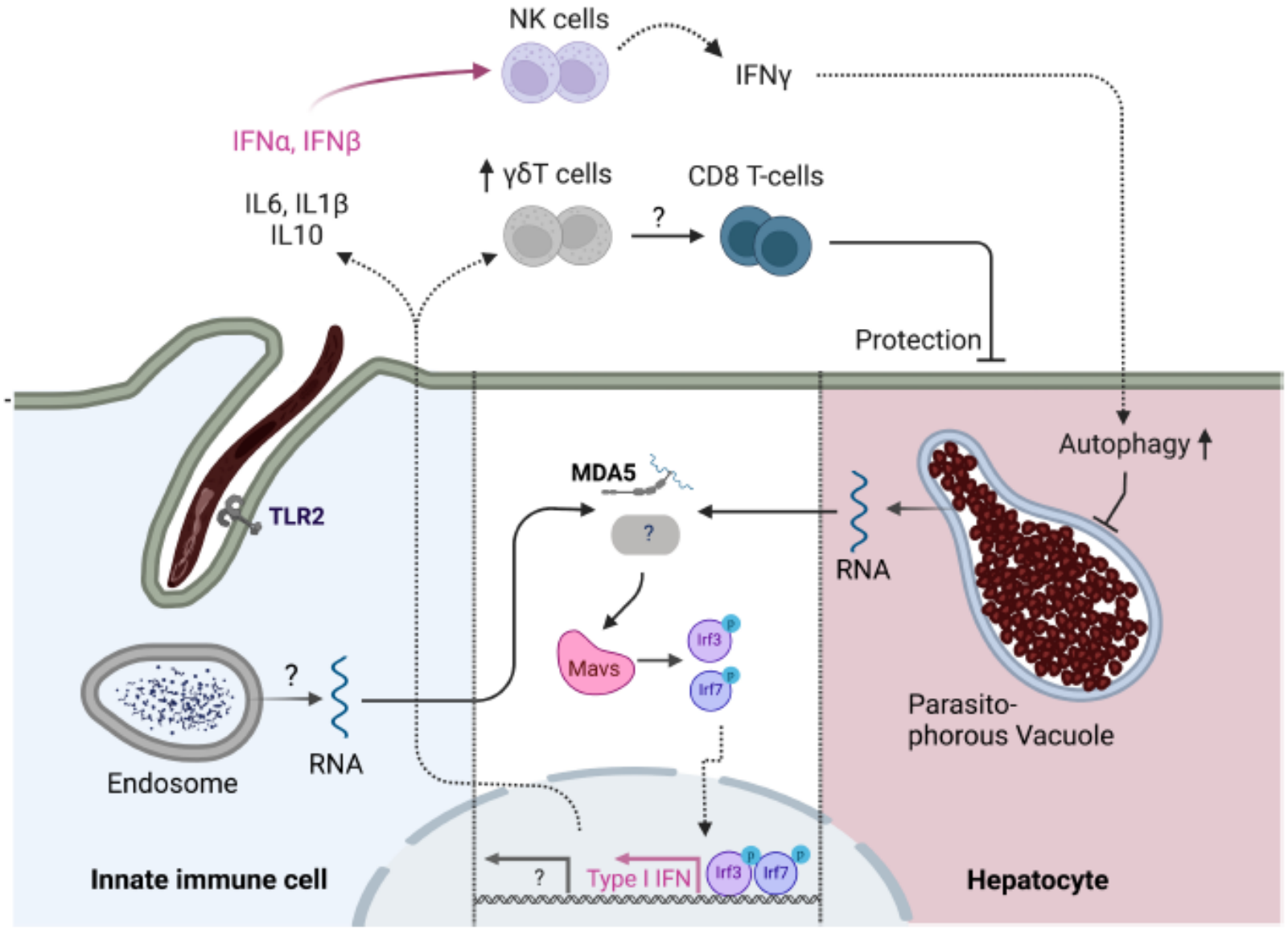


RIG-I, MDA5 – Detectam RNA de fita simples, RNA de dupla fita ou RNA complexado a DNA no citosol.

MAVS – RIG-I/MDA-5 ativados sinalizam via MAVS para induzir sinalização via IRF3 e IRF7 e induzir transcrição de IFN do tipo I.

Murphy, Weaver, Berg, Janeway's Immunobiology 10a. Edição, 2022.

Ativação de imunidade inata durante a fase pré-eritrocítica



- RNA de esporozoítos e esquizontes hepáticos ativam MDA-5 (família RIG-I) – MAVS – produção de IFN do tipo I

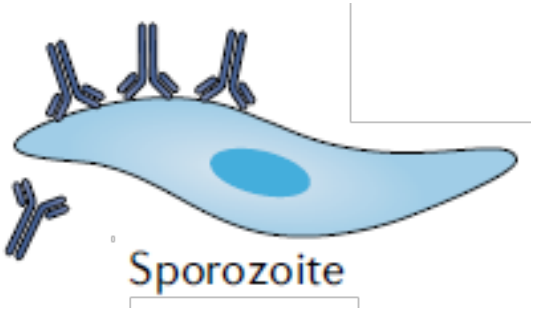
- Ativação de células NK – produção de IFN-gama – ativação de fagócitos (mecanismos microbicidas) e hepatócitos (autofagia).

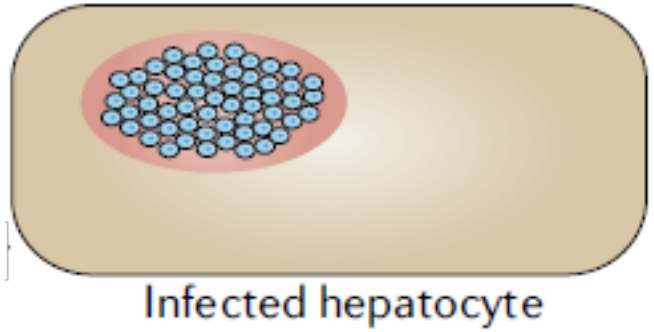
- TLR2 – IL-6 e TNF - inflamação

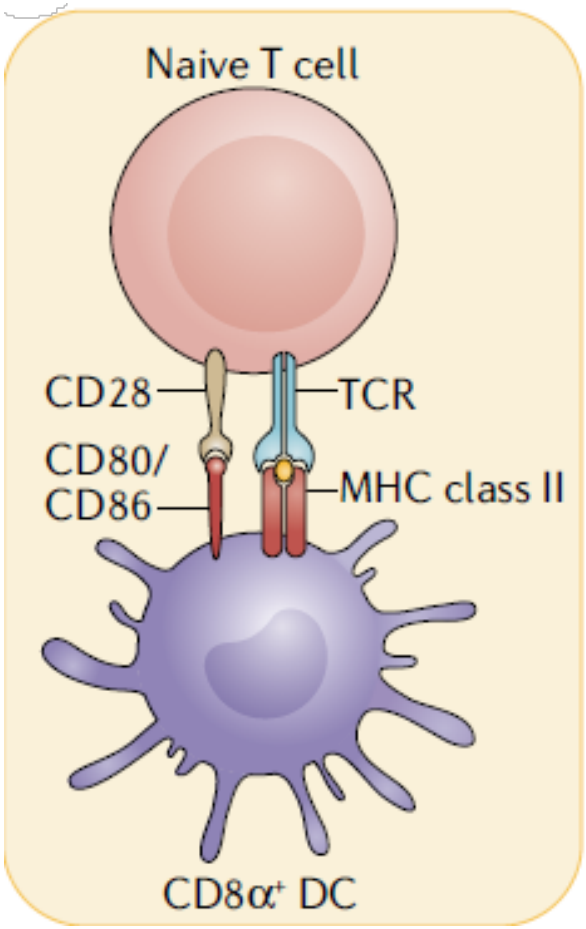
Pohl K e Cockburn IA, Front. Immunol., 2022

Ativação de imunidade adaptativa durante a fase pré-eritrocítica

Linfonodo da pele



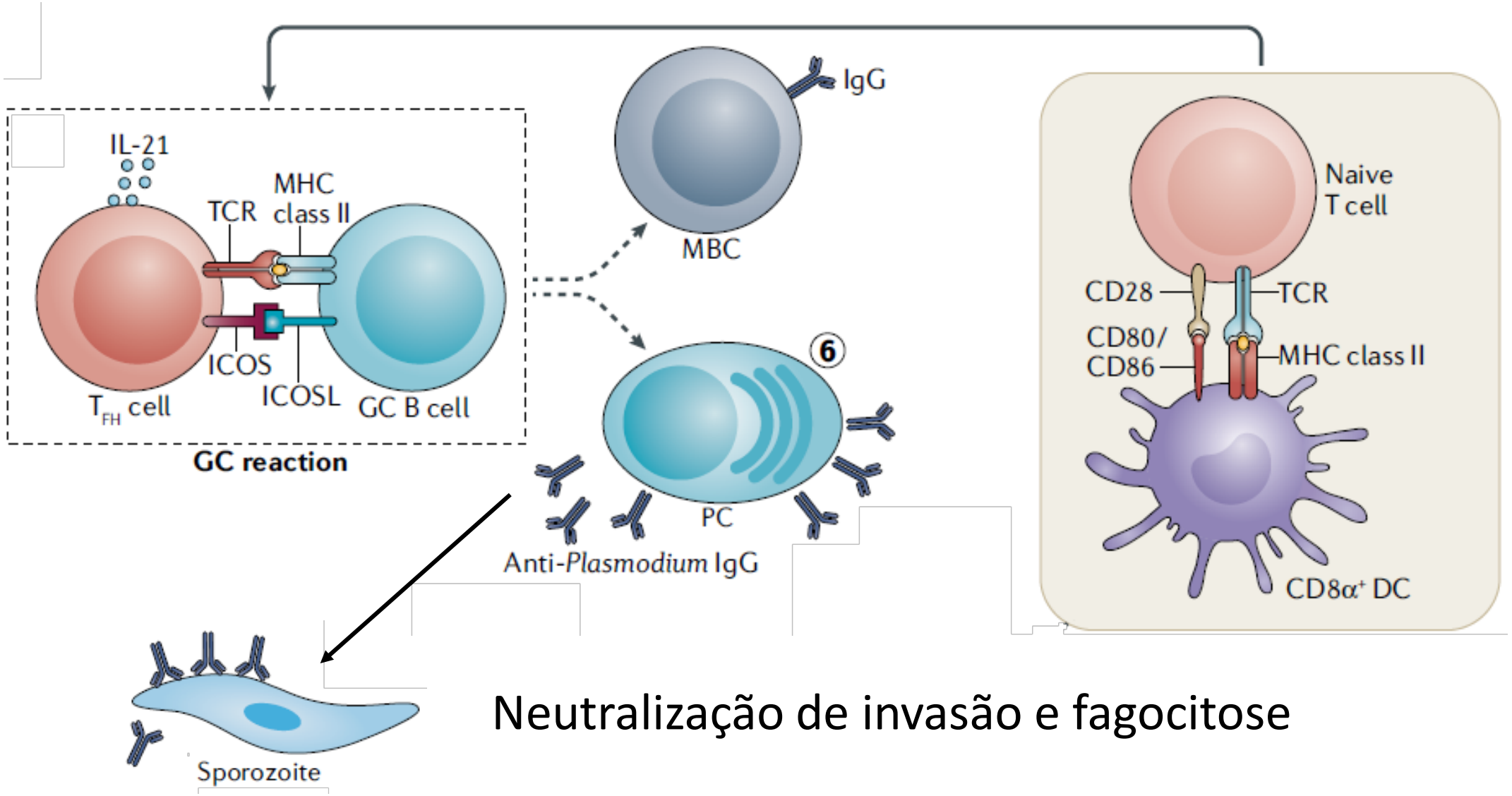




Linfonodo hepático

Kurup S et al., Nat Rev Immunol, 2019

Imunidade humoral – fase pré-eritrocítica



Neutralização de invasão e fagocitose

Kurup S et al., Nat Rev Immunol, 2019

Vacina anti-malária

Health Topics | Countries | Newsroom | Emergencies | Data | About WHO

Home / Initiatives / Malaria vaccine implementation programme

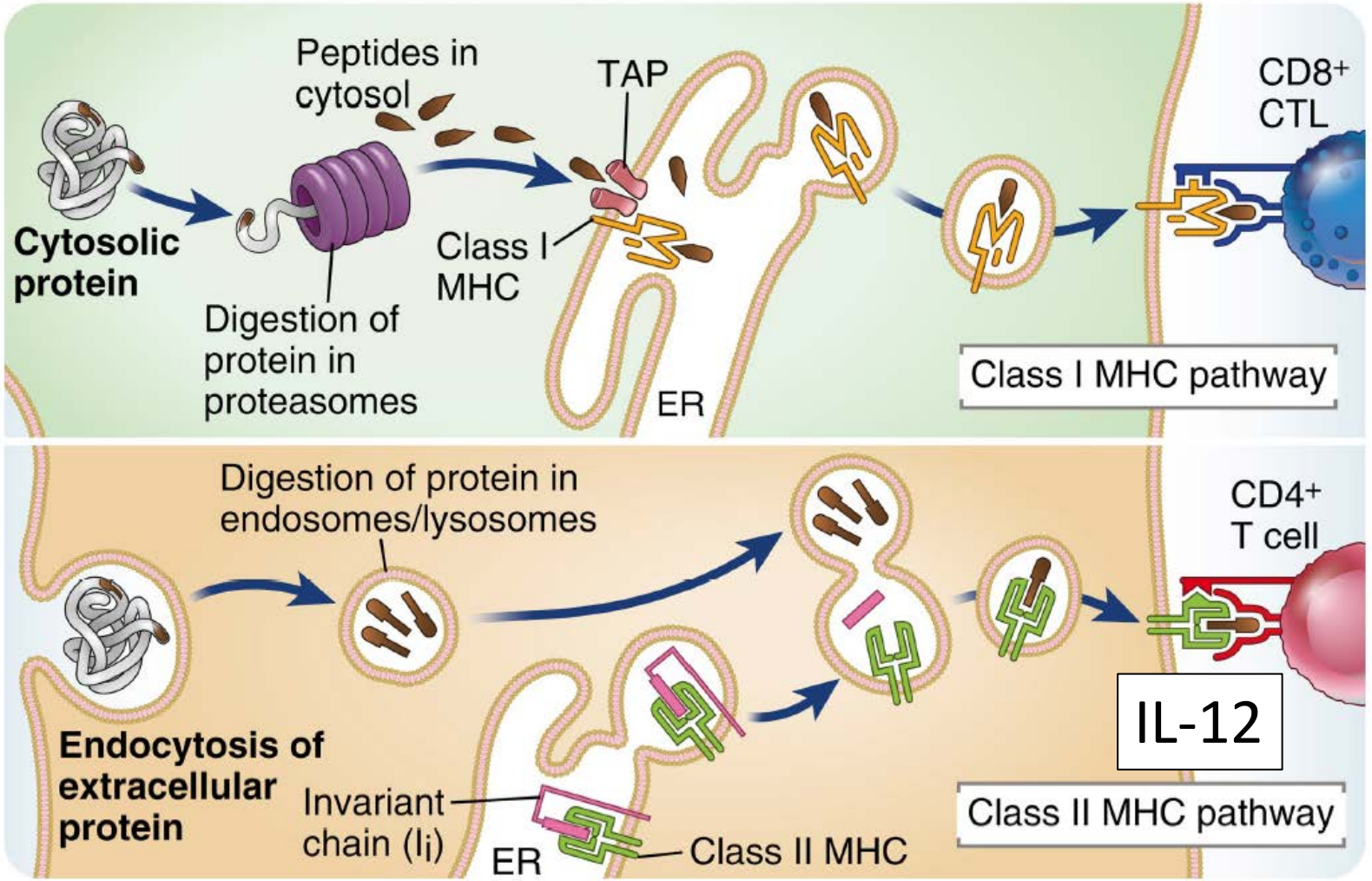
- RTS/S
- R21

As of October 2023, **WHO recommends the programmatic use of malaria vaccines for the prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission.** This applies to both RTS,S/AS01 and R21/Matrix-M vaccines.

The first malaria vaccine, RTS,S, was recommended by WHO to prevent malaria in children in October 2021. The vaccine has reached nearly 2 million children in Ghana, Kenya and Malawi through the Malaria Vaccine Implementation Programme, MVIP, since 2019.

https://www.who.int/initiatives/malaria-vaccine-implementation-programme

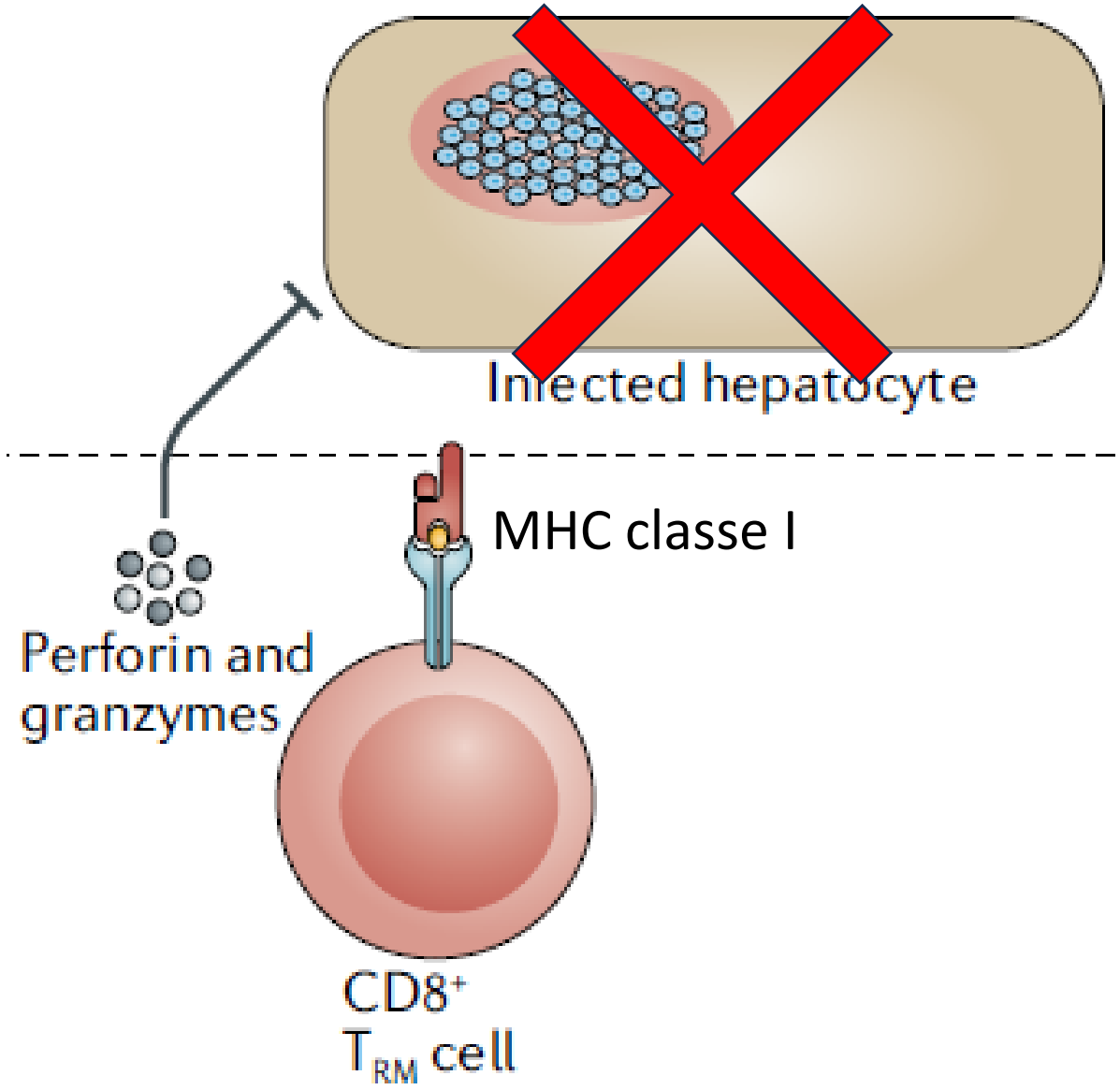
Imunidade celular – fase pré-eritrocítica



IL-2
IFN-gama
CD40L/CD40

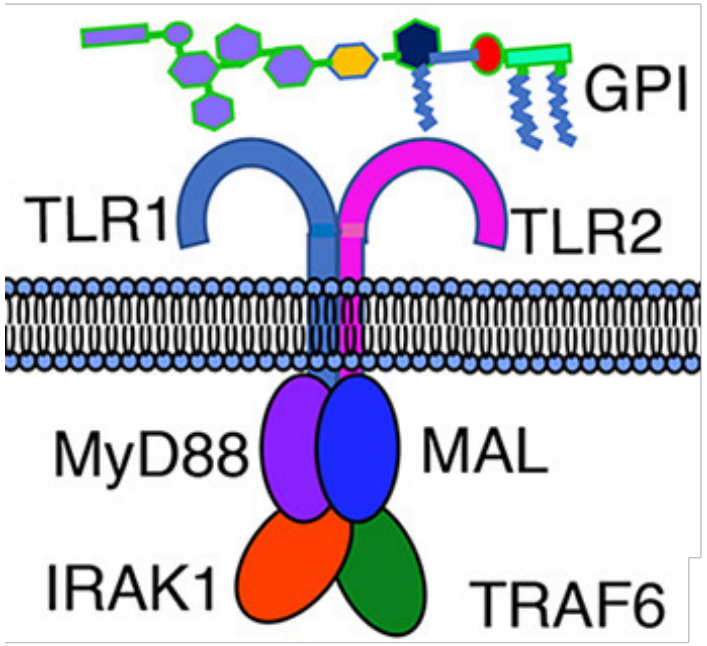
Abbas, Lichtman, Pillai, 10a. Edição, 2022.

Eliminação de hepatócitos infectados por linfócitos T CD8+ citotóxicos



Kurup S et al., Nat Rev Immunol, 2019

Ativação de imunidade inata durante a fase eritrocítica – TLR2



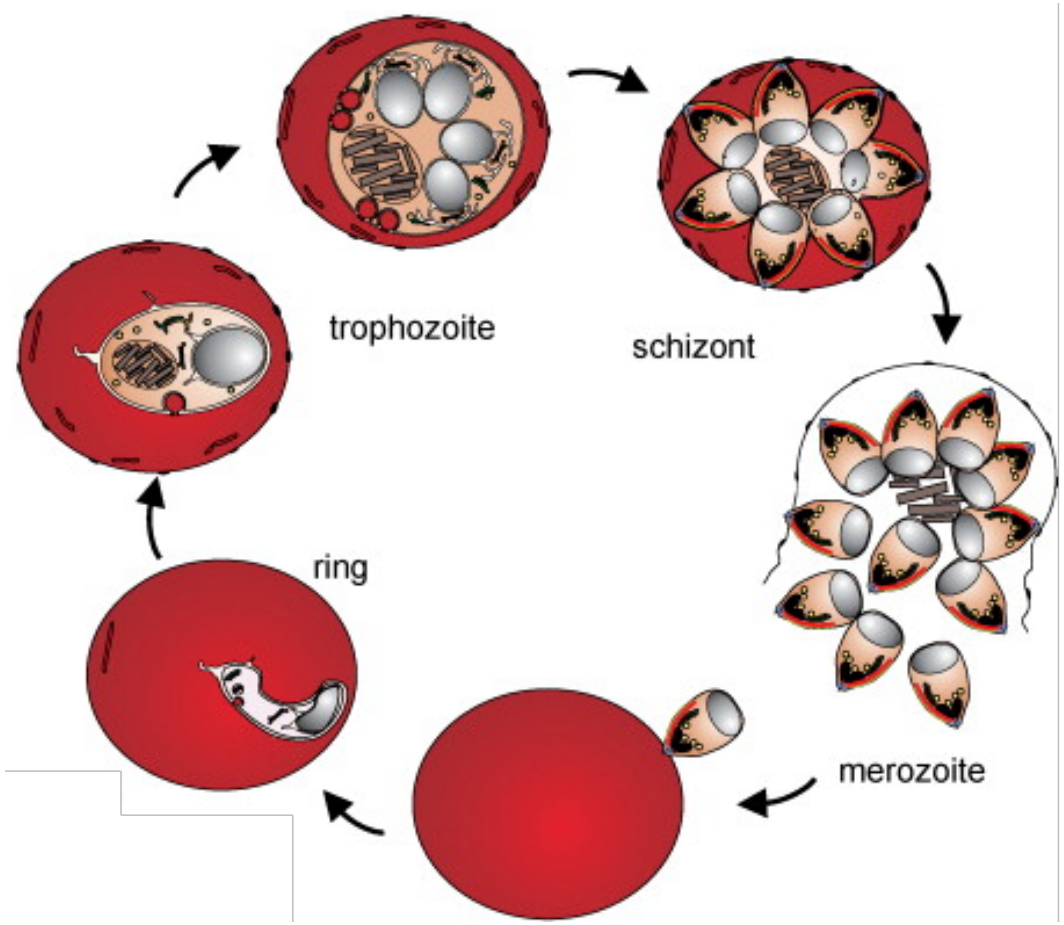
Pro-IL-1β

TNF

GPI - Glicofosfatidilinositol

Gowda & Wu, Front. Immunol., 9:3006, 2018.

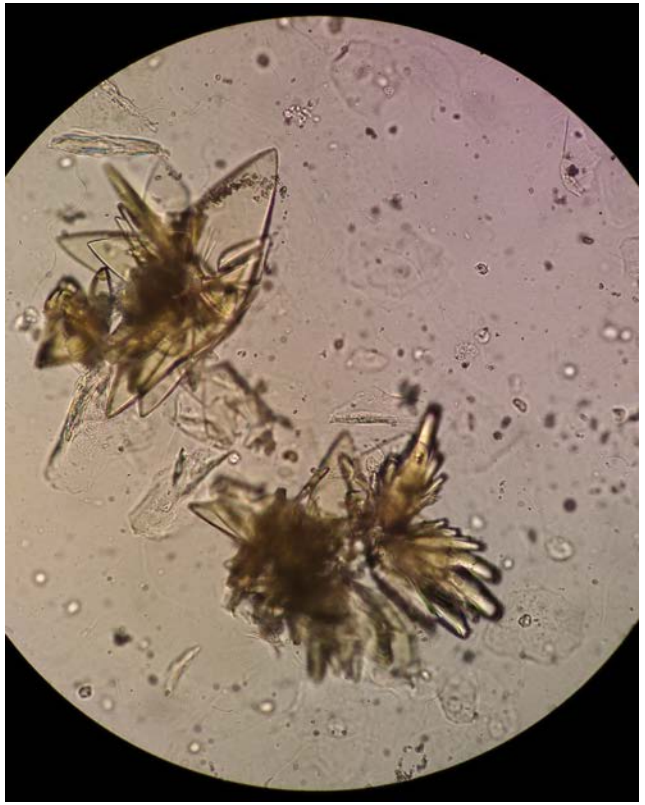
Liberação de Hemozoína e Ác. Úrico



Hemozoína

https://news.vt.edu/articles/2008/05/2008-322.html

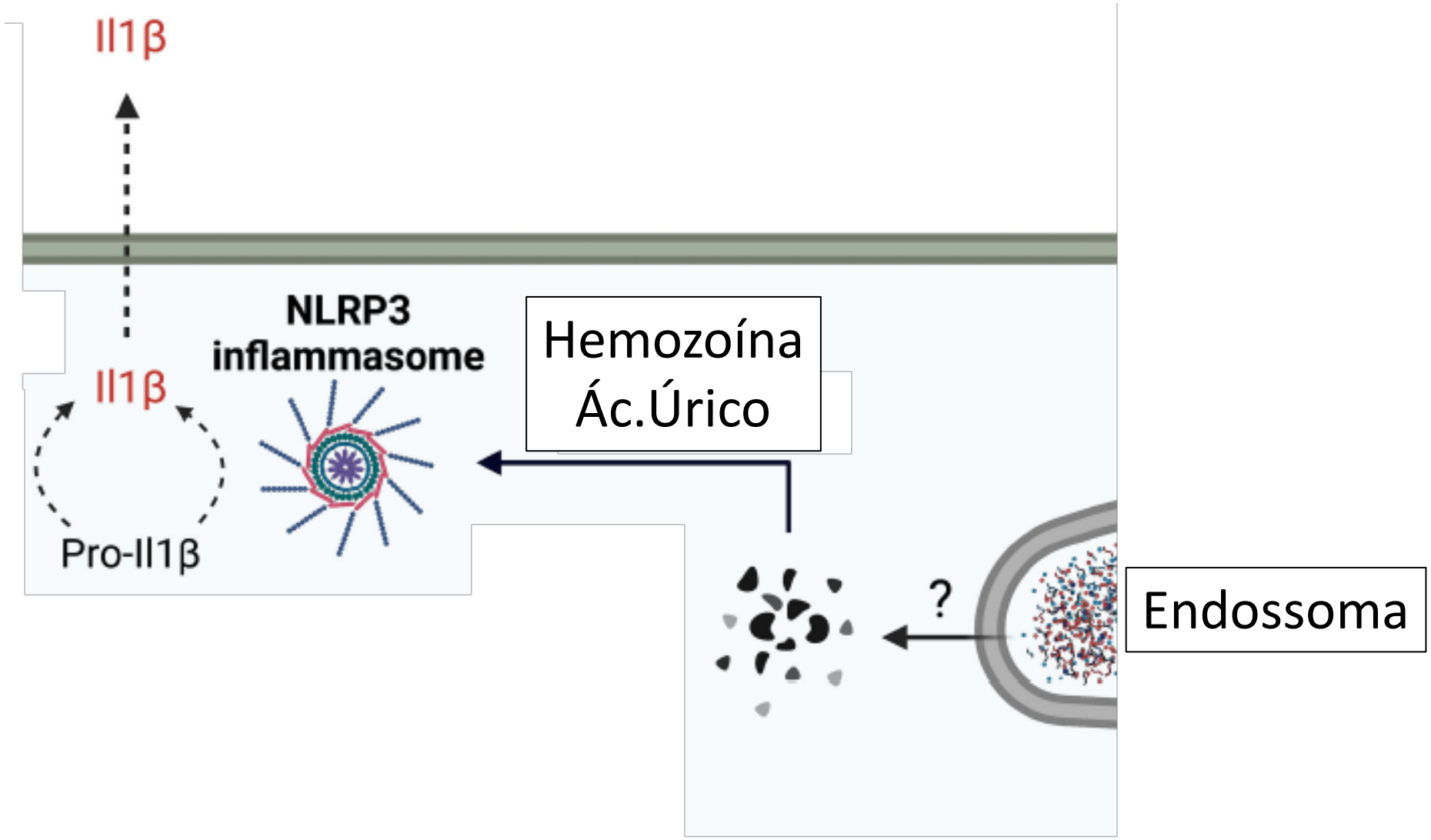
Ácido Úrico



https://www.reddit.com/r/MicroPorn/comments/73edl5/oc_uric_acid_crystals_in_urine_4096x2304_x400/

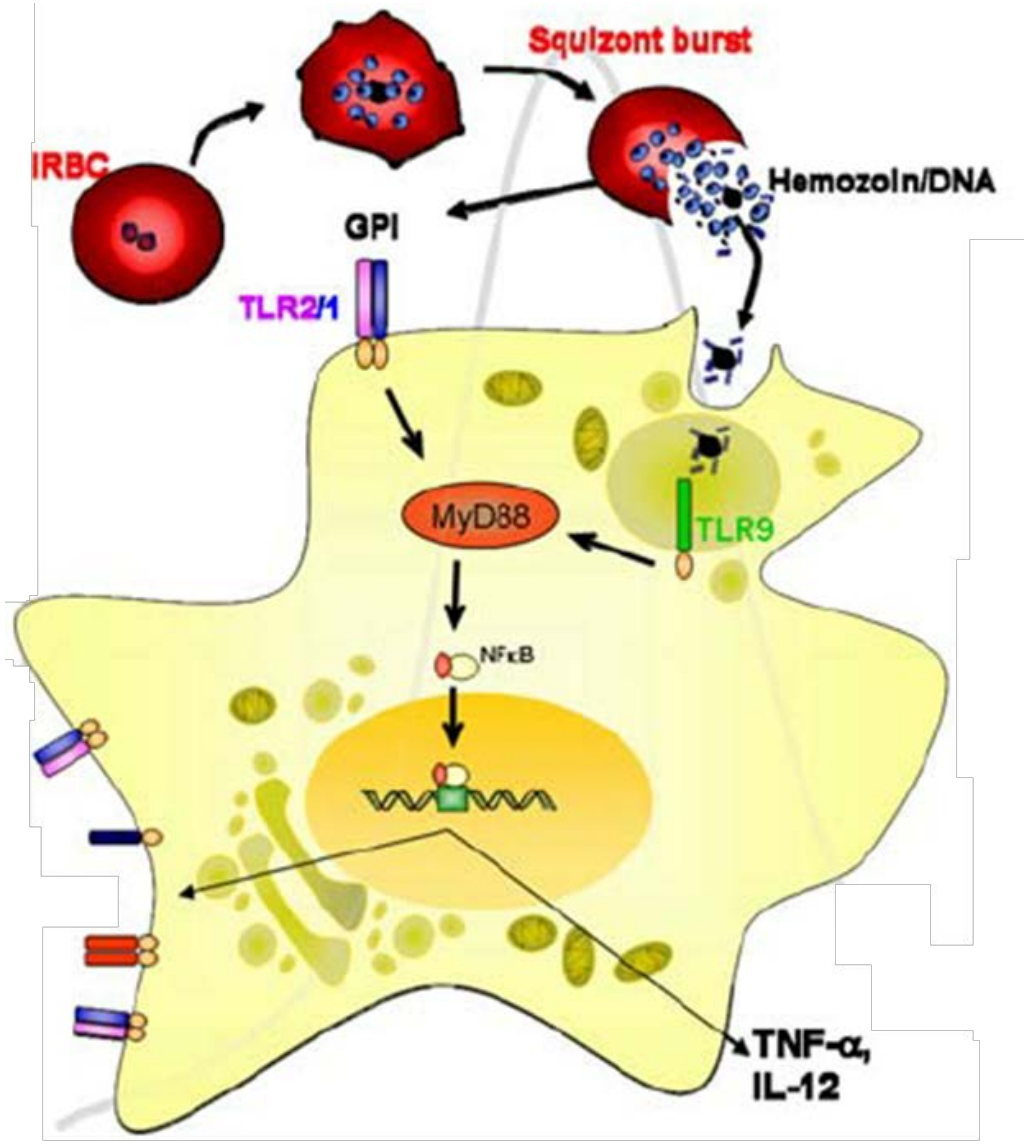
Tillei L et al., Int J Biochem Cell Biol 2011

Atívação de inflamassoma por Hemozoína e Ác.Úrico



Abbas, Lichtman, Pillai, 7a. Edição, 2012.

Ativação de TLRs durante fase eritrocítica da malária



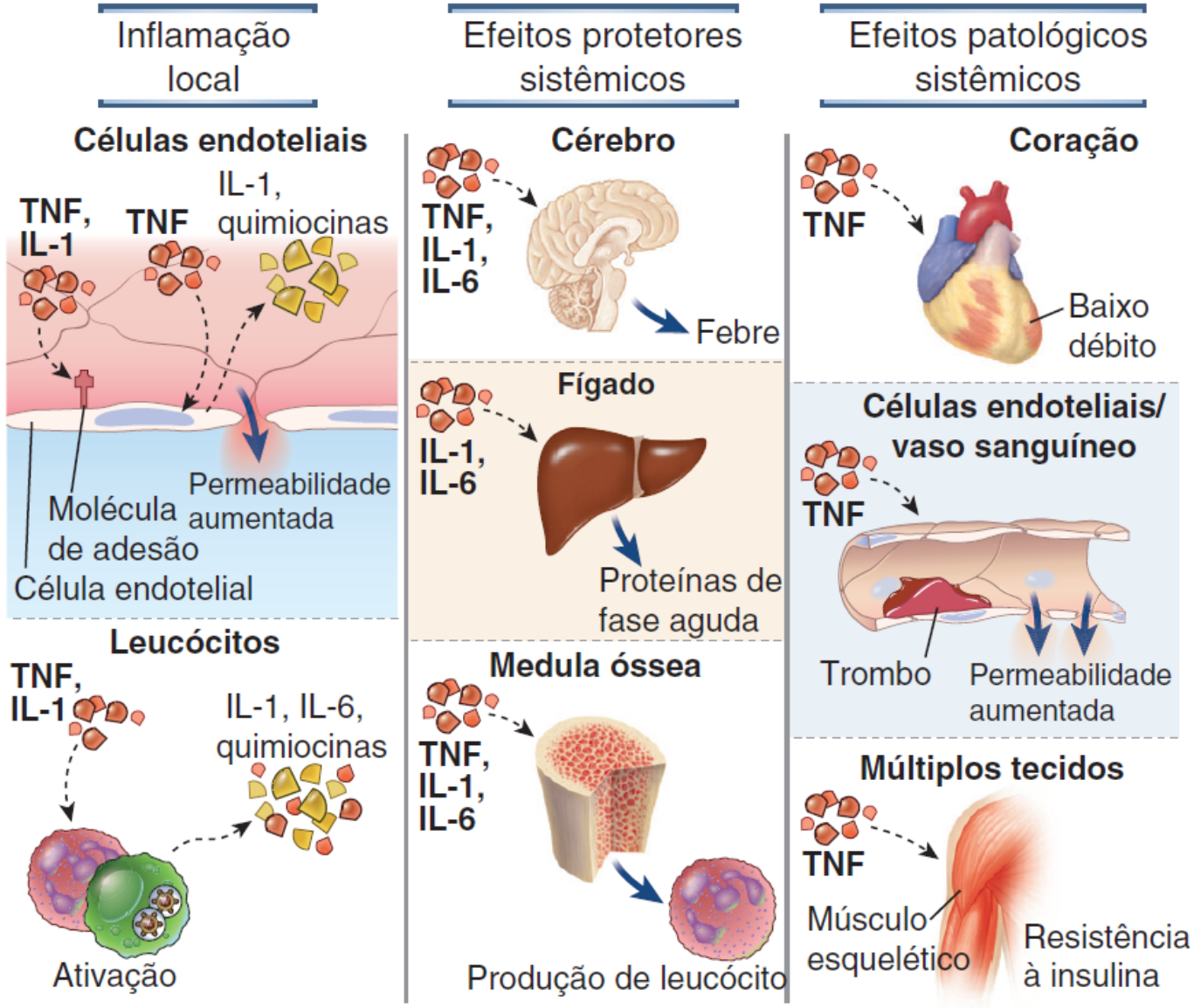
- Hemozoína liga a DNA do patógeno e ativa TLR9 no endossoma

- Junto à ligação a TLR2 por GPI
- Produção de IL-12 e TNF

- DAMPS – inflamassoma – IL1β

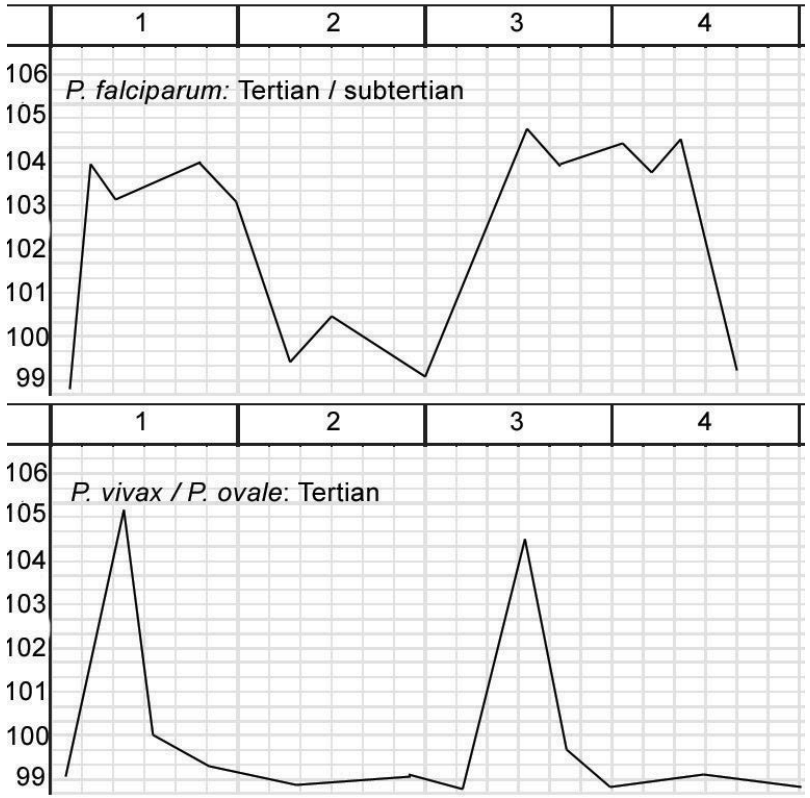
Roppert et al., Sem Immunol 2007

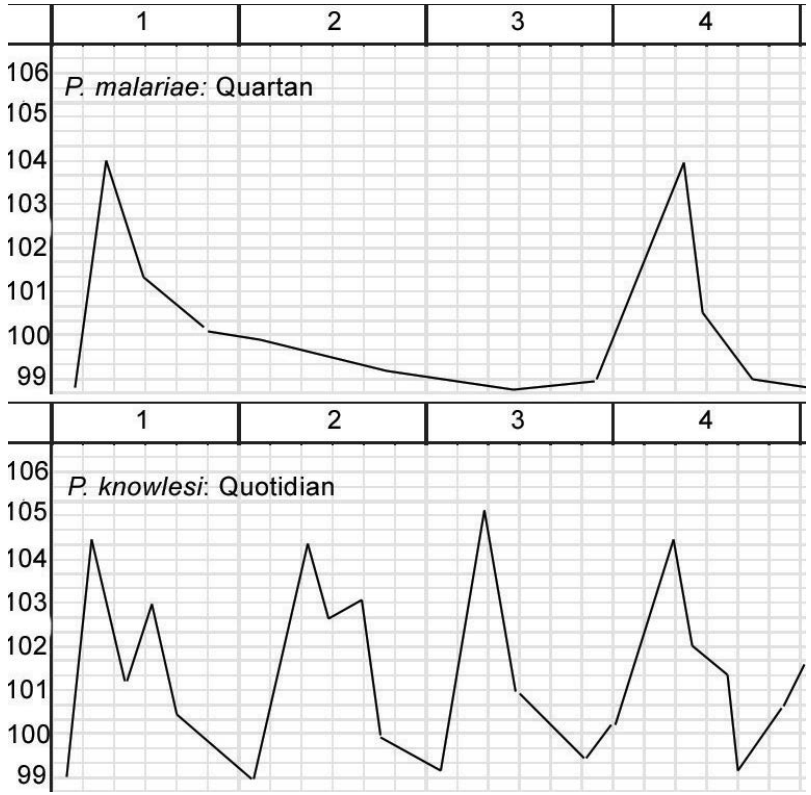
Efeitos sistêmicos de citocinas inflamatórias



Abbas, Lichtman, Pillai, 9a. Edição, 2019.

Episódios de febre recorrente em malária são causados por liberação de mediadores inflamatórios

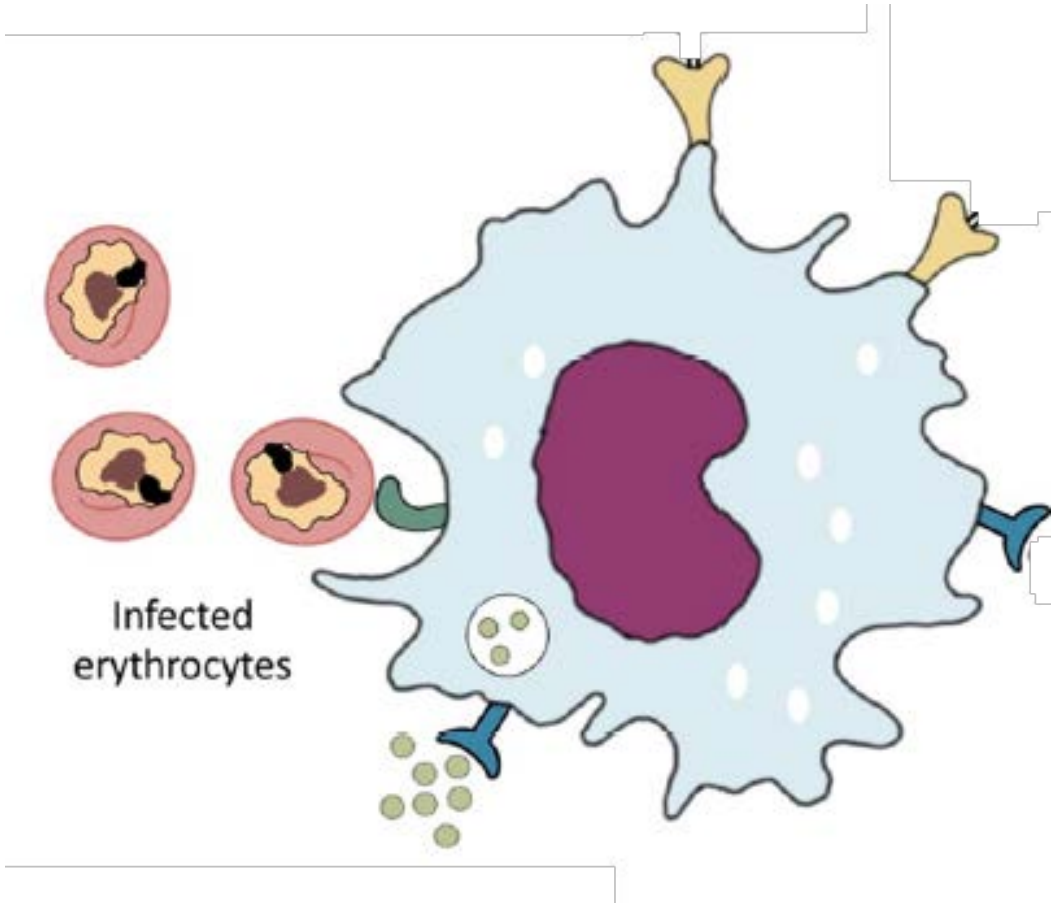




Desenvolvimento de febre decorrente de ciclo de replicação parasitária e ruptura de hemácias infectadas – DAMPS - TNF

https://i0.wp.com/www.malariasite.com/wp-content/uploads/2018/02/fever.jpg?ssl=1

Remoção de hemácias infectadas

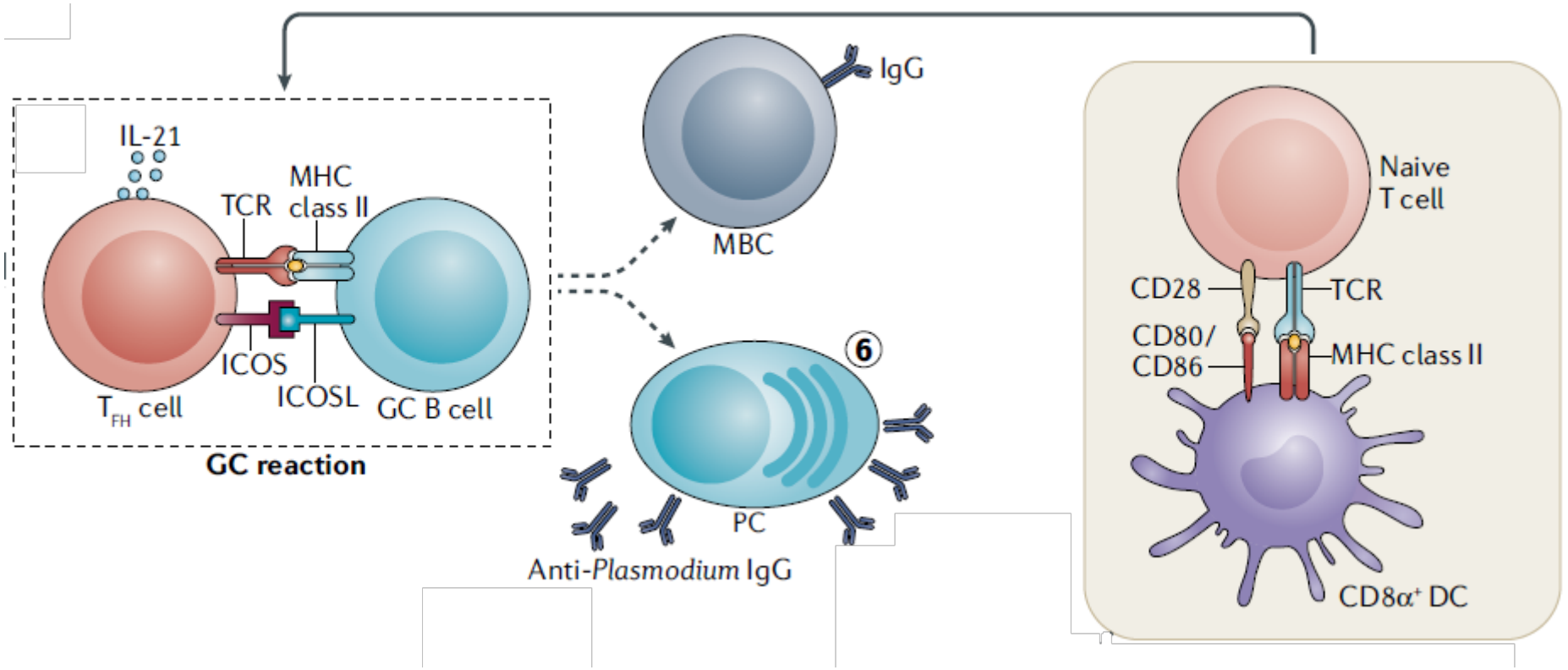


- Depuração de hemácias infectadas no baço por fagócitos (macrófagos)

- Ligação CD36 – PfEMP1

Chua CLL et al., Malaria J, 2021

Imunidade adaptativa fase eritrocítica

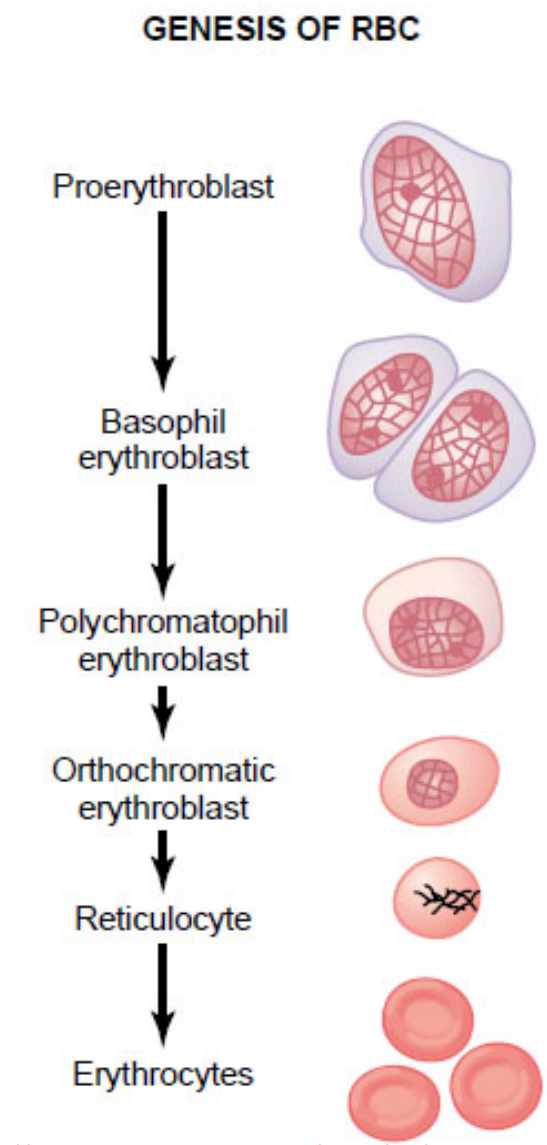


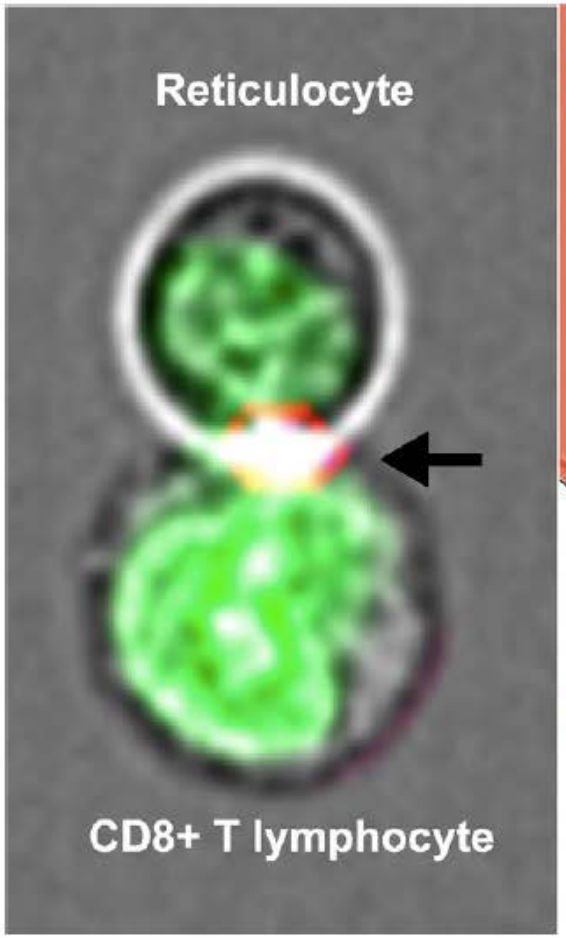
Th1 – IFN-gama

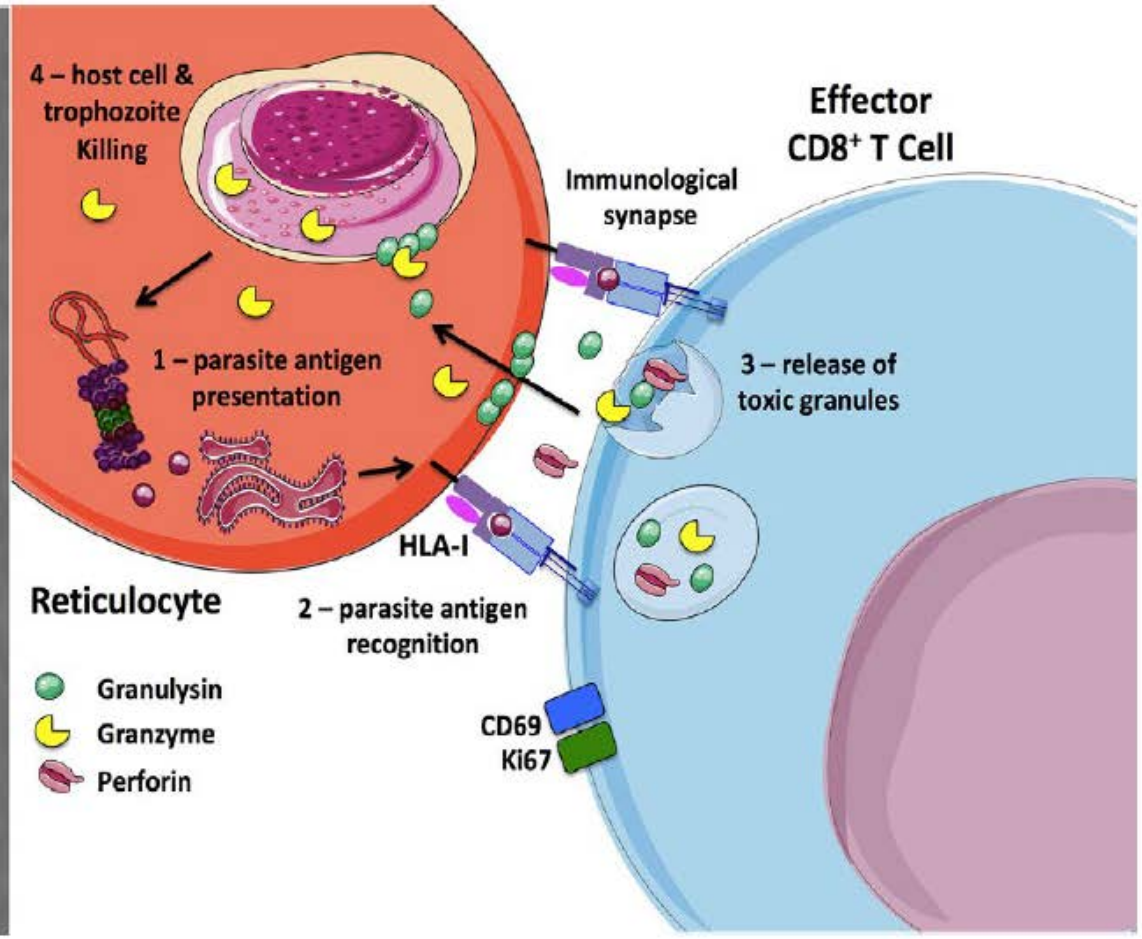
TCD8+ Citotóxica

Kurup S et al., Nat Rev Immunol, 2019

Linfócitos T CD8+ citotóxicos eliminam reticulócitos infectados por *P. vivax*



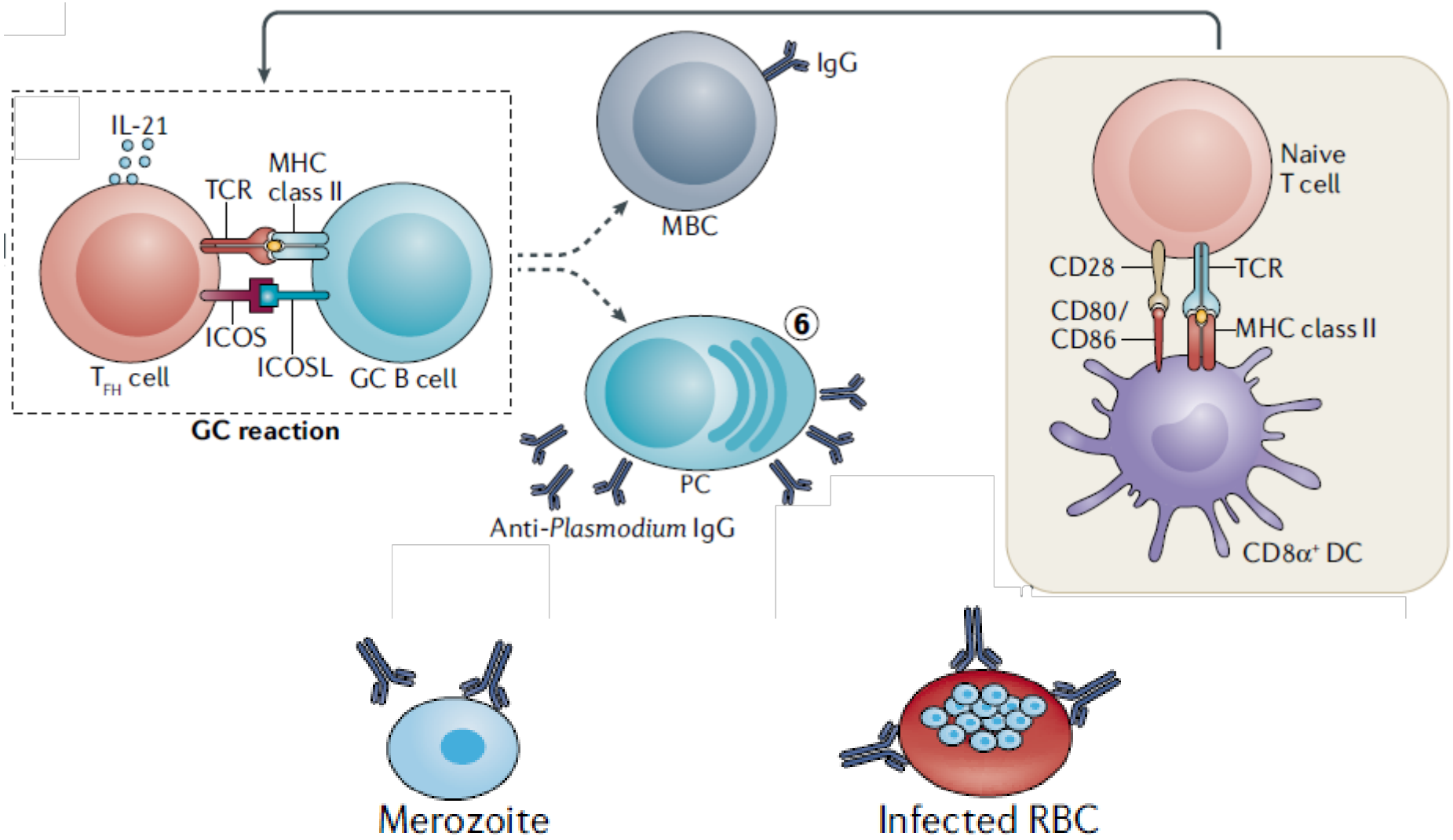




https://www.medicinehack.com/2011/05/red-blood-cell-formation.html

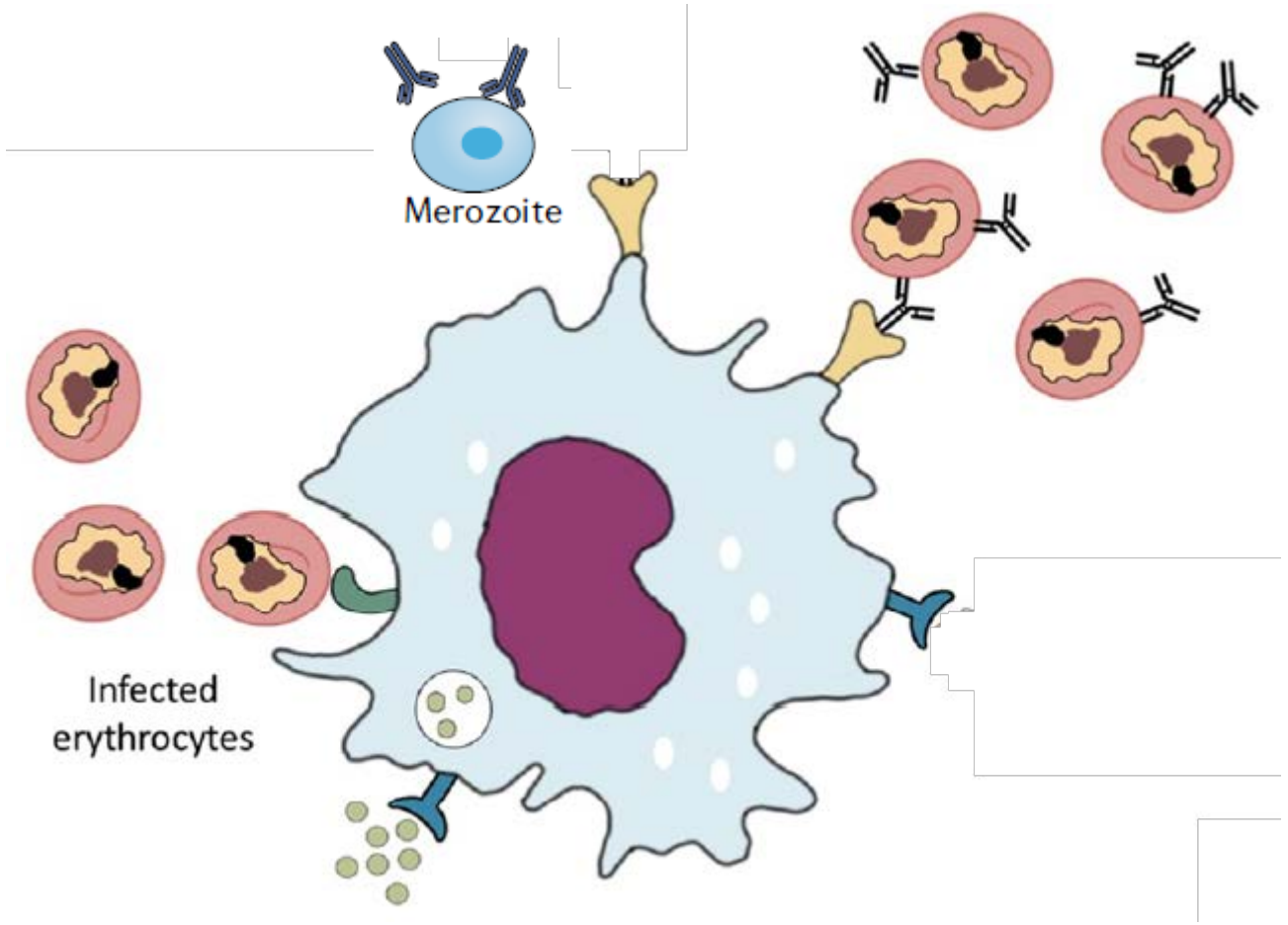
Antonelli et al., Immunol Rev, 2019

Imunidade humoral fase eritrocítica – antígenos de *Plasmodium* em merozoítos ou na superfície de hemácias infectadas



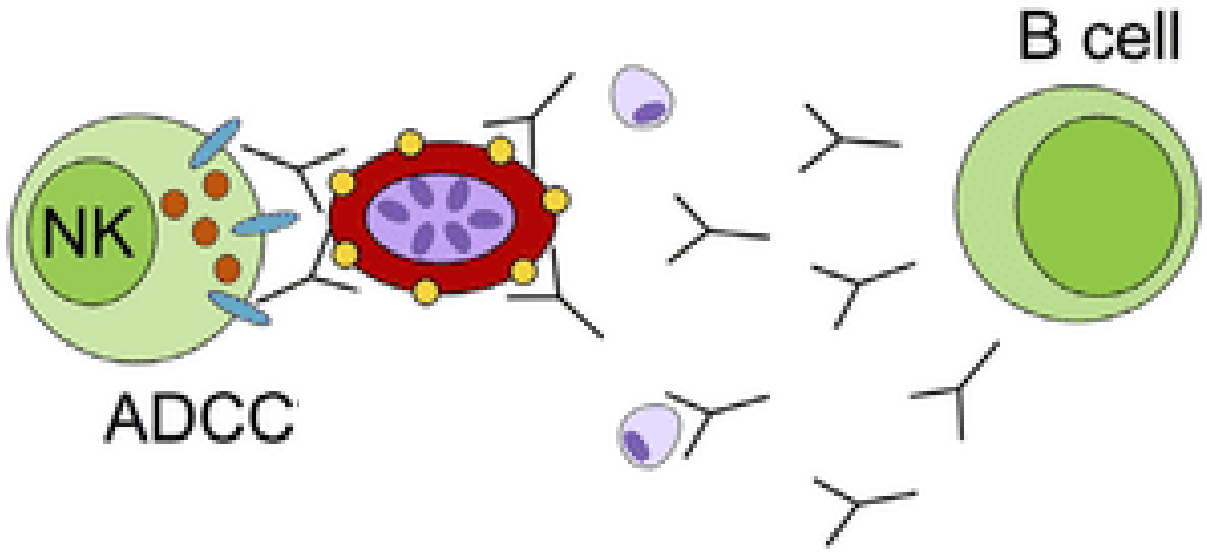
Kurup S et al., Nat Rev Immunol, 2019

Opsonização de merozoítos e hemácias infectadas



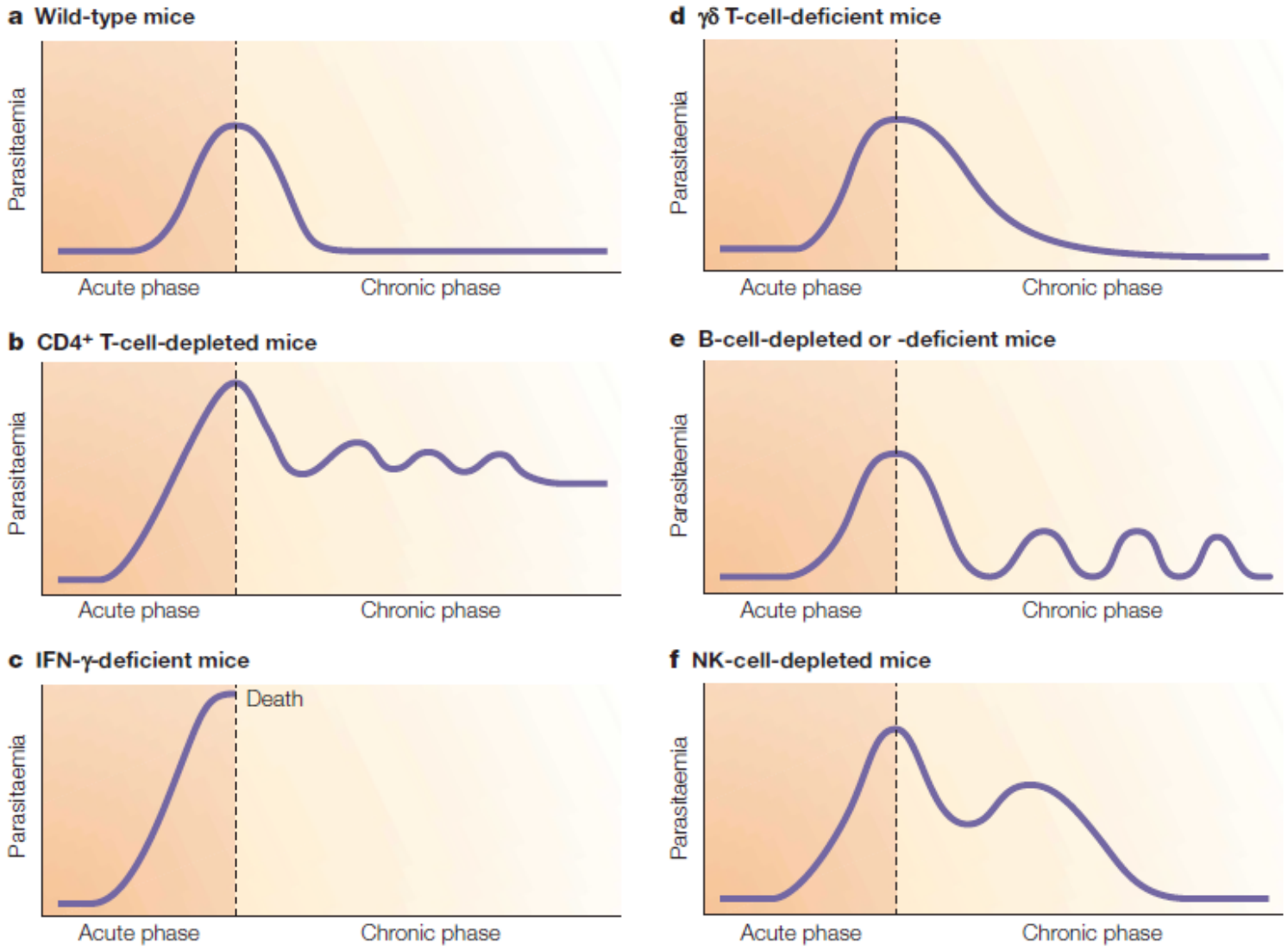
Chua CLL et al., Malaria J, 2021

Citotoxicidade dependente de anticorpos por células NK



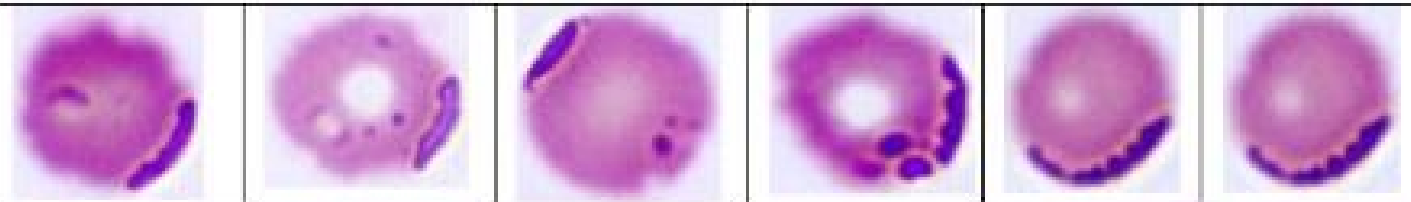
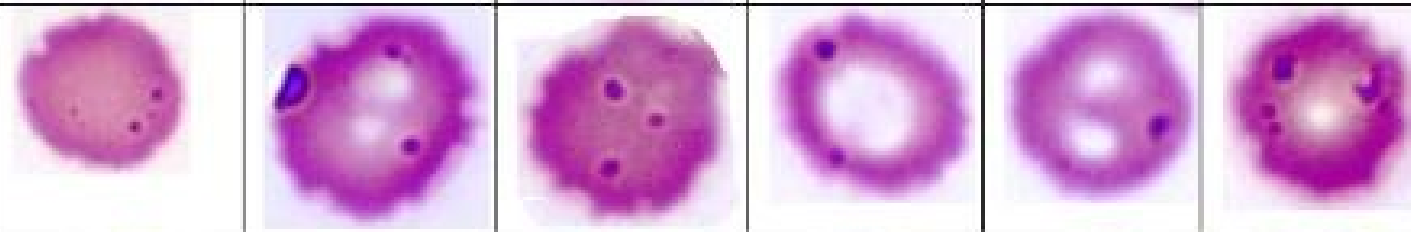
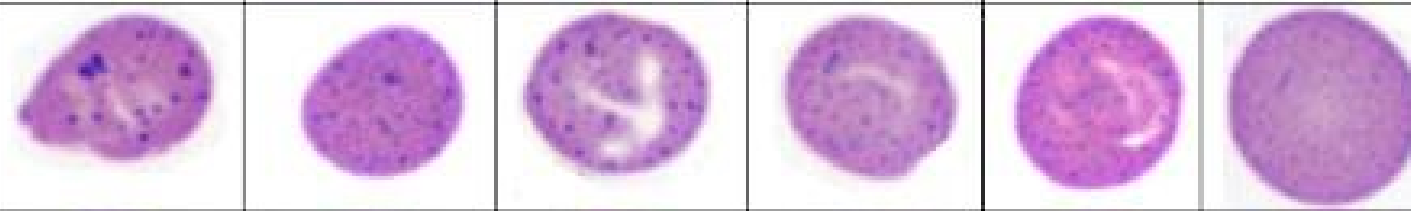
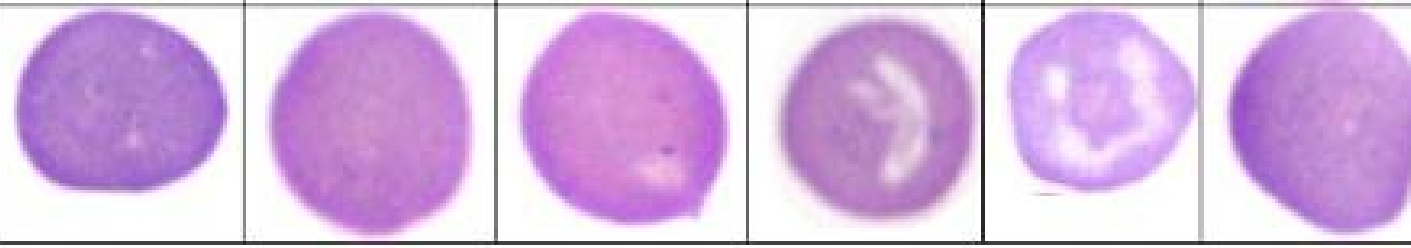
Wolf AS et al., Front Immunol, 2017

Modelos experimentais revelam papel da resposta imune contra malária



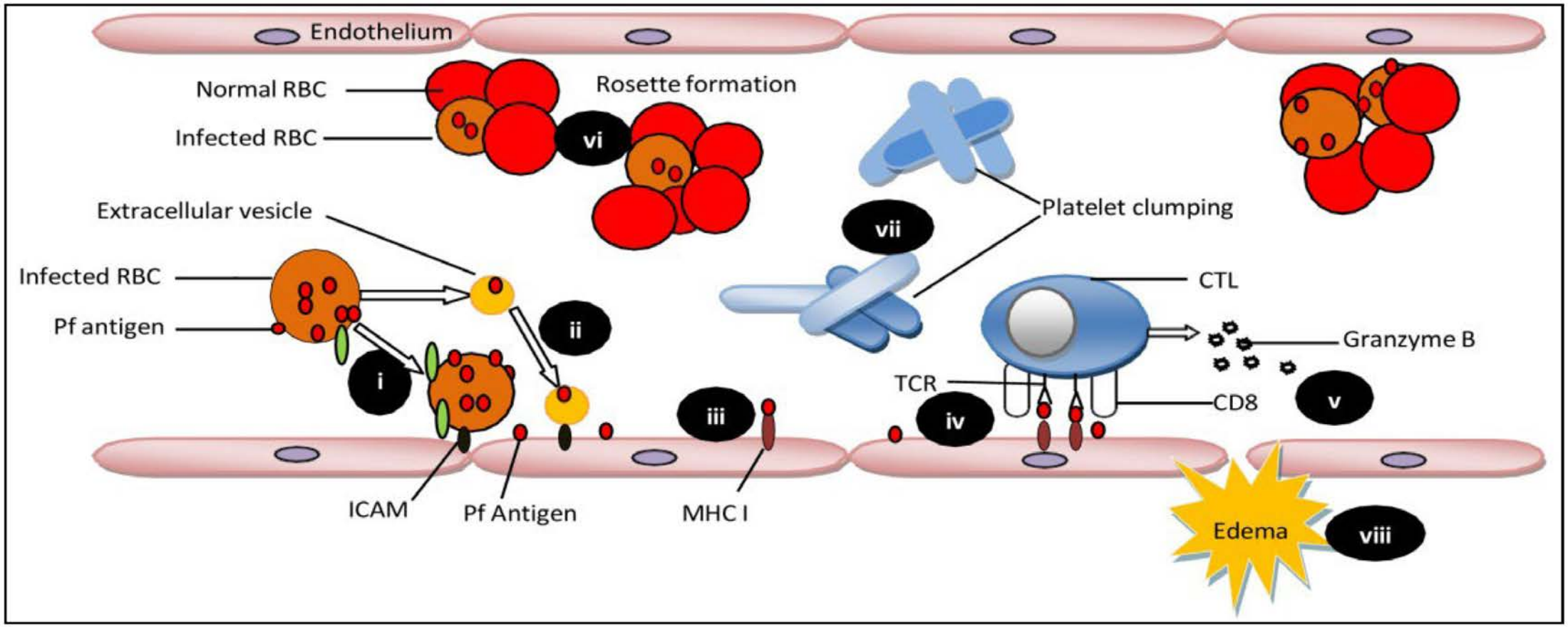
Oakley et al., Trends Parasitol., 2710):442-9, 2011.

P. falciparum – hemácias com morfologia alterada

Type of Malaria	RBCs
P.Malaria	
P.Falciparum	
P.Ovale	
P.Vivax	

file:///C:/Users/dlcos/OneDrive/Desktop/ComparisonofDifferentClassificationTechniquesUsingKnowledgeDiscoverytoDetectMalaria-infectedRedBloodCells.pdf

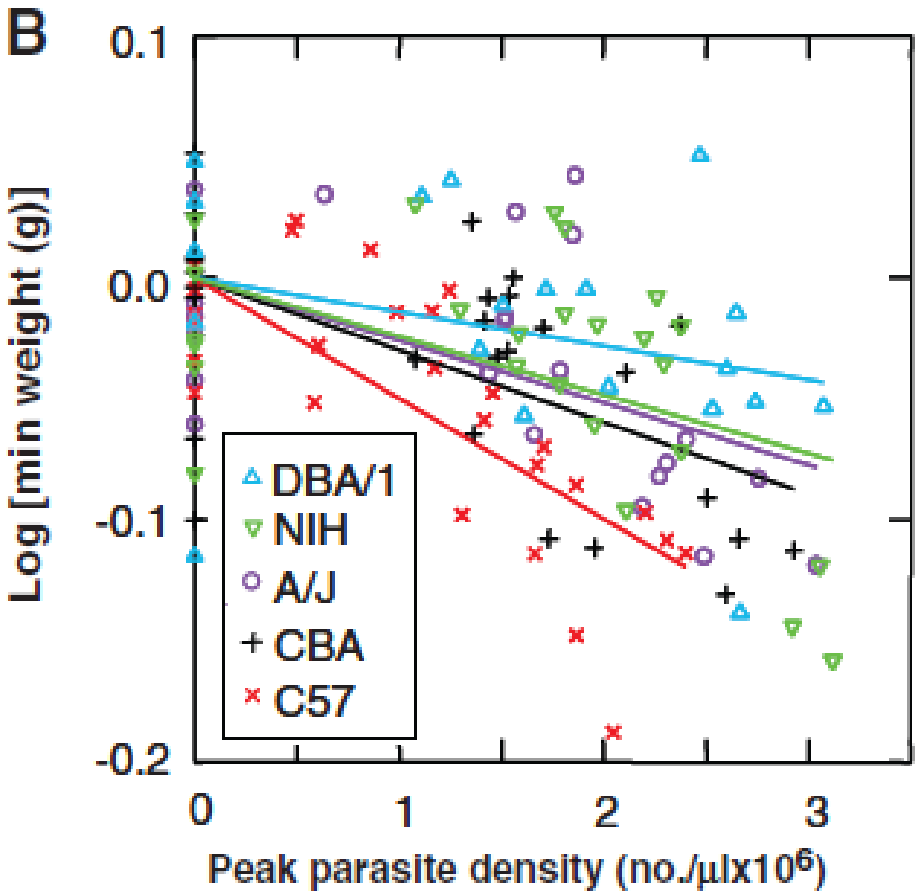
Malária cerebral por *P. falciparum*

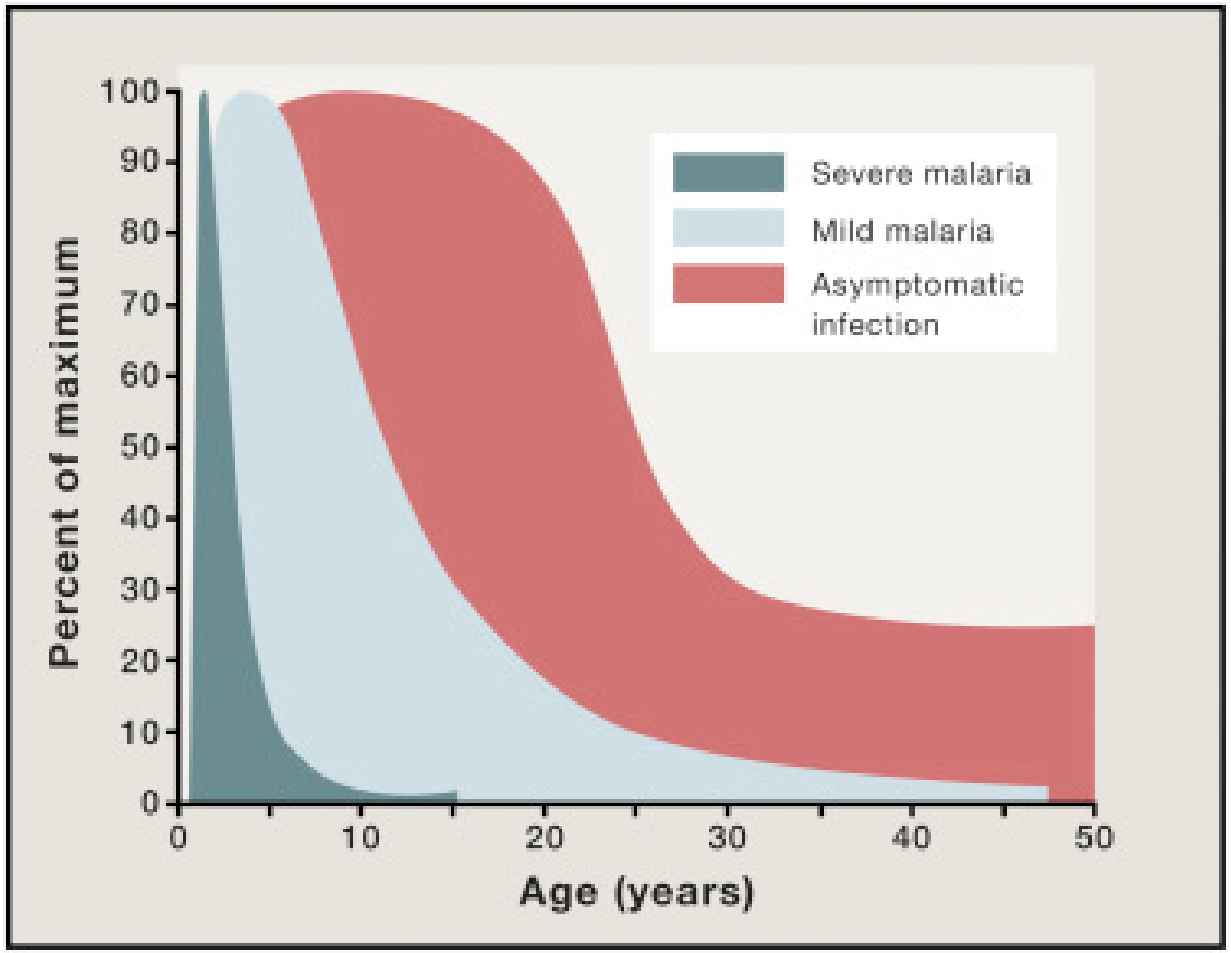


Rosetas de hemácias infectadas – coagulação; CD8+ citotóxicas e NK atacam endotélio

Chaudhary A et al., Bioengineering 2022

Tolerância à doença – Malária é um ótimo exemplo – carga parasitária nem sempre se traduz em sintomas





Raberg L et al., Science 2007

Cowman AF et al., Cell 2016

Questões