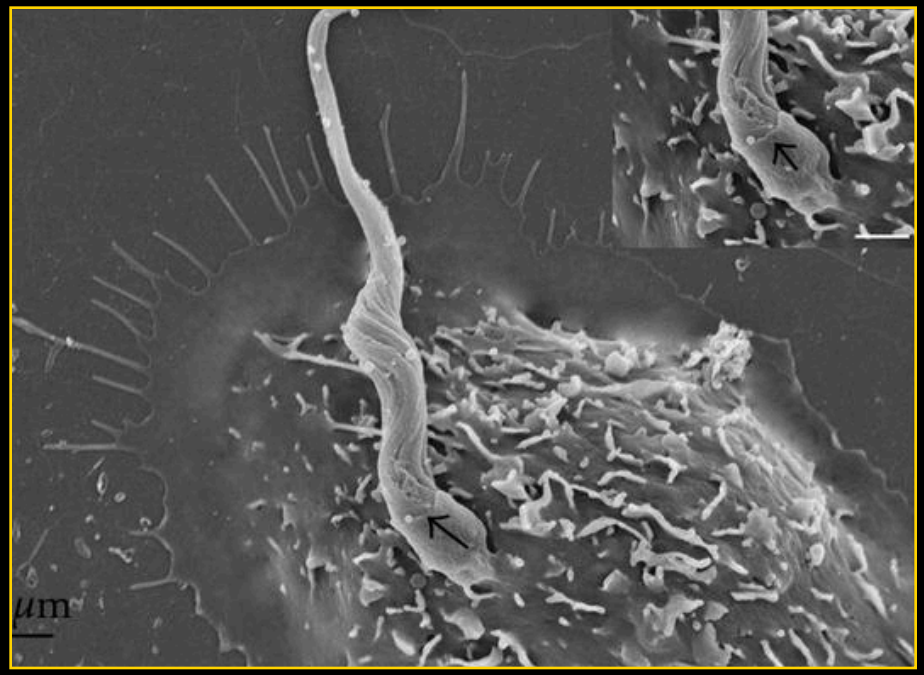
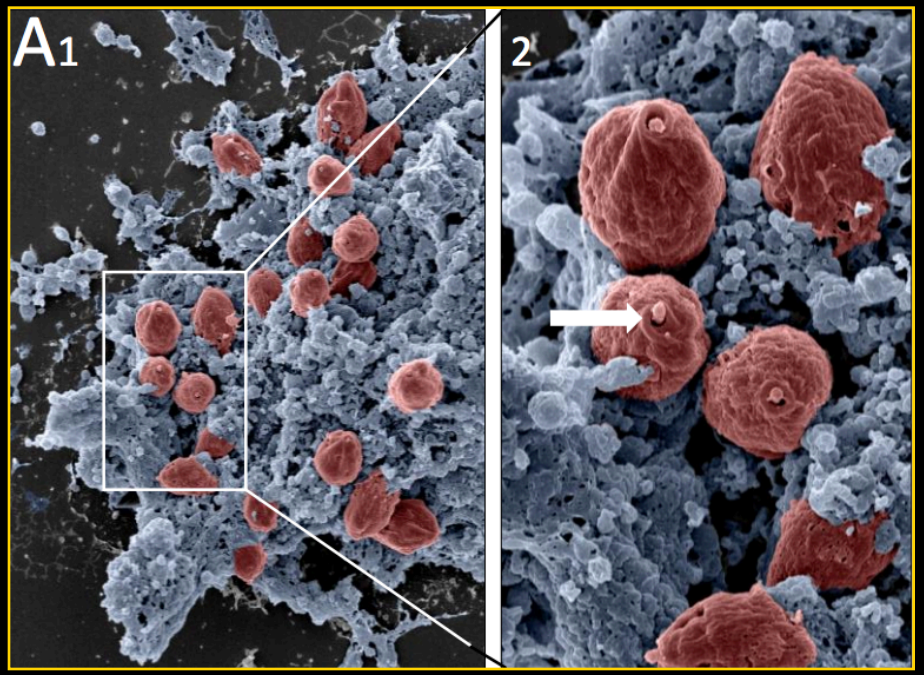
Biologia celular e molecular de tripanosomatídeos intracelulares



de Souza et al., 2010



Rosazza et al., 2020

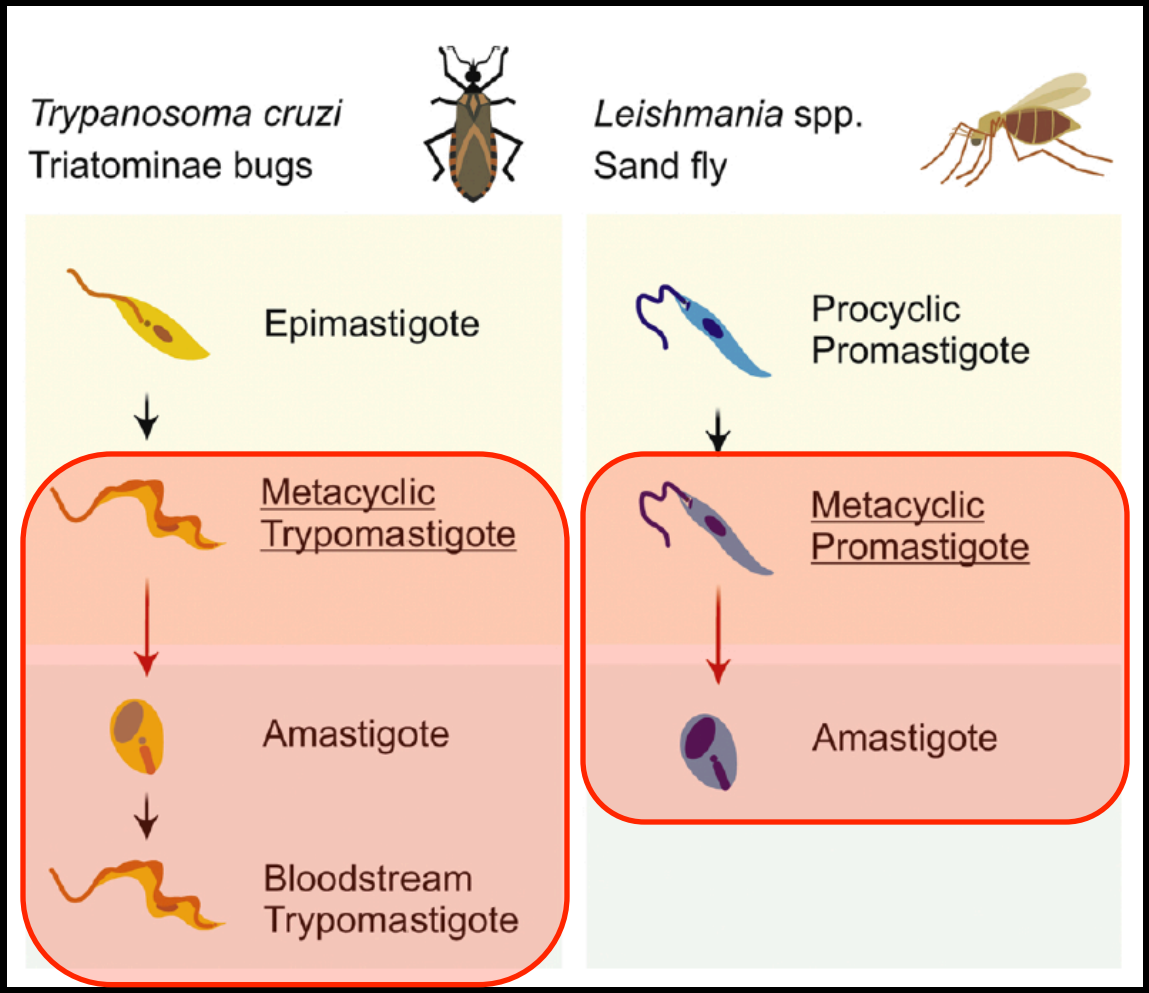
Mauro Cortez

mcortez@usp.br

BMP0103/5794 – Biologia celular e molecular de parasitas

Importantes pontos – formas infectivas

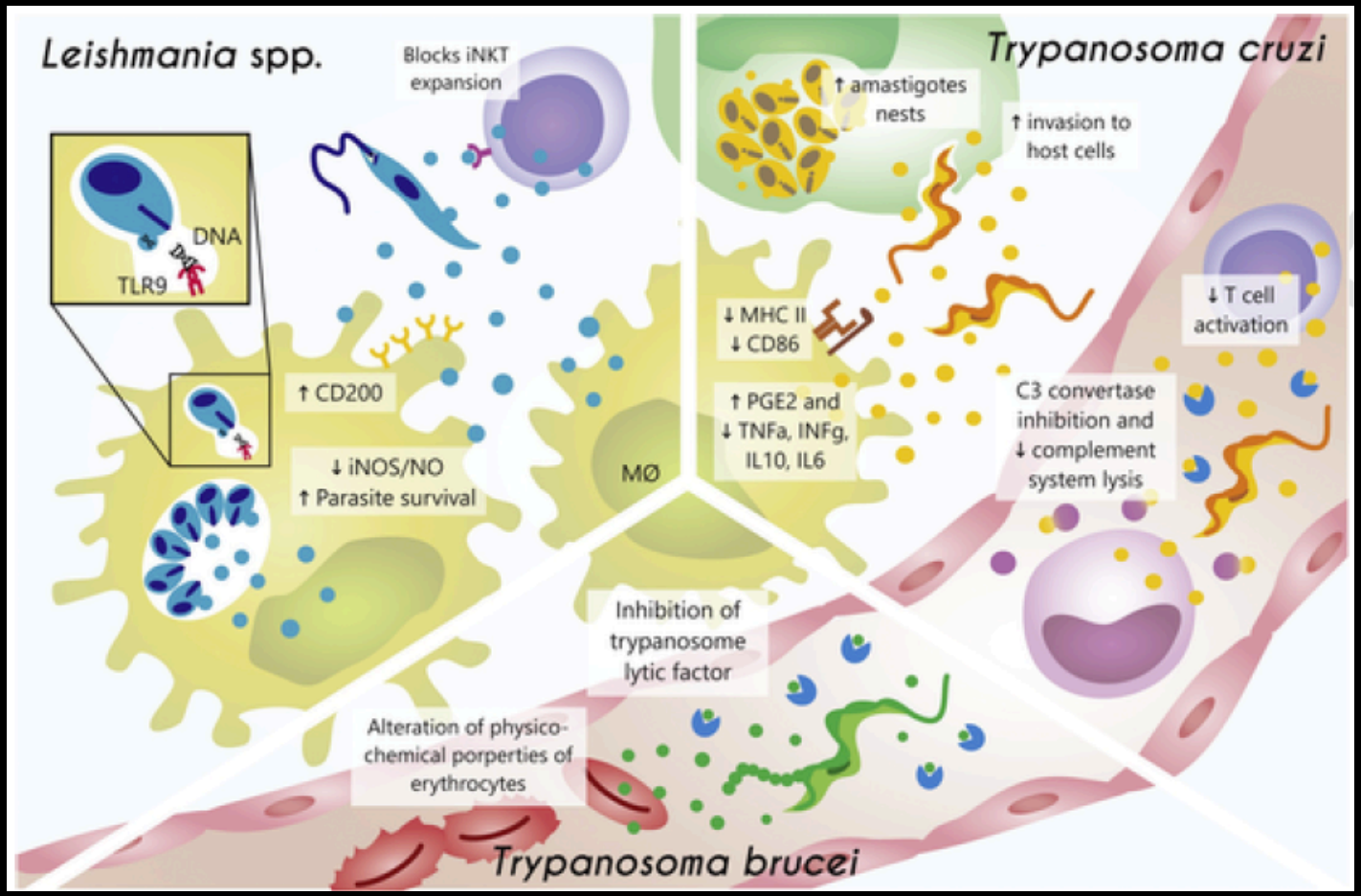
- Formas infectivas de *Trypanosoma cruzi* e *Leishmania*.



Rossi et al., 2021

Importantes pontos – Processo de infecção

- *Trypanosoma cruzi* e *Leishmania* precisam evadir a resposta do hospedeiro



Rossi et al., 2021

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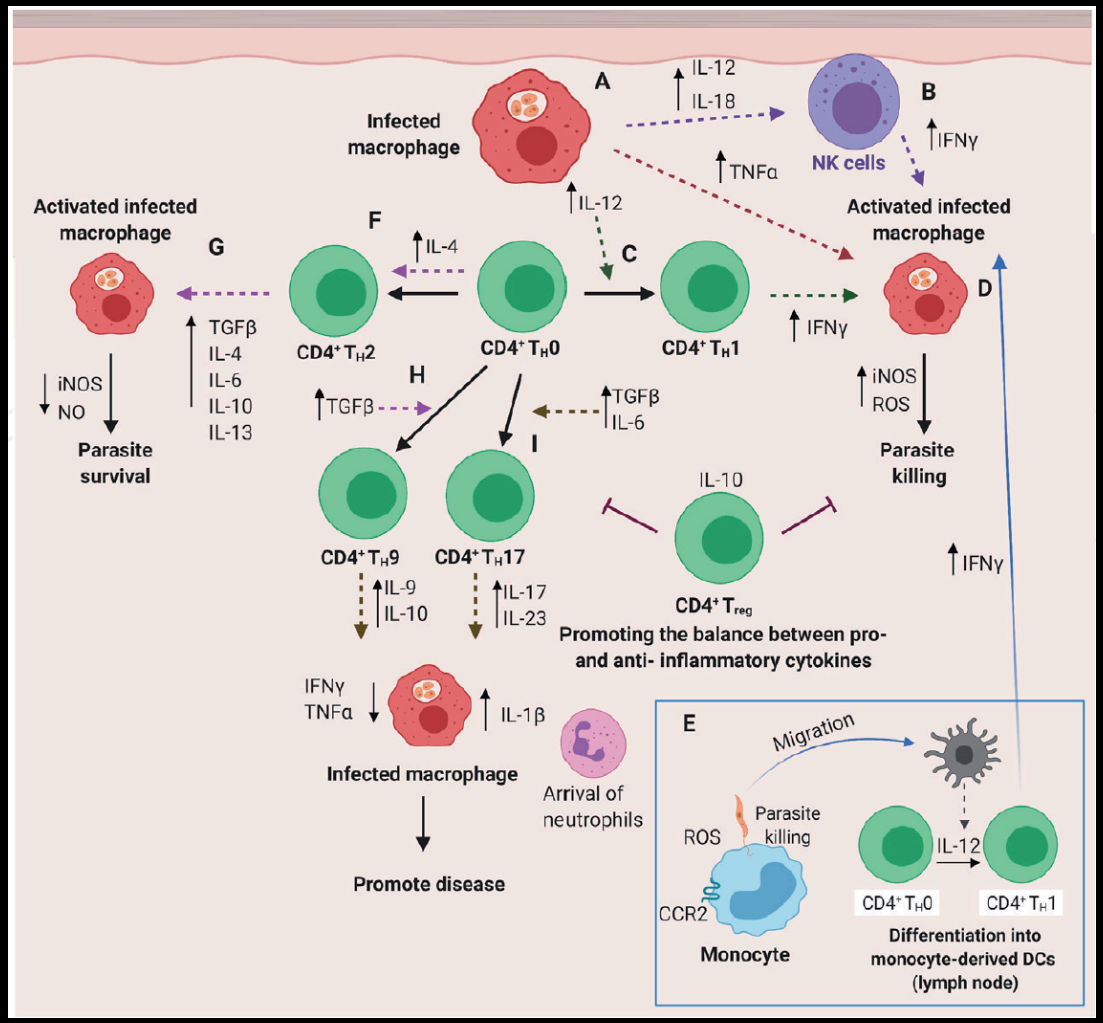
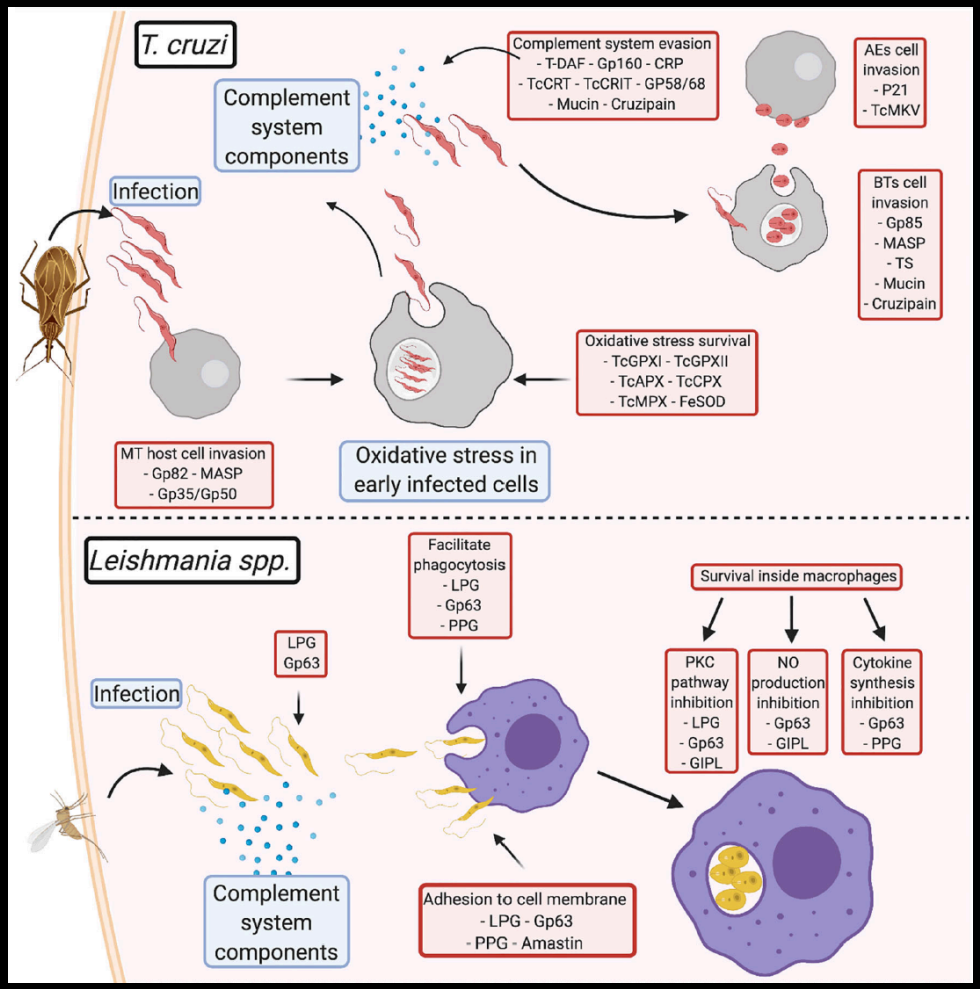


Panahi et al., 2021

Diferentes fases da infecção– moléculas importantes no processo

- *Trypanosoma cruzi* e *Leishmania*.



Castro Neto et al., 2021

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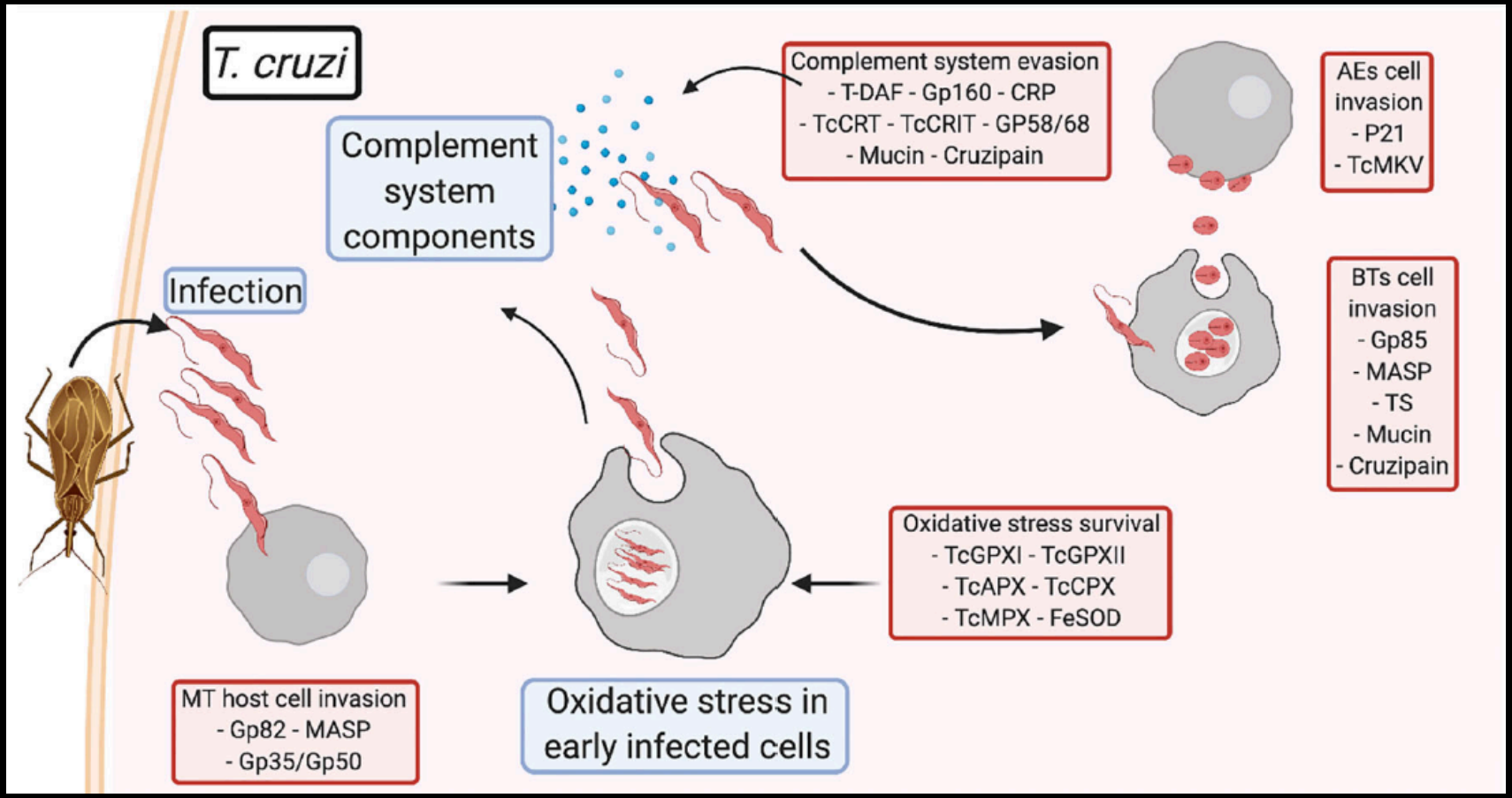
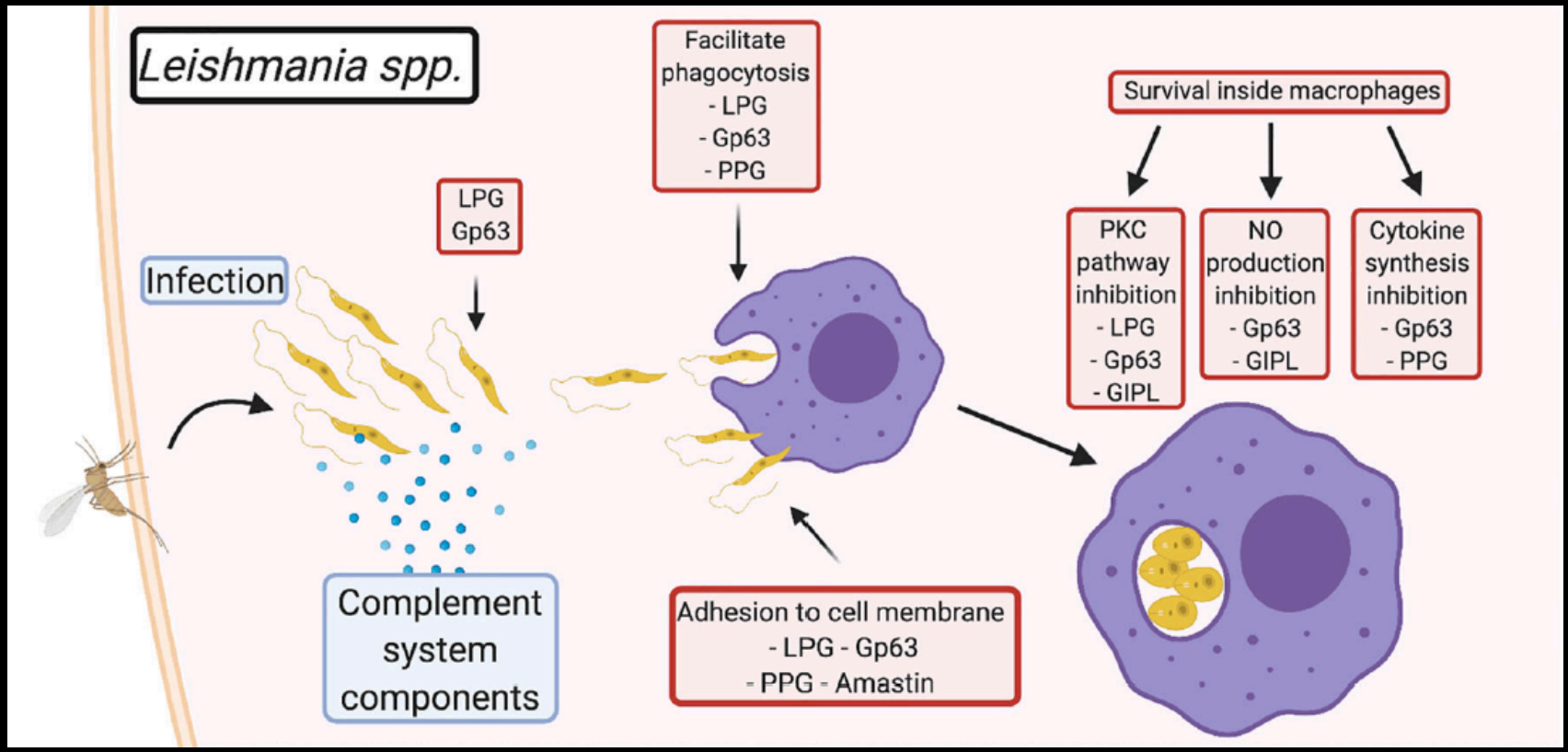
- *Trypanosoma cruzi*.



Castro Neto et al., 2021

Diferentes fases da infecção– moléculas importantes no processo

- *Leishmania*.



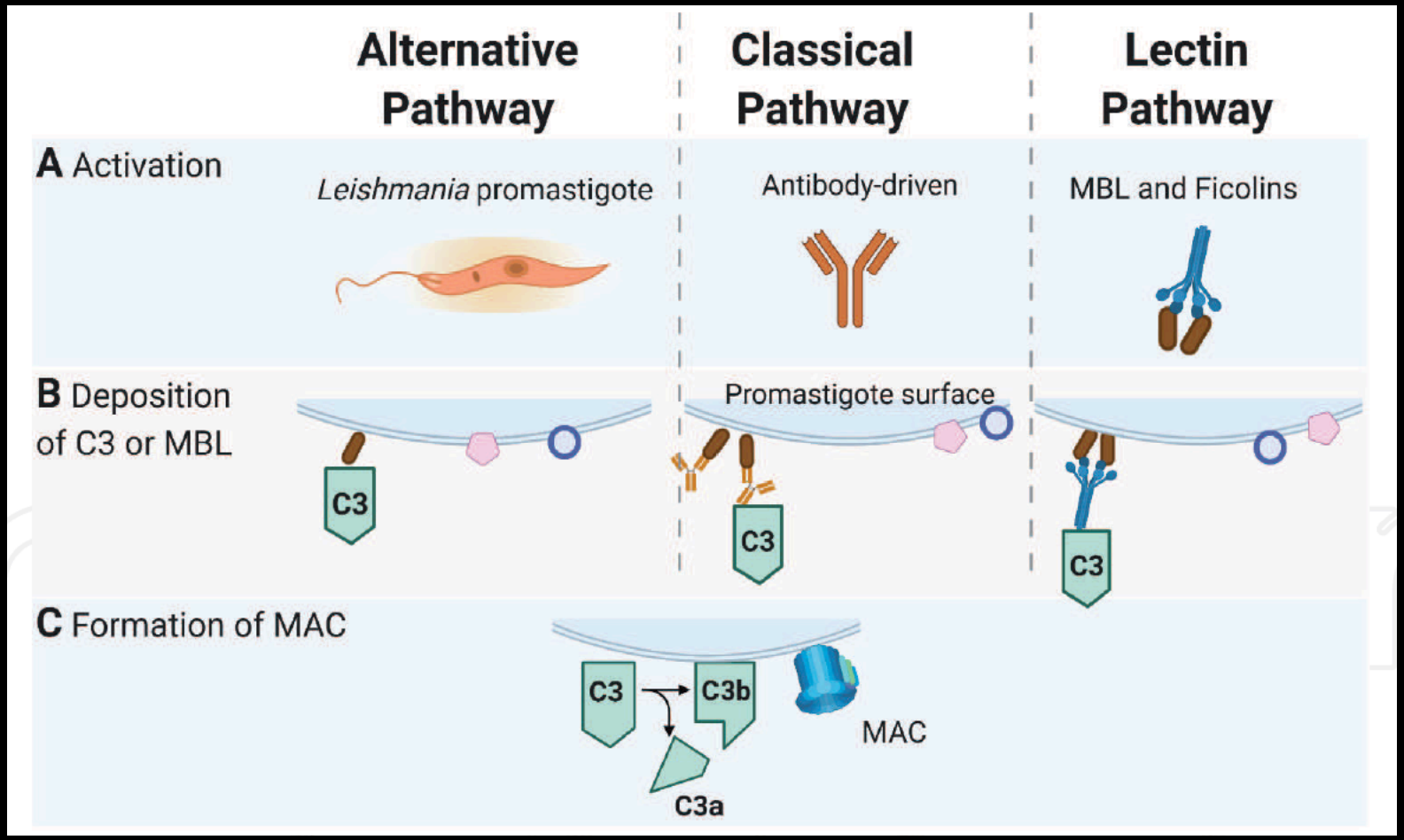
Castro Neto et al., 2021

Quais são os principais mecanismos para conseguir sobreviver e proliferar?

- Celulares
- Moleculares

Diferentes fases da infecção– moléculas importantes no processo

- *Leishmania*.



Panahi et al., 2021

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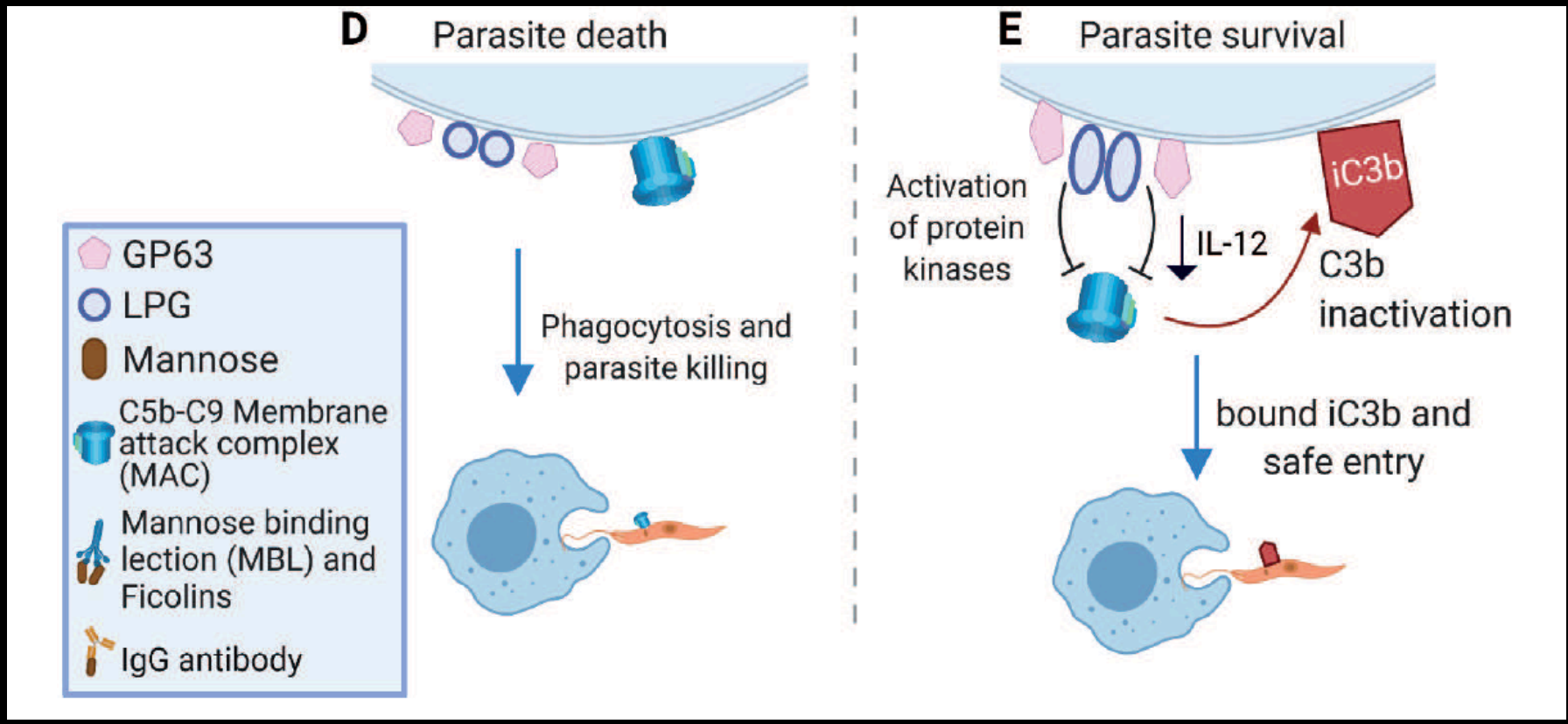
- *Leishmania*.



Panahi et al., 2021

Diferentes fases da infecção– inibição da célula hospedeira (macrófagos)

- *Trypanosoma cruzi* e *Leishmania* modulam células da imunidade inata.

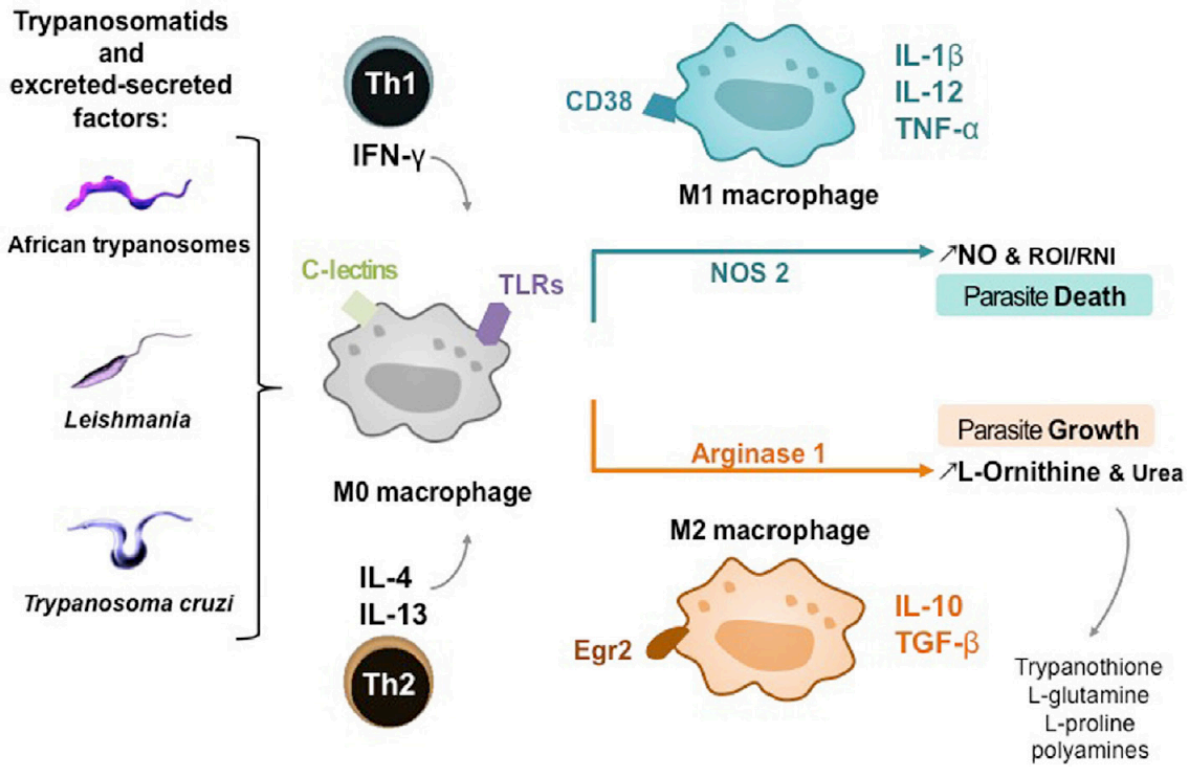


FIGURE 2 | Macrophage activation pathways in trypanosomatid infections. T-cell subsets potentiating M0 macrophage differentiation into M1 or M2 subtype; Th, helper T lymphocyte; IFN-γ, interferon-γ; IL, interleukin. Host cell receptors involved in trypanosomatid detection: C-lectins and toll-like receptors (TLRs). Phenotypic markers and cytokines of macrophage polarization: cluster of differentiation (CD) 38, Egr2, early growth response protein 2; TNF-α, tumor necrosis factor; TGF-β, transforming growth factor. Products of macrophage polarization influencing the death or growth of trypanosomatids; NO, nitric oxide.

Holzmuller et al., 2018

Diferentes fases da infecção– inibição da célula hospedeira (macrófagos)

- *Trypanosoma cruzi* e *Leishmania* modulam fatores da célula.

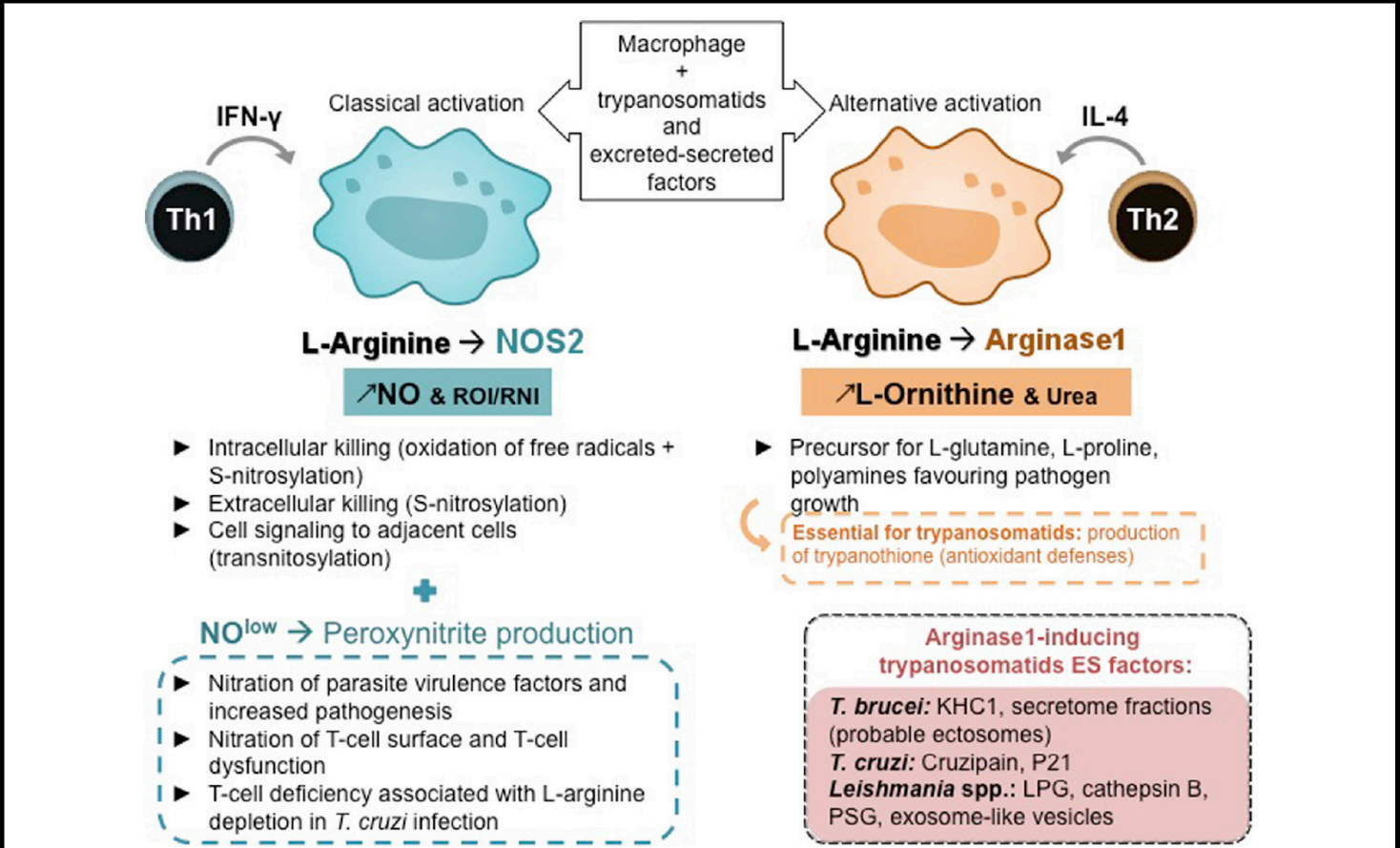


FIGURE 3 | Macrophage polarization, T-helper subsets, and L-arginine metabolism. Th, helper T lymphocyte; IFN-γ, interferon; IL, interleukin; NO, nitric oxide; ROI, reactive oxygen species; RNI, reactive nitrogen species.

Holzmuller et al., 2018

Diferentes fases da infecção– inibição da célula hospedeira (macrófagos)

- *Trypanosoma cruzi* e *Leishmania* modulam fatores da célula.

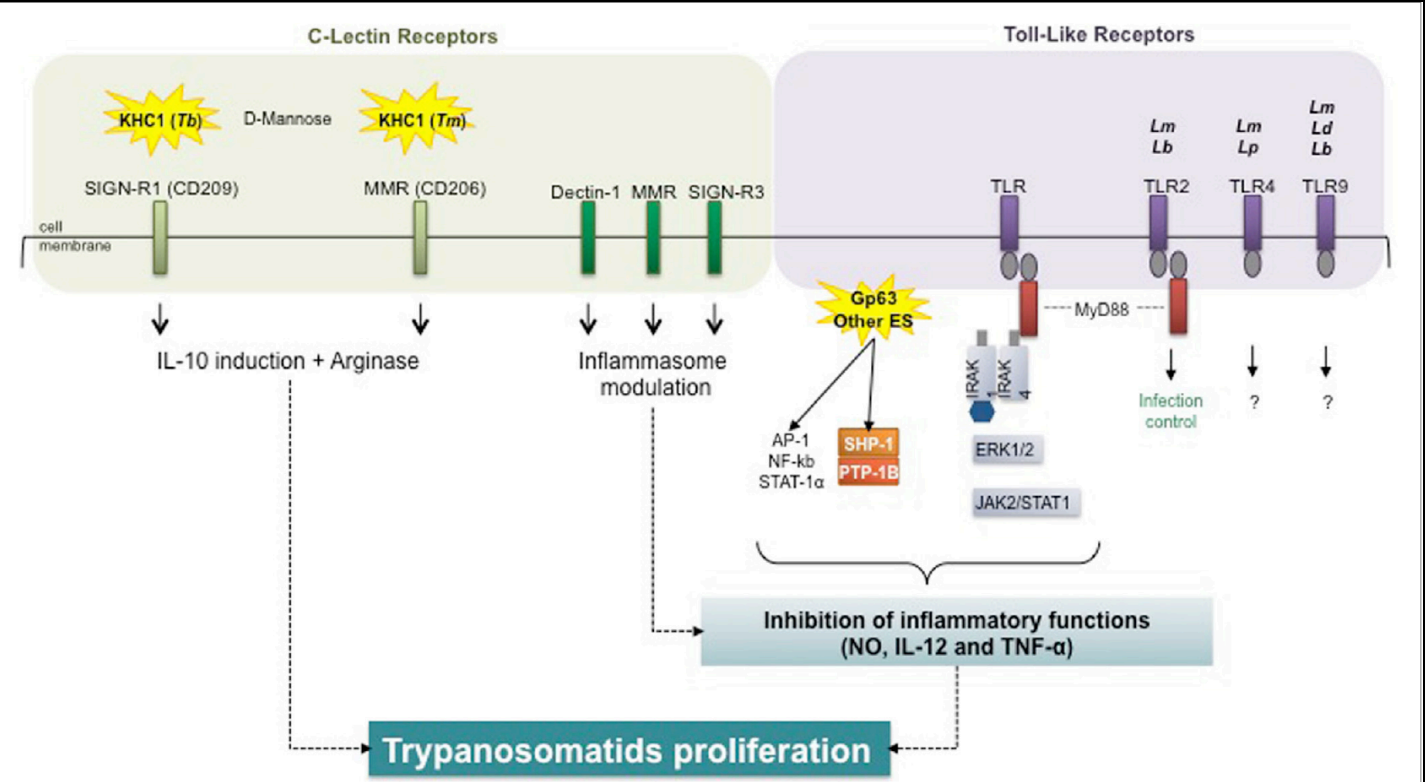
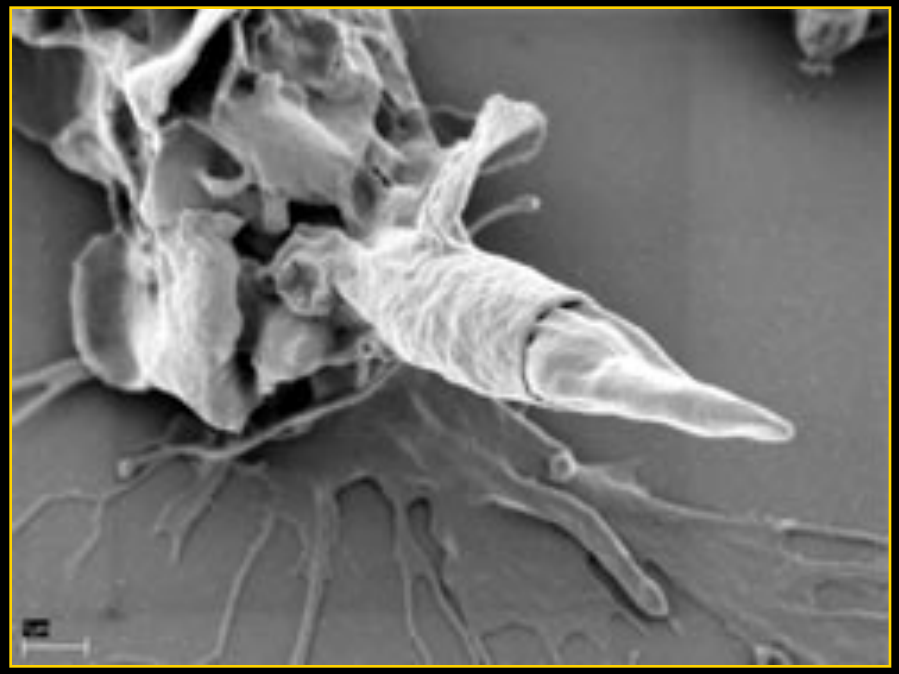


FIGURE 5 | Host receptors in trypanosomatid-mediated arginase modulation. Trypanosomatids and virulence factors: *Tb*, *Trypanosoma brucei; Tm, T. musculi; Lm*, *Leishmania major*; *Lb, L. braziliensis; Lp, L. pifanoi*; *Ld, L. donovani*; Gp, glycoprotein; ES, excreted–secreted. Macrophage receptors: SIGN-R1, specific intercellular adhesion molecule grabbing non-integrin receptor 1; MMR, macrophage mannose receptor; TLR, toll-like receptor. Signal transduction molecules: MyD88, myeloid differentiation primary response 88; IRAK, interleukin-1 receptor-associated kinase; AP, activator protein; NF-κB, nuclear factor-kappa B; STAT, signal transducers and activators of transcription; SHP, Src homology region 2 domain-containing phosphatase; PTB, protein tyrosine phosphatase; ERK, extracellular signal-regulated kinase; JAK, Janus kinase (or just another kinase). Inflammatory markers: NO, nitric oxide; IL, interleukin; TNF, tumor necrosis factor.

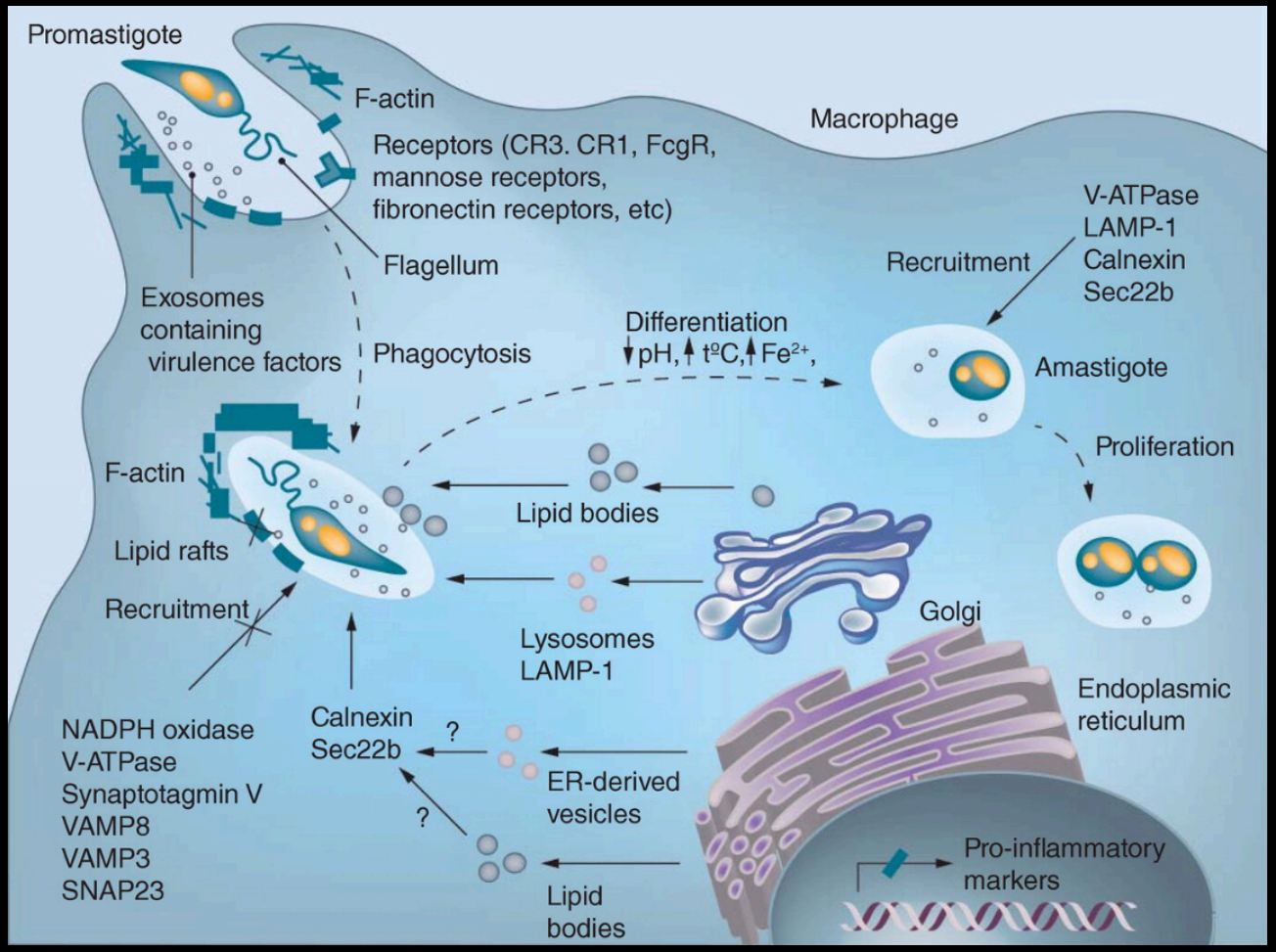
Holzmuller et al., 2018

Processo de invasão celular



Diferentes fases da infecção– moléculas importantes no processo

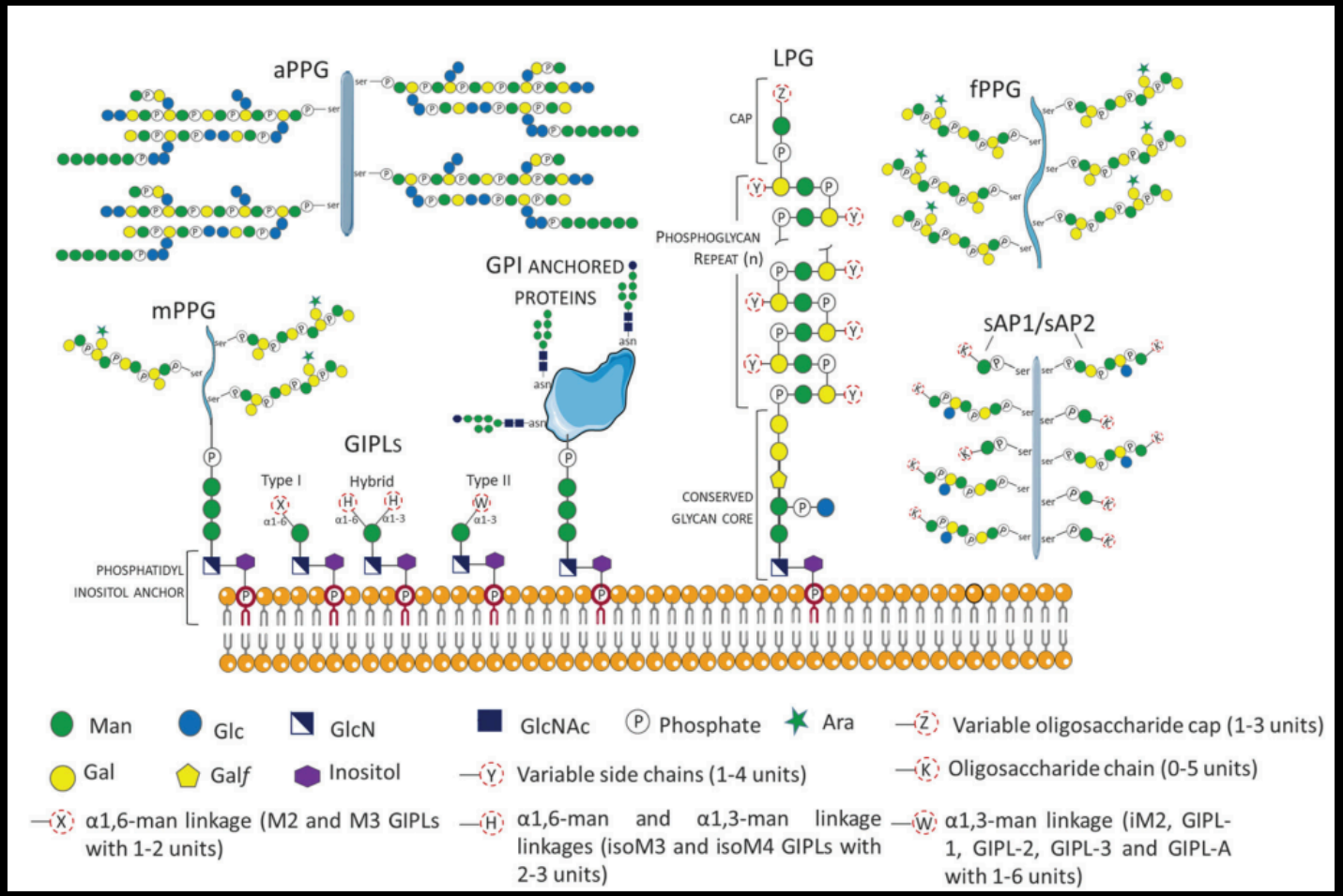
- *Leishmania*.



Podinovskaia e Descoteaux., 2015

Diferentes fases da infecção– moléculas importantes no processo

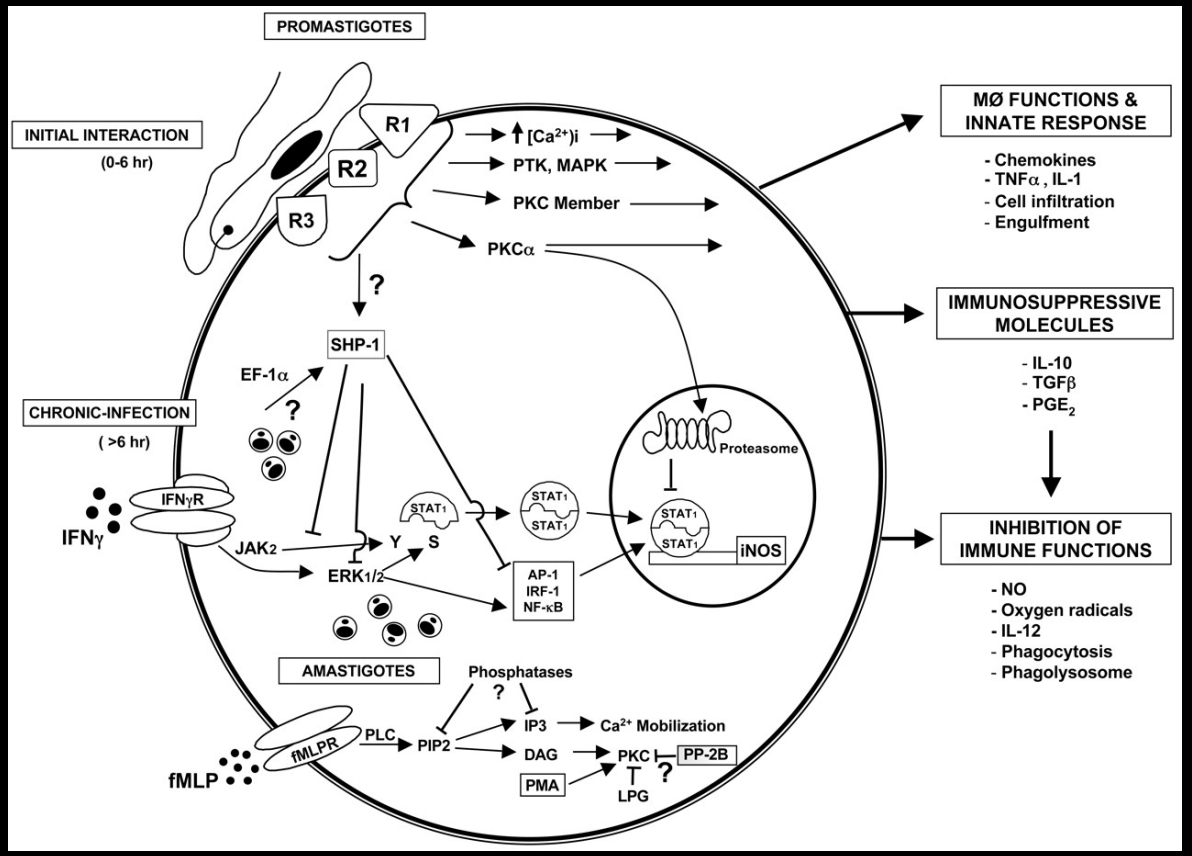
- *Leishmania*.



Mule et al., 2021

Diferentes fases da infecção– moléculas importantes no processo

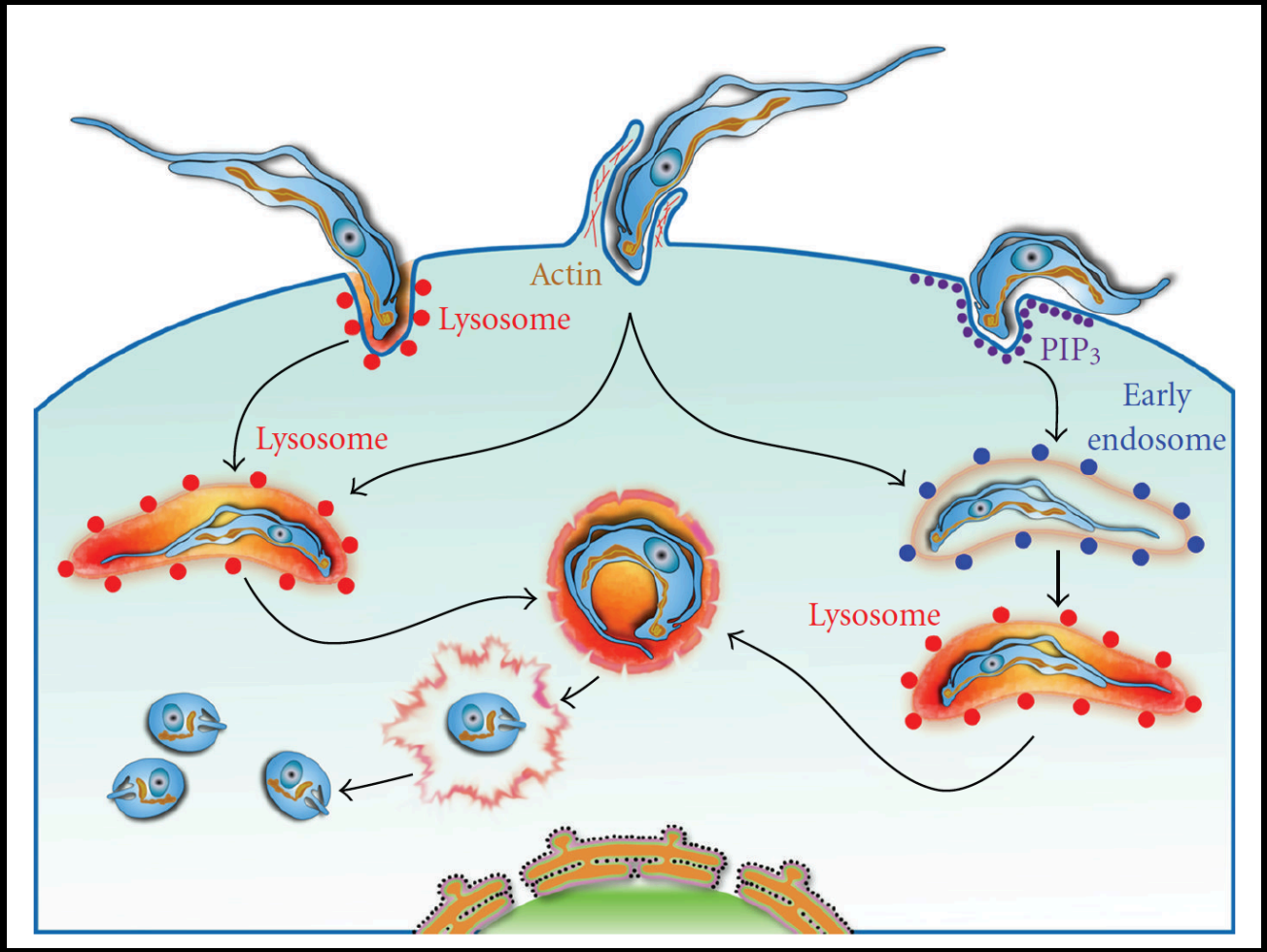
- *Leishmania*.



Olivier et al., 2005

Diferentes fases da infecção– moléculas importantes no processo

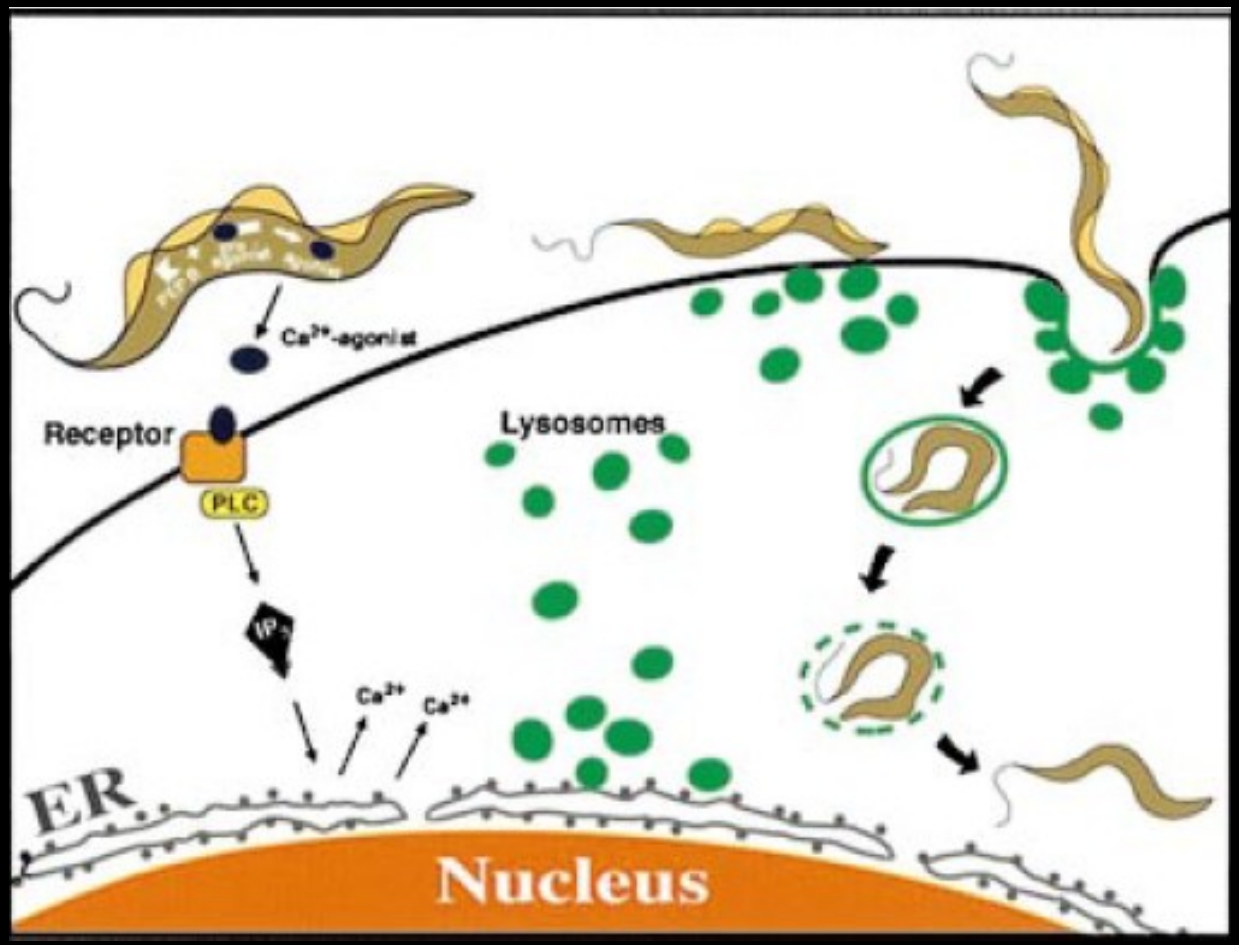
- *Trypanosoma cruzi*.



Castro Neto et al., 2021

Processo de invasão– mecanismos

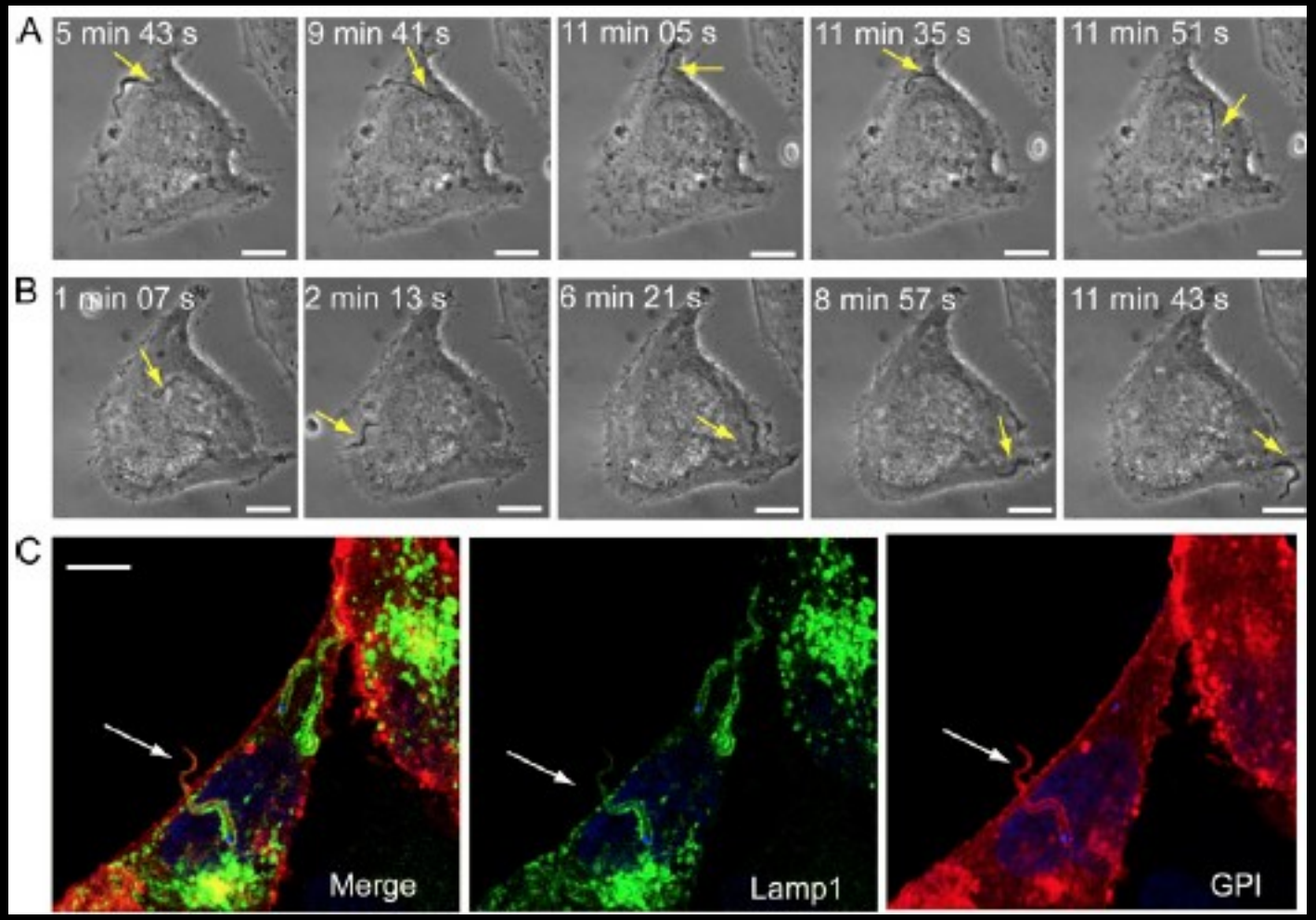
- Vias de infecção por *T. cruzi* na célula hospedeira:



Siblei and Andrews et al Traffic Rev. 2000

Processo de invasão– mecanismos

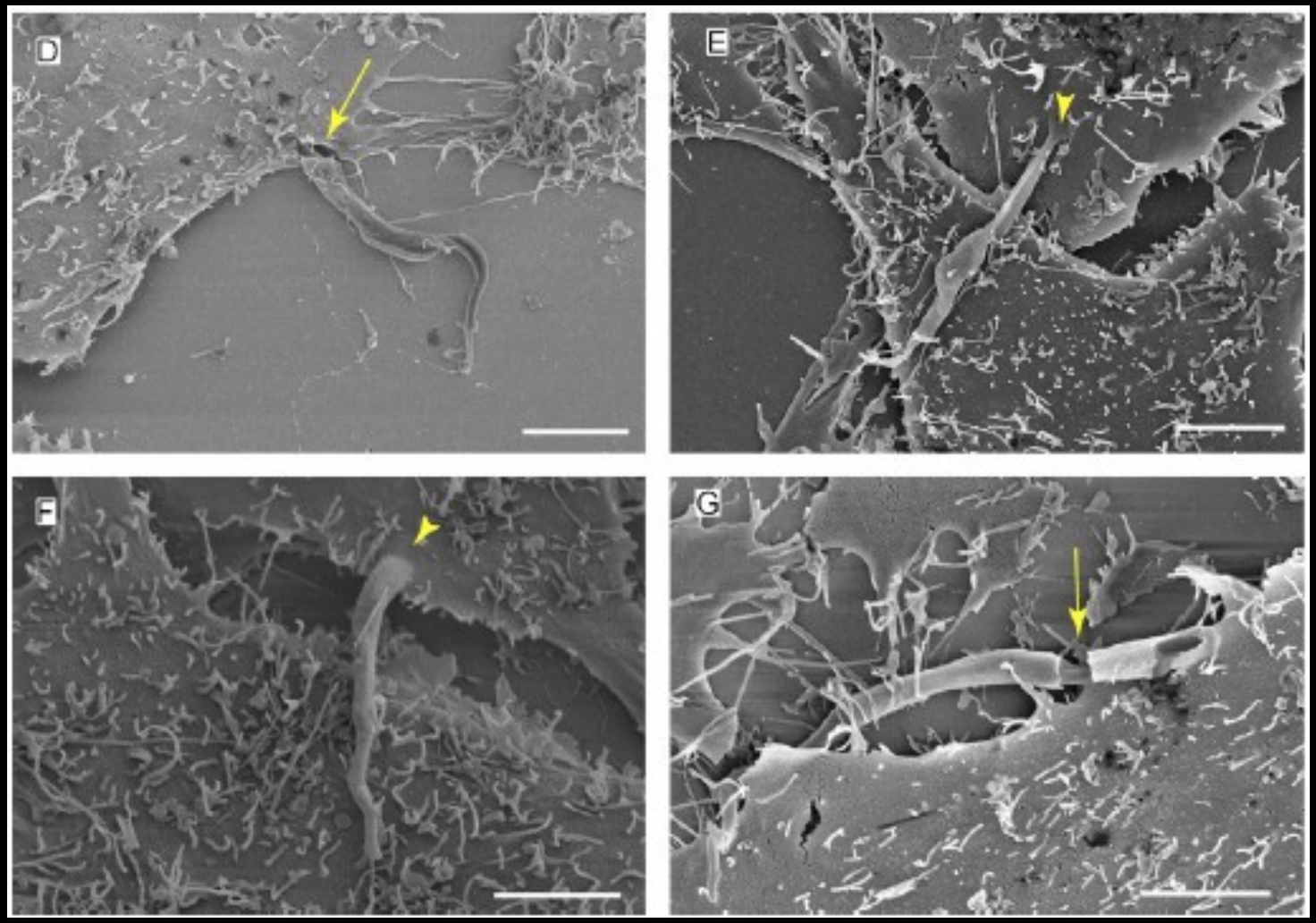
- Mecanismo de entrada: Ativação da maquinaria de reparo de membrana para invadir as células



Fernandes et al 2011. *JEM. 2011.*

Processo de invasão– reparo de membrana

- Mecanismo de entrada: Ativação da maquinaria de reparo de membrana para invadir as células



Fernandes et al 2011. *JEM. 2011.*

Processo de invasão– reparo de membrana

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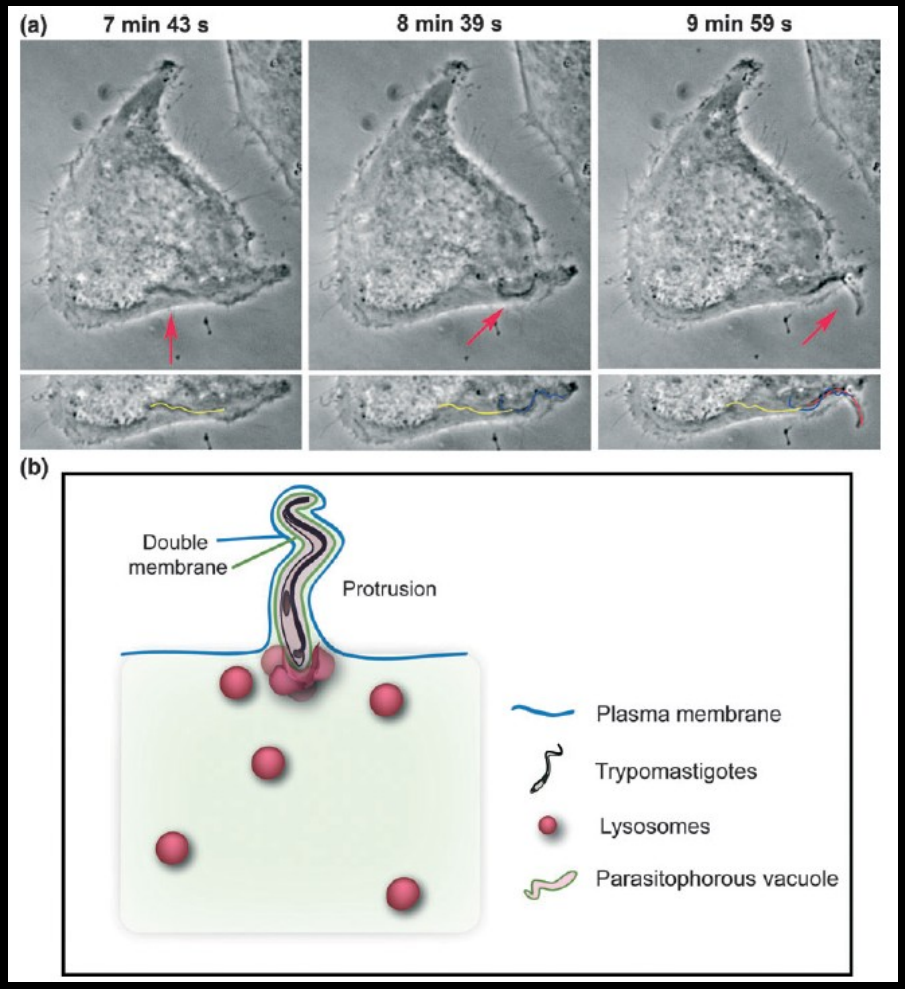
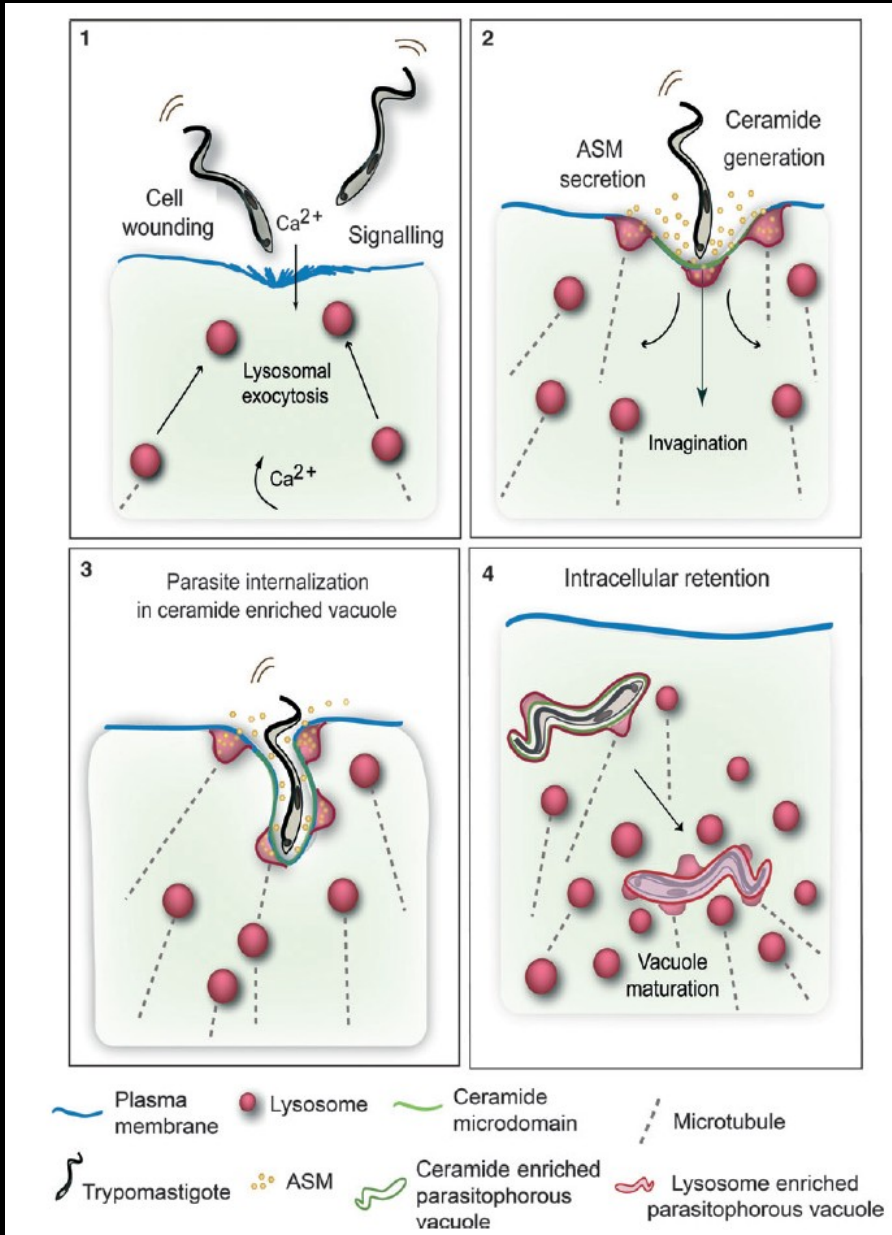


Fernandes and Andrews I 2011. FEMS Microb Rev. 2012.

Processo de invasão– reparo de membrana



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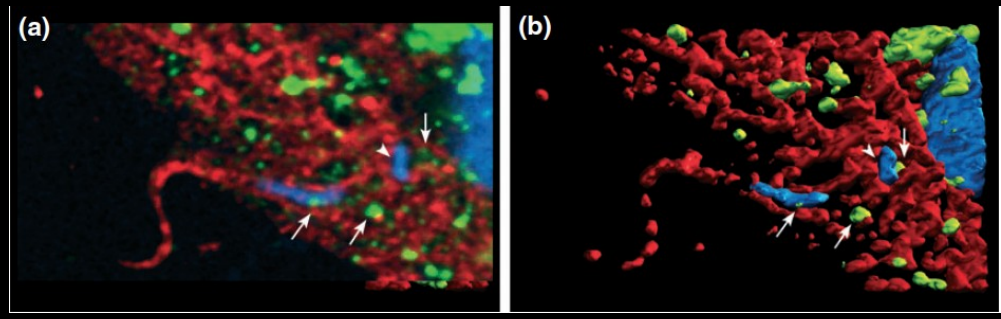
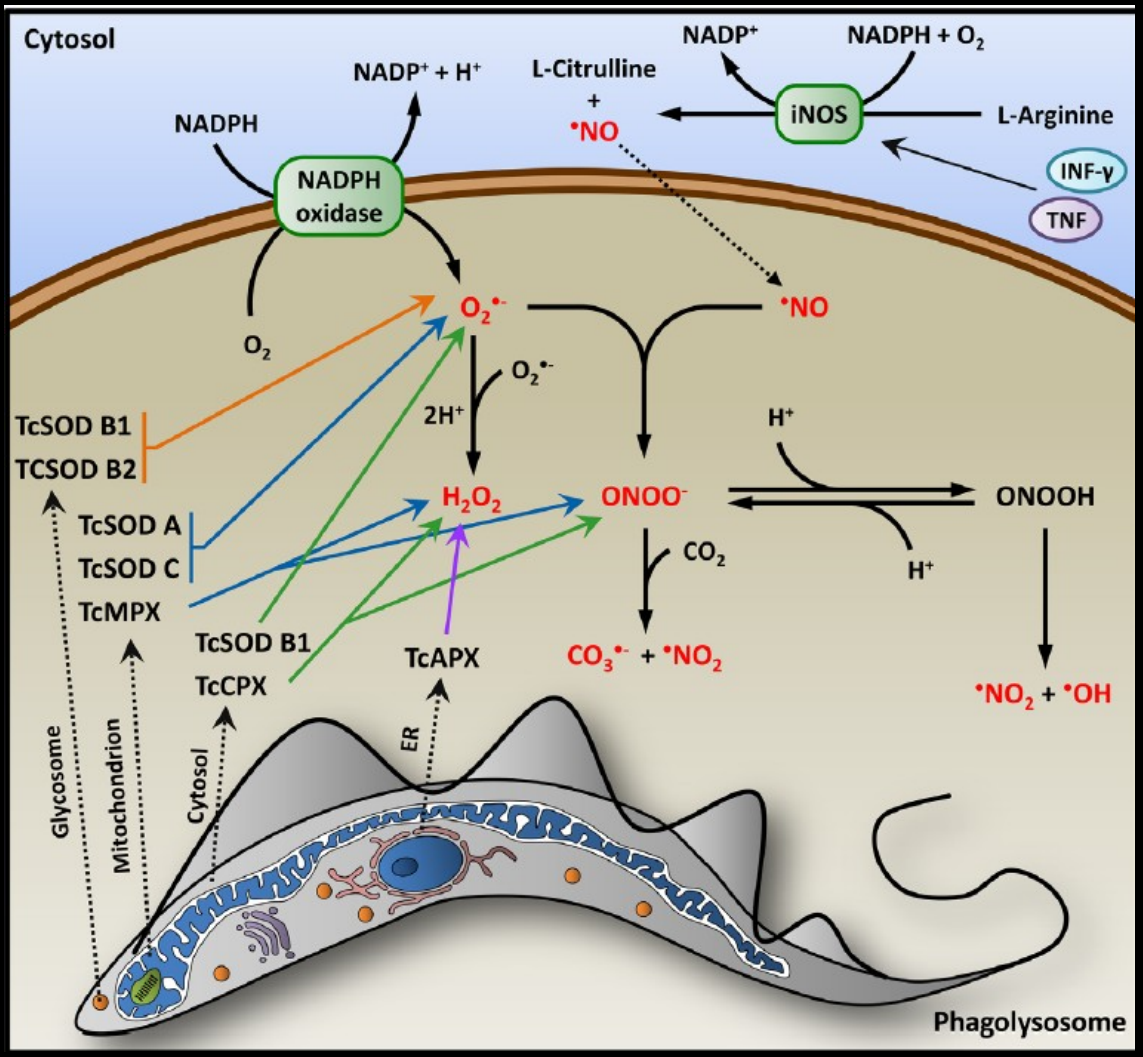


Fernandes and Andrews I 2011. FEMS Microb Rev. 2012.

Processo de invasão– outras moléculas

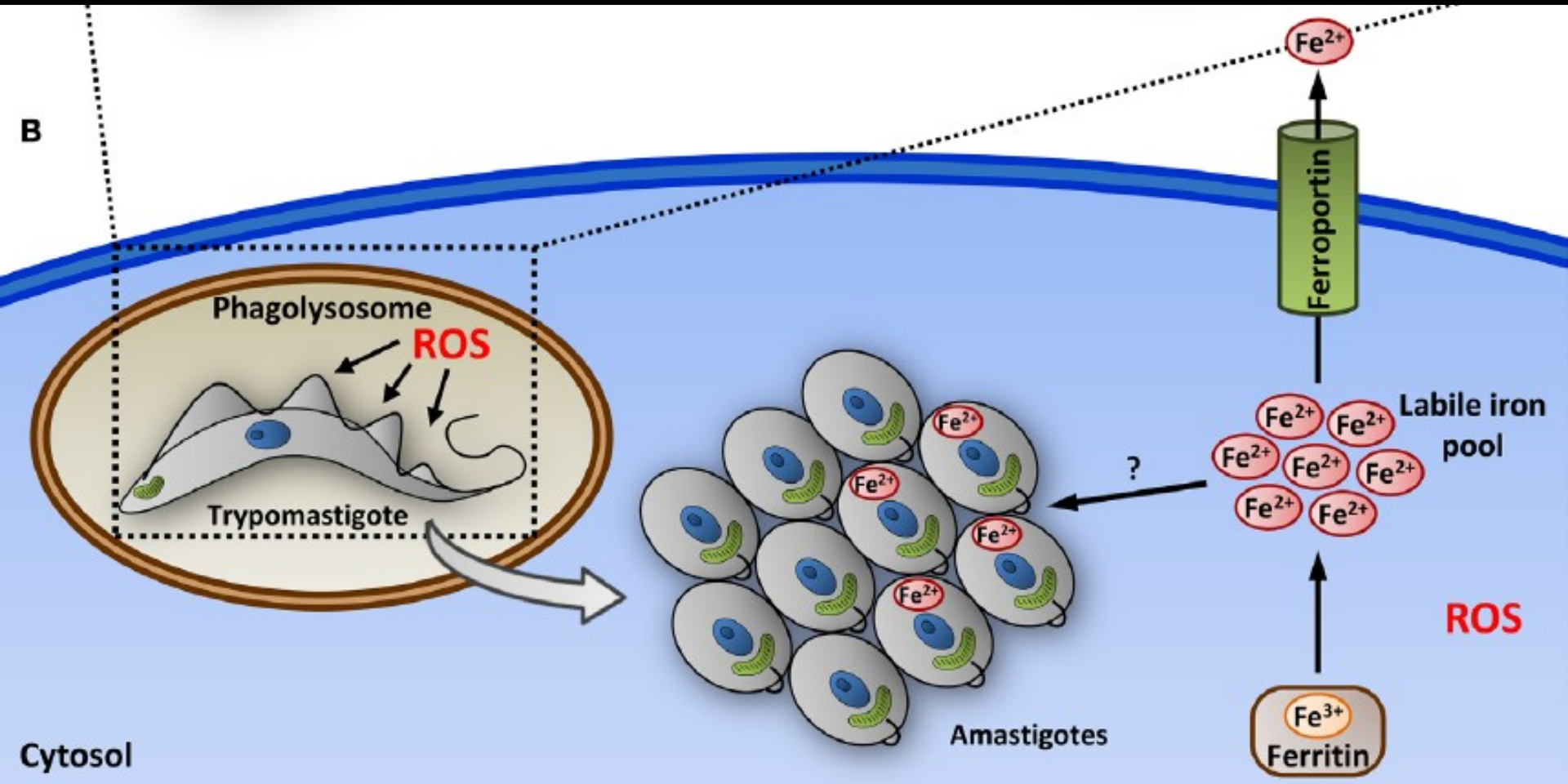
- Mecanismo de sobrevida: Ativação da maquinaria de evasão intracelular



Cardoso et al 2016. FRONTIERS in Immun Rev. 2016.

Processo de invasão intracelular

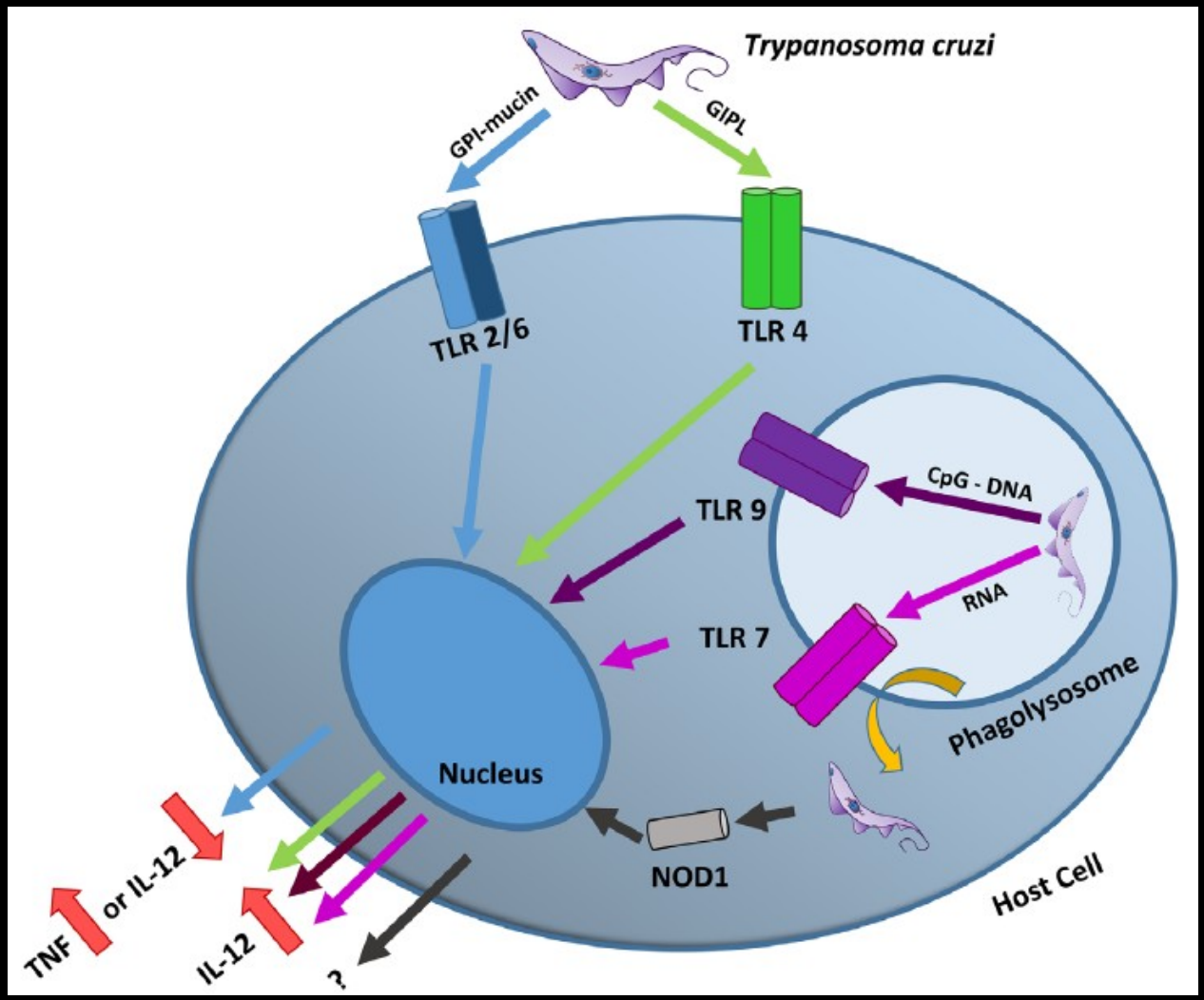
- Mecanismo de escape: Saída dos parasitas do vacúolo parasitóforo ao citoplasma da célula hospedeira



Cardoso et al 2016. FRONTIERS in Immun Rev. 2016.

Processo de invasão– vias de sinalização

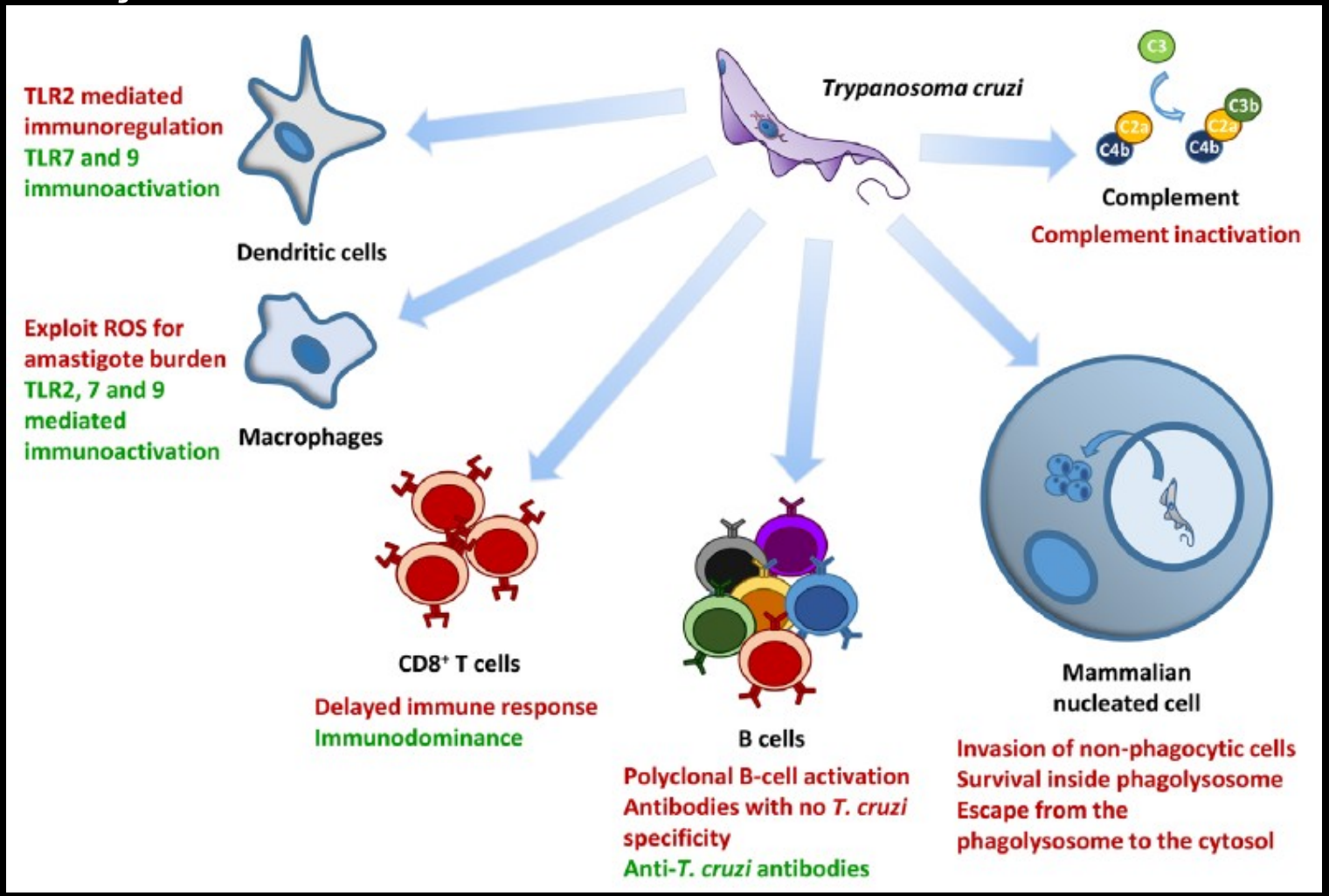
- Mecanismo de evasão: Ativação/inibição de vias de sinalização intracelulares



Cardoso et al 2016. FRONTIERS in Immun Rev. 2016.

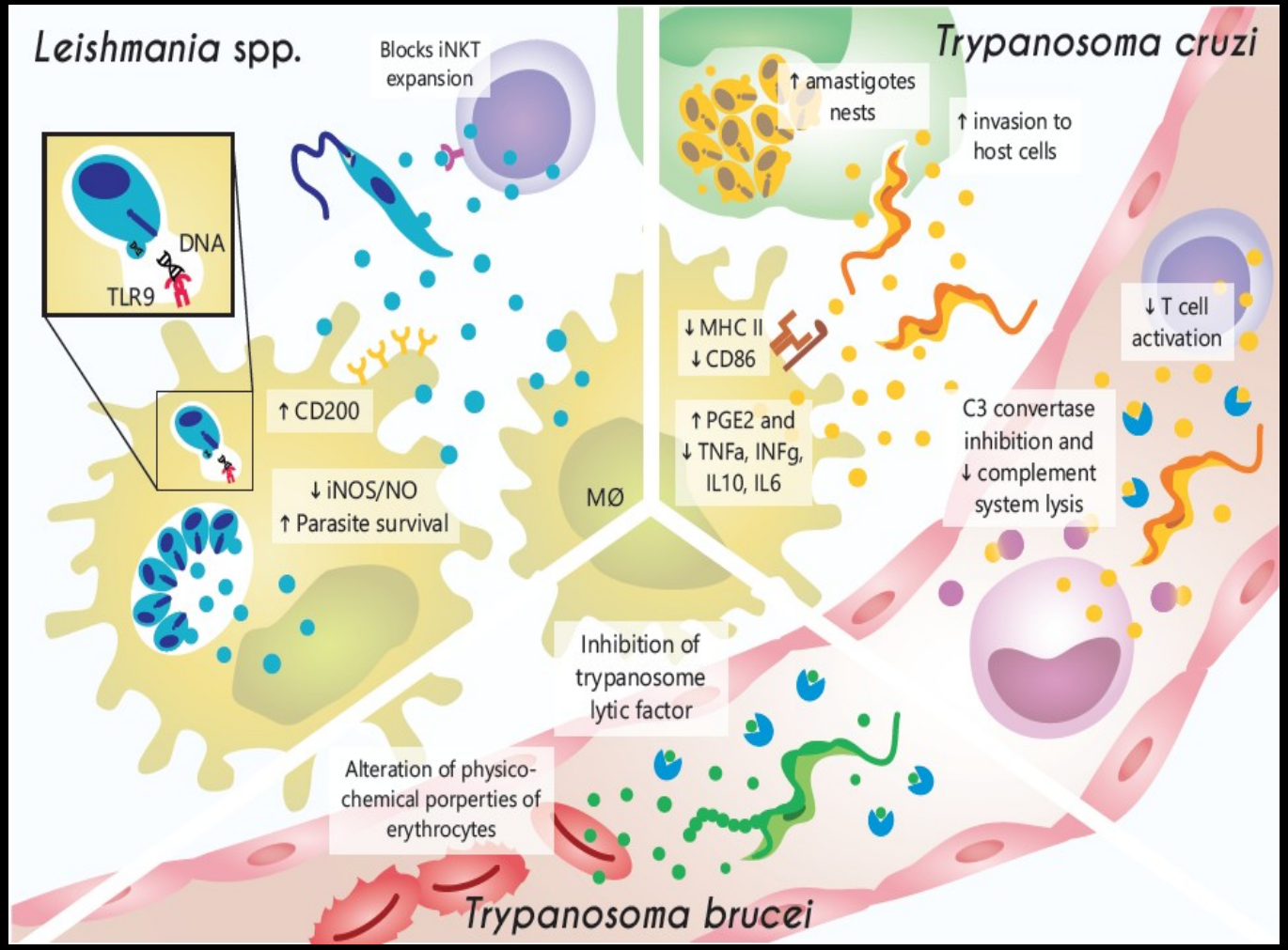
Processo de invasão– inibição da resposta

- Principais mecanismos envolvidos na sobrevida de *T. cruzi* durante infecção.



Cardoso et al 2016. FRONTIERS in Immun Rev. 2016.

Envolvimento de vesículas extracelulares na biologia da interação célula-parasita

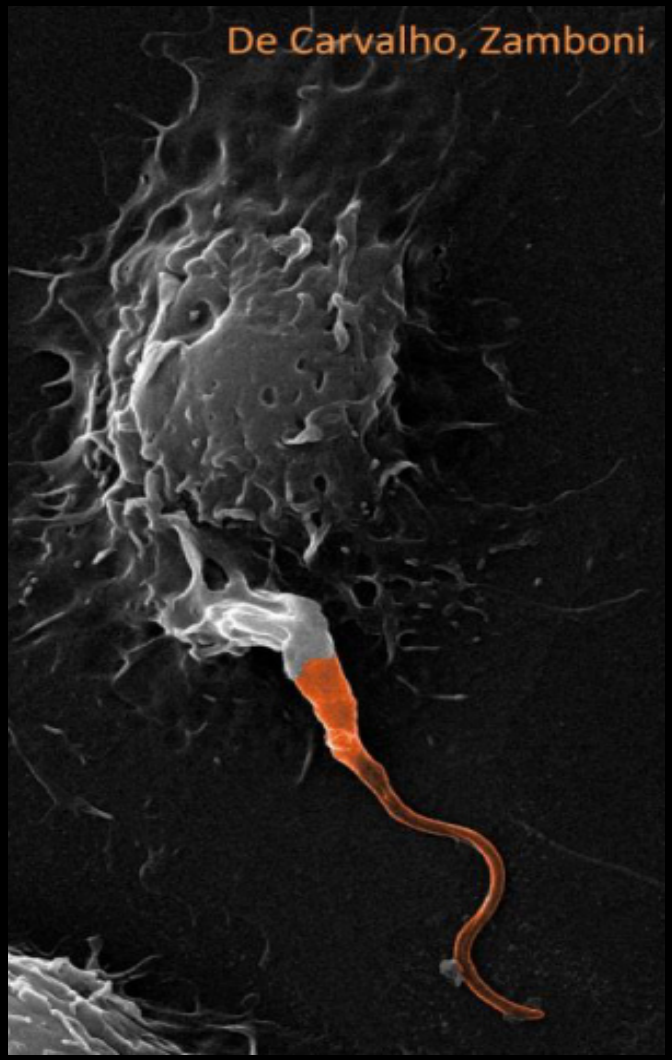


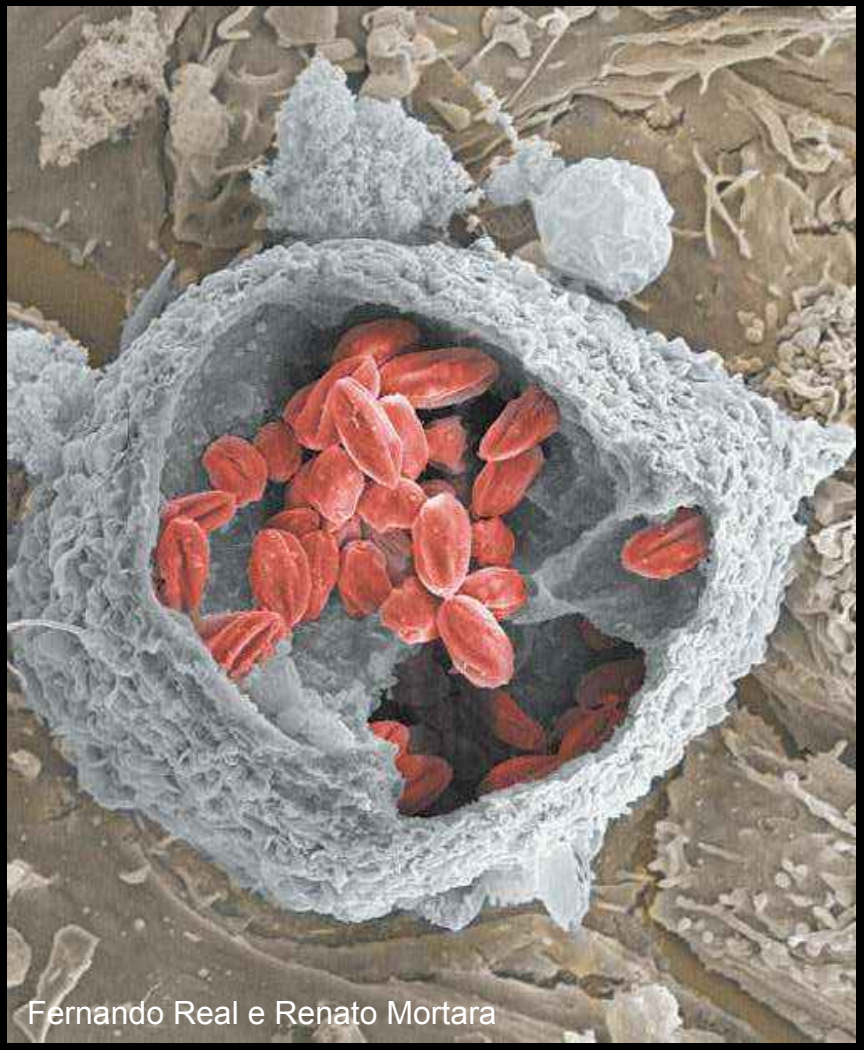
Rossi *et al. Mol Immunol*, 2021

Quais são as principais diferenças entre os tripanosomatídeos intracelulares?

-Invasão
-evasão

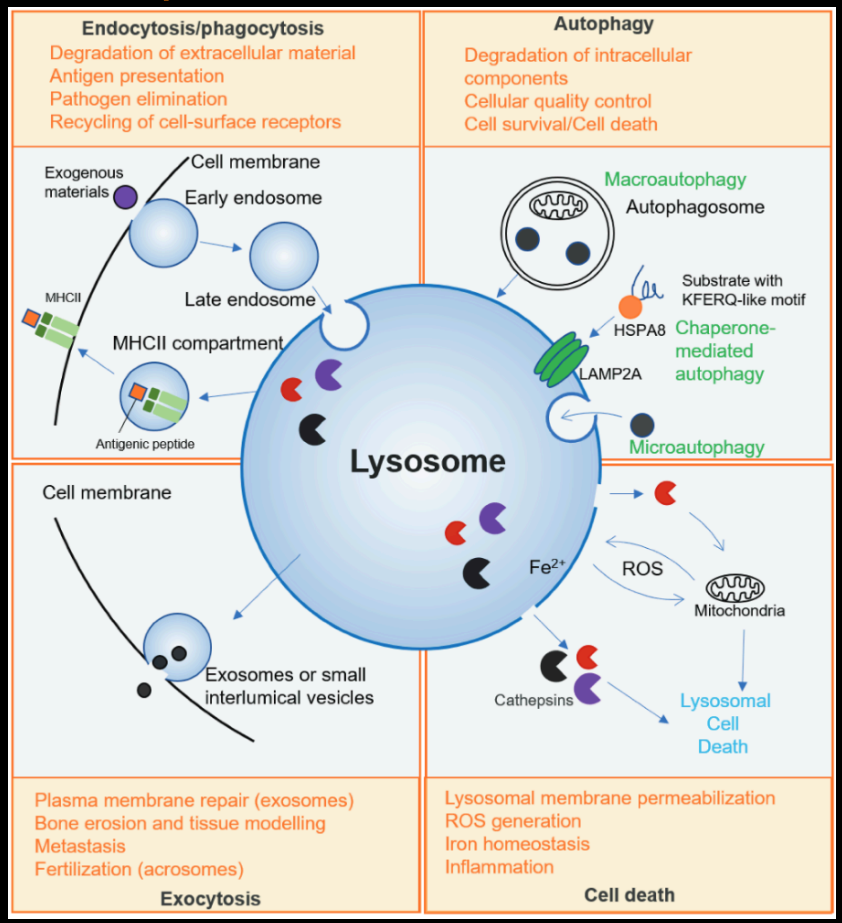
Formas infectivas

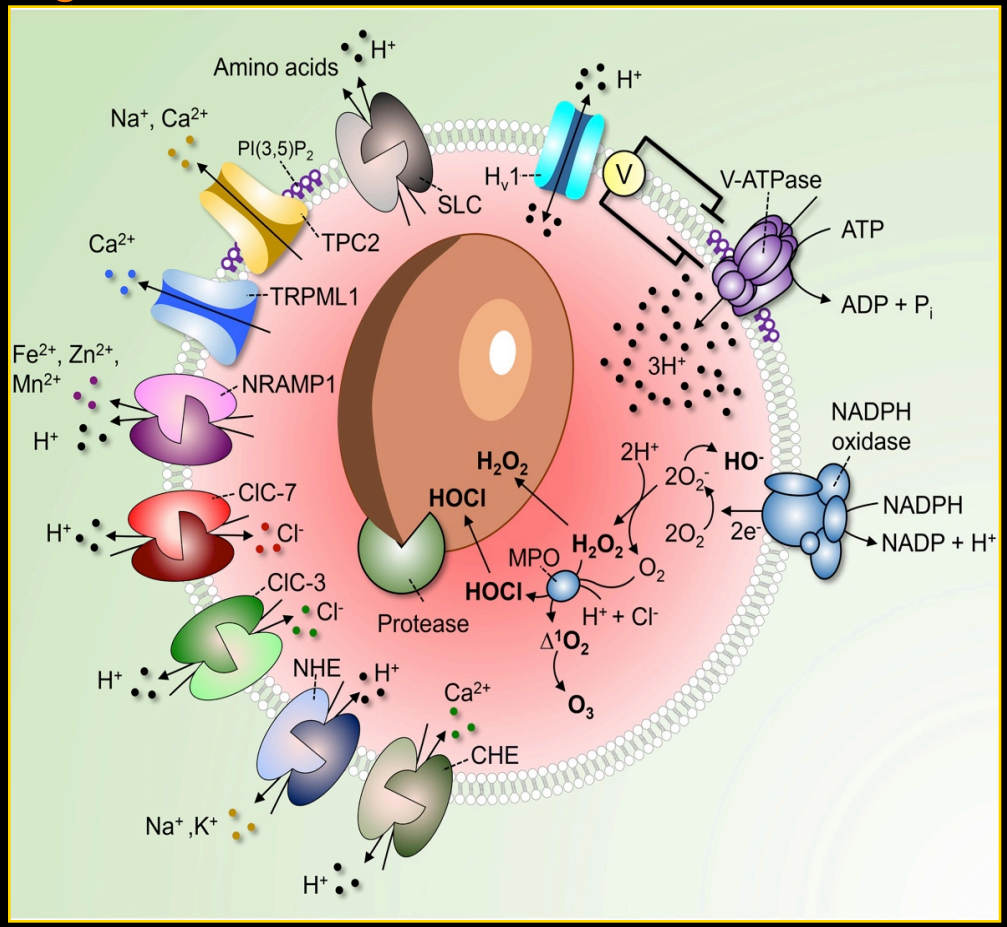




Patogenia– Fatores envolvidos

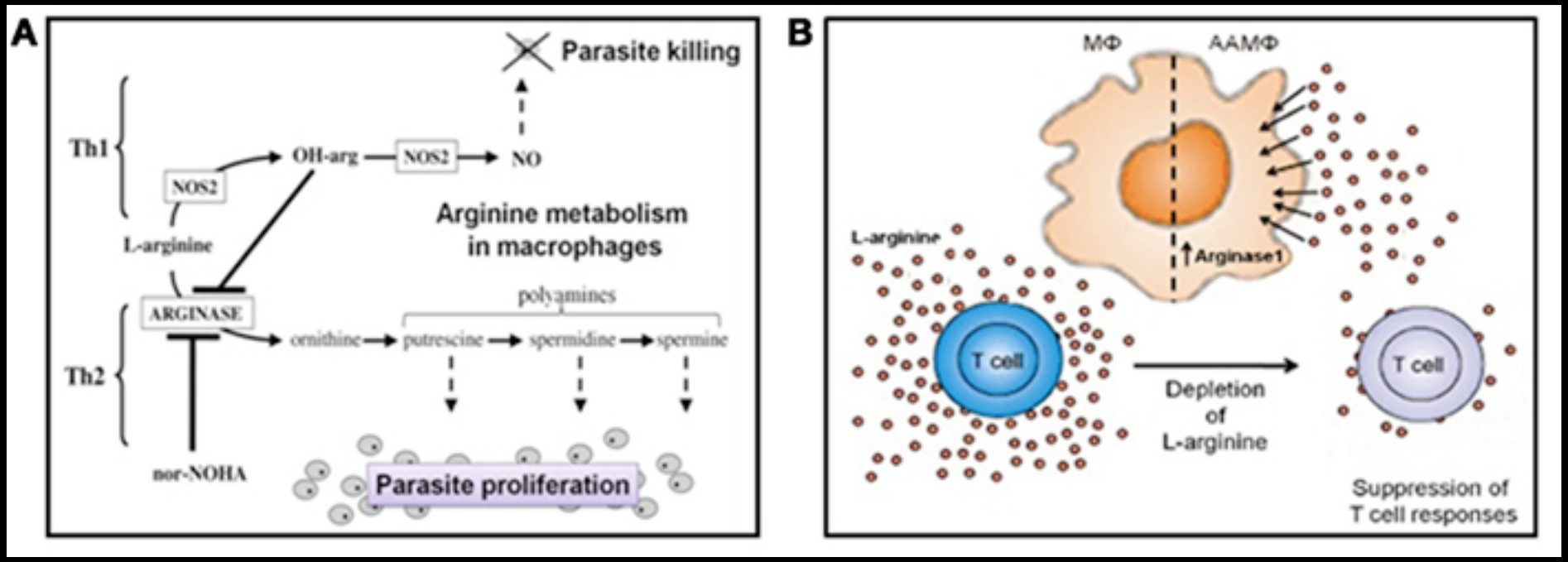
- Resposta celular: Mecanismos biológicos da célula





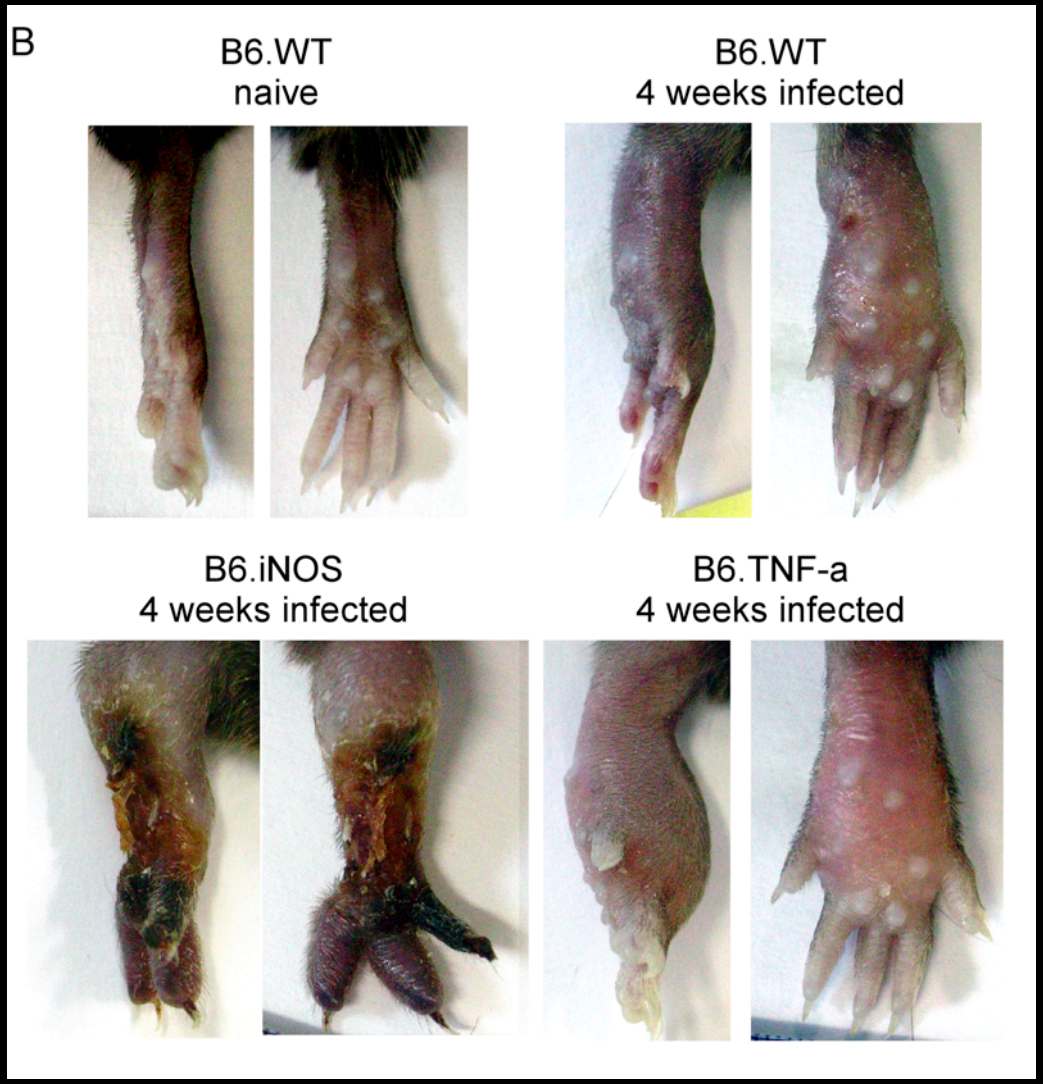
Processo de invasão– *Leishmania*

Oxido nítrico (NO): Importante molécula que elimina patógenos intracelulares.



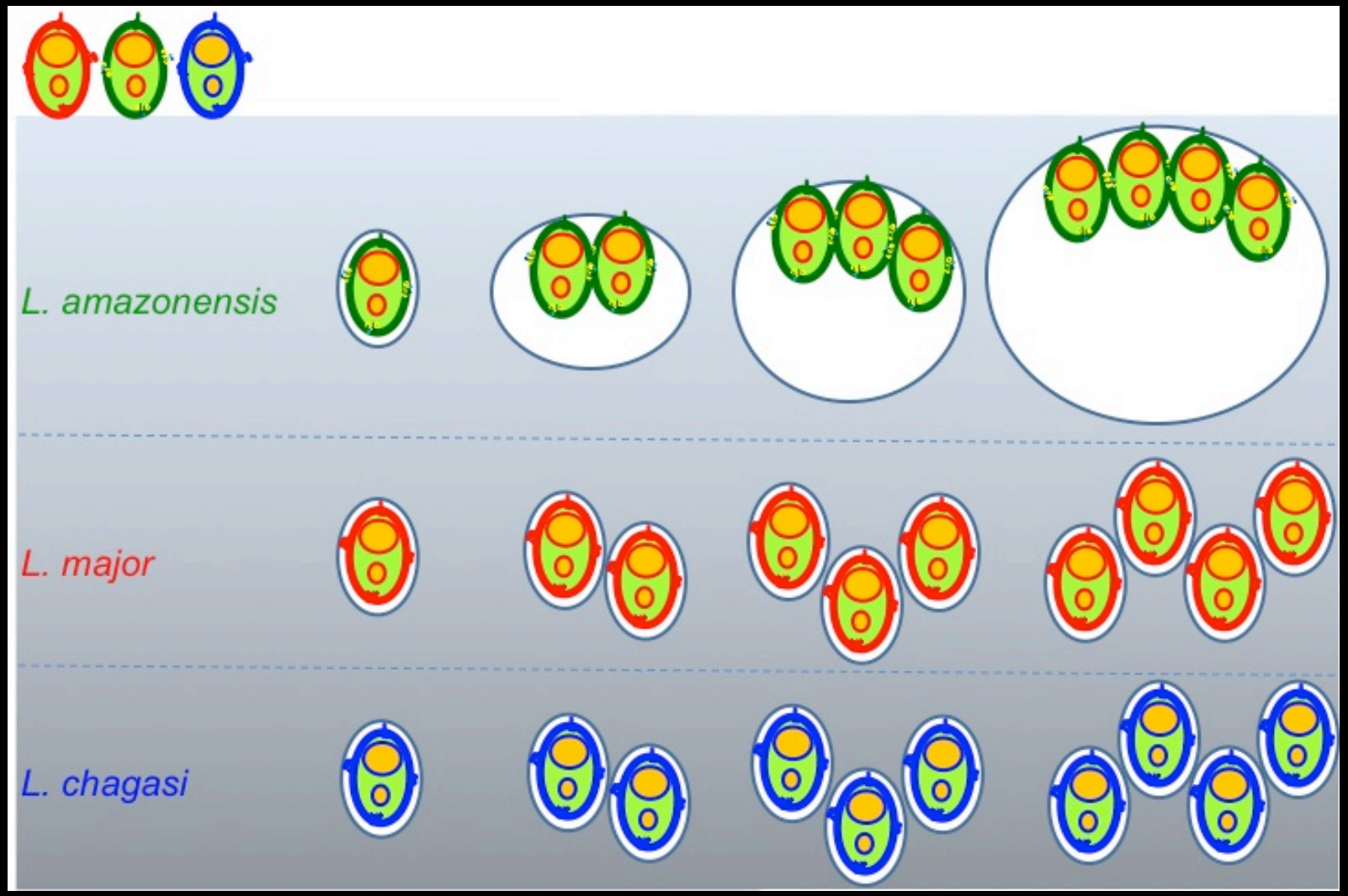
Rogers. Front Microbiol. 2012

Oxido nítrico (NO): Importante molécula que elimina patógenos intracelulares.



De Trez et al., PLOS Pathogens. 2009.

Função do macrófago (resposta imune inata) na infecção por *Leishmania*



Função do macrófago (resposta imune inata) na infecção por *Leishmania*

Espécies associadas à leishmaniose cutânea:

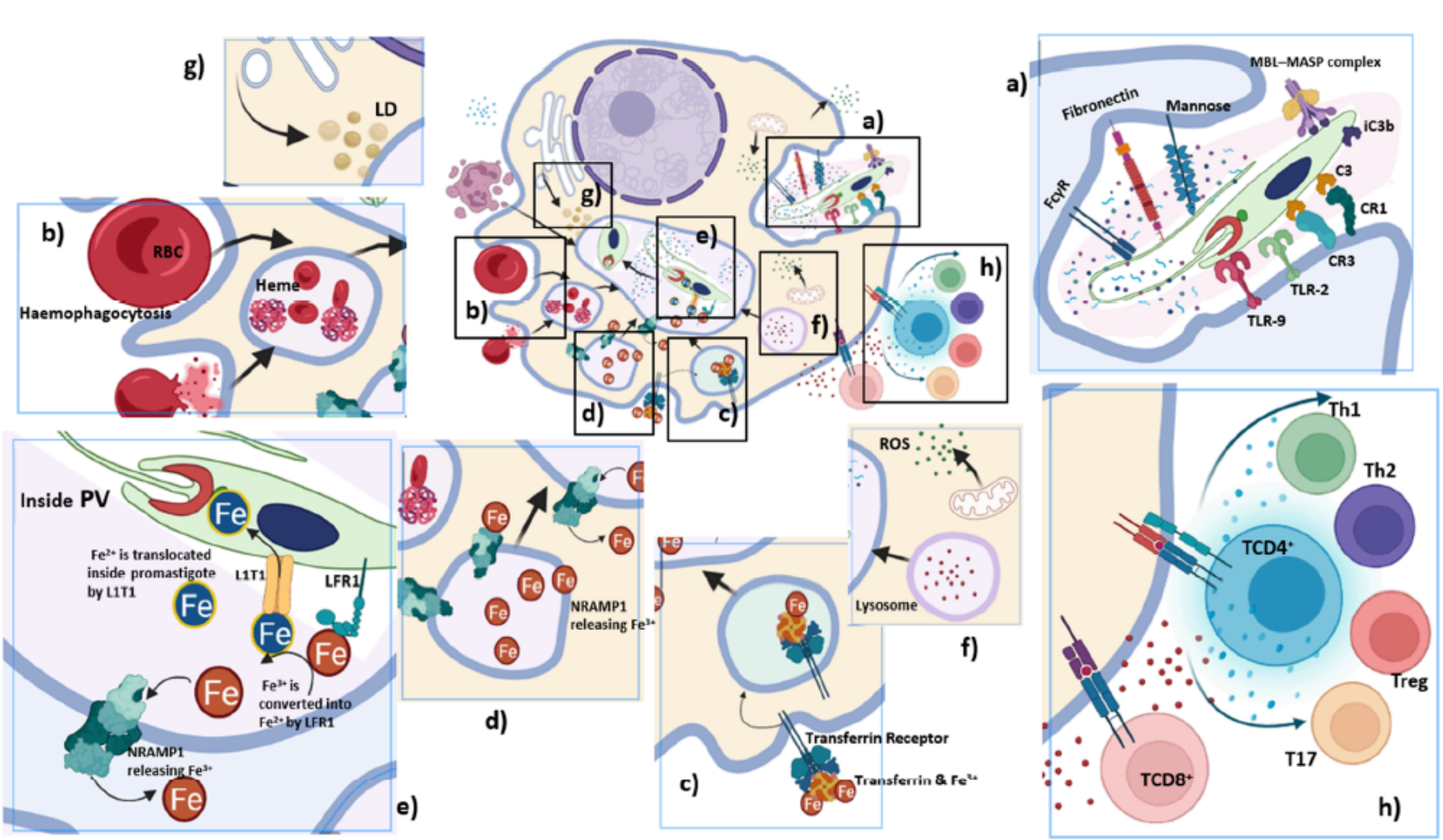
Table 1. Leishmania species and associated human diseases

Disease form	New World species		Old World species	
Cutaneous				
	L. (L.) mexicana complex	*L. (L.) mexicana* *L. (L.) amazonensis* *L. (L.) pifanoi* *L. (L.) venezuelensis*	*L (L.) major* complex	*L (L) major* *L (L) tropica* *L (L) aethiopica*
	L (Viannia) subgenus	*L. (V.) braziliensis* *L. (V.) peruviana* *L. (V.) lansoni* *L. (V.) naiff* *L. (V.) lansoni* *L. (V.) panamensis* *L. (V.) guyanensis*		
Diffuse cutaneous	*L (L.) amazonensis* *L (L.) pifanoi*			*L (L) aethiopica*
Mucocutaneous	*L (V.) braziliensis*			
Visceral	*L (L.) donovani* complex	*L. (L.) chagasi**		*L (L) infantum** *L (L) donovani*

*Generally, *L. infantum* and *L. chagasi* are the causative agents of visceral leishmaniasis; however, cases of cutaneous leishmaniasis have been reported (214, 215).

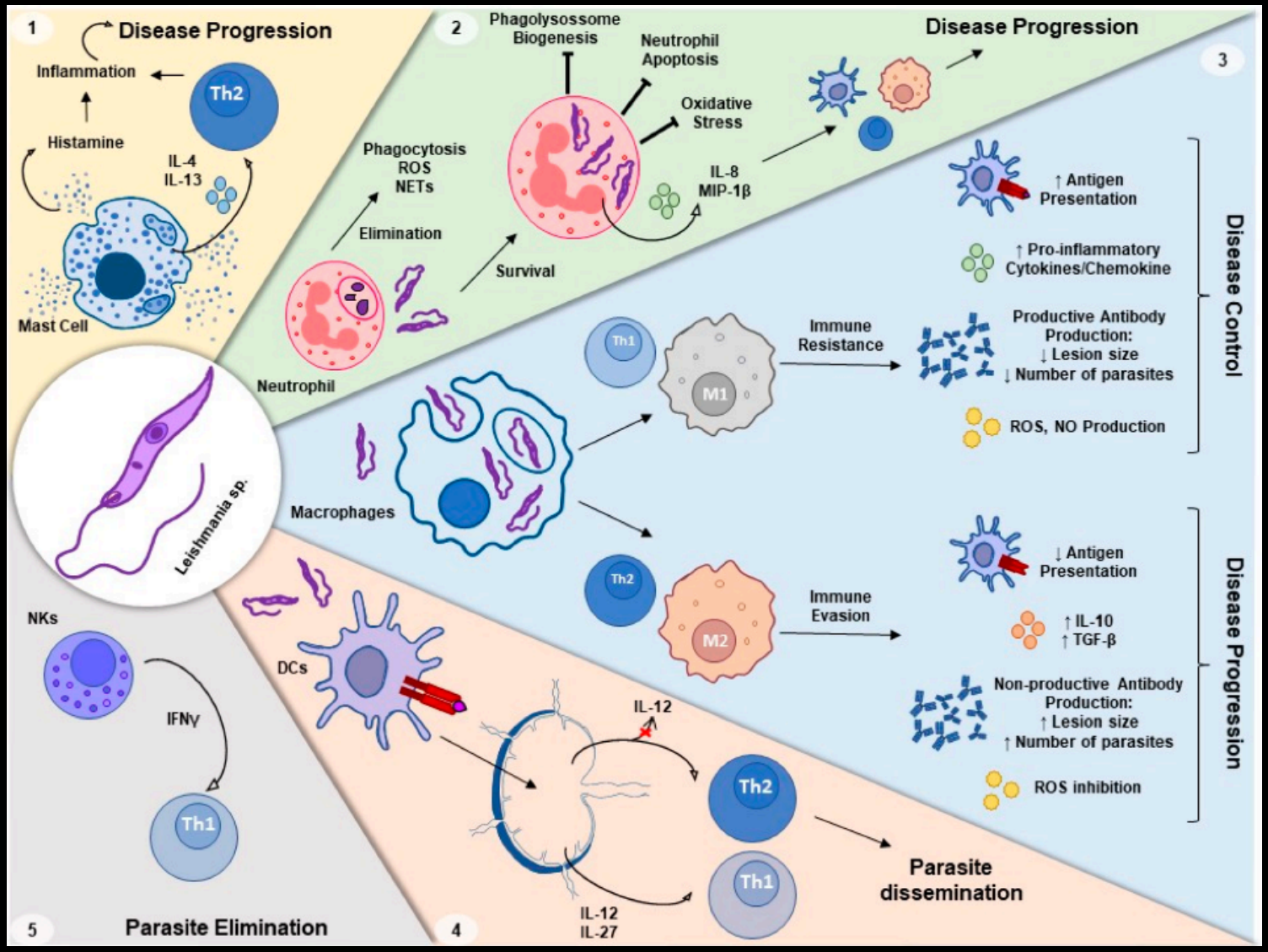
Lipoldová *et al. Nature Reviews Genetics* 7, (April 2006)

Fatores envolvidos na infecção do macrófago por *Leishmania*



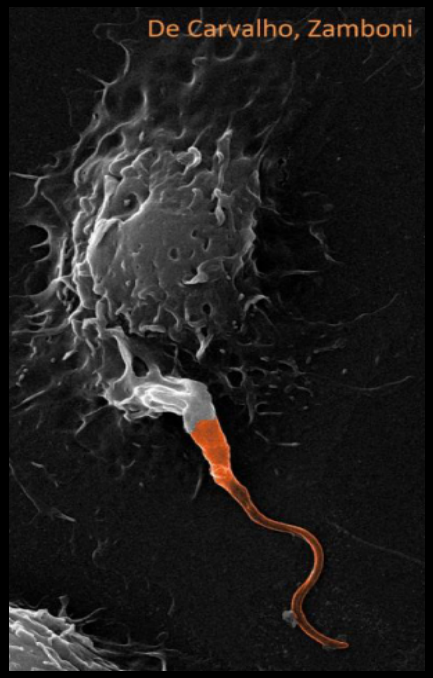
Yasmin *et al.* *Immuno*. 2022

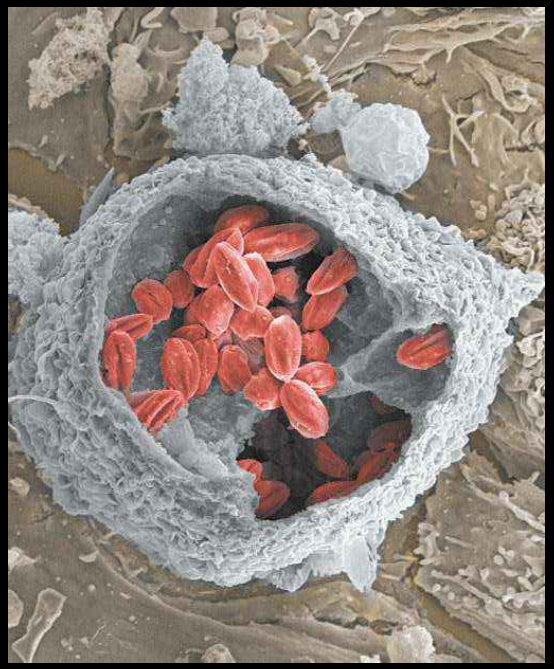
Fatores envolvidos na infecção do macrófago por *Leishmania*

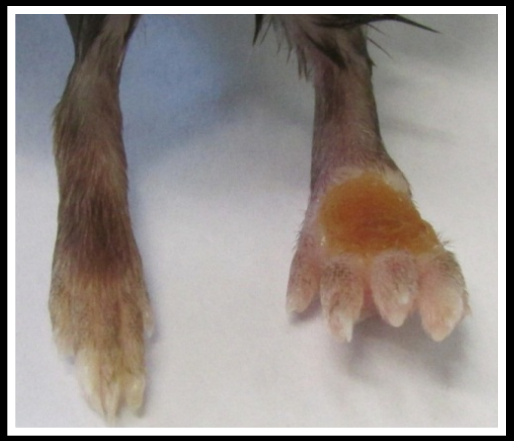


Costa da Silva *et al.* *Trop Med Inf Dis*. 2022

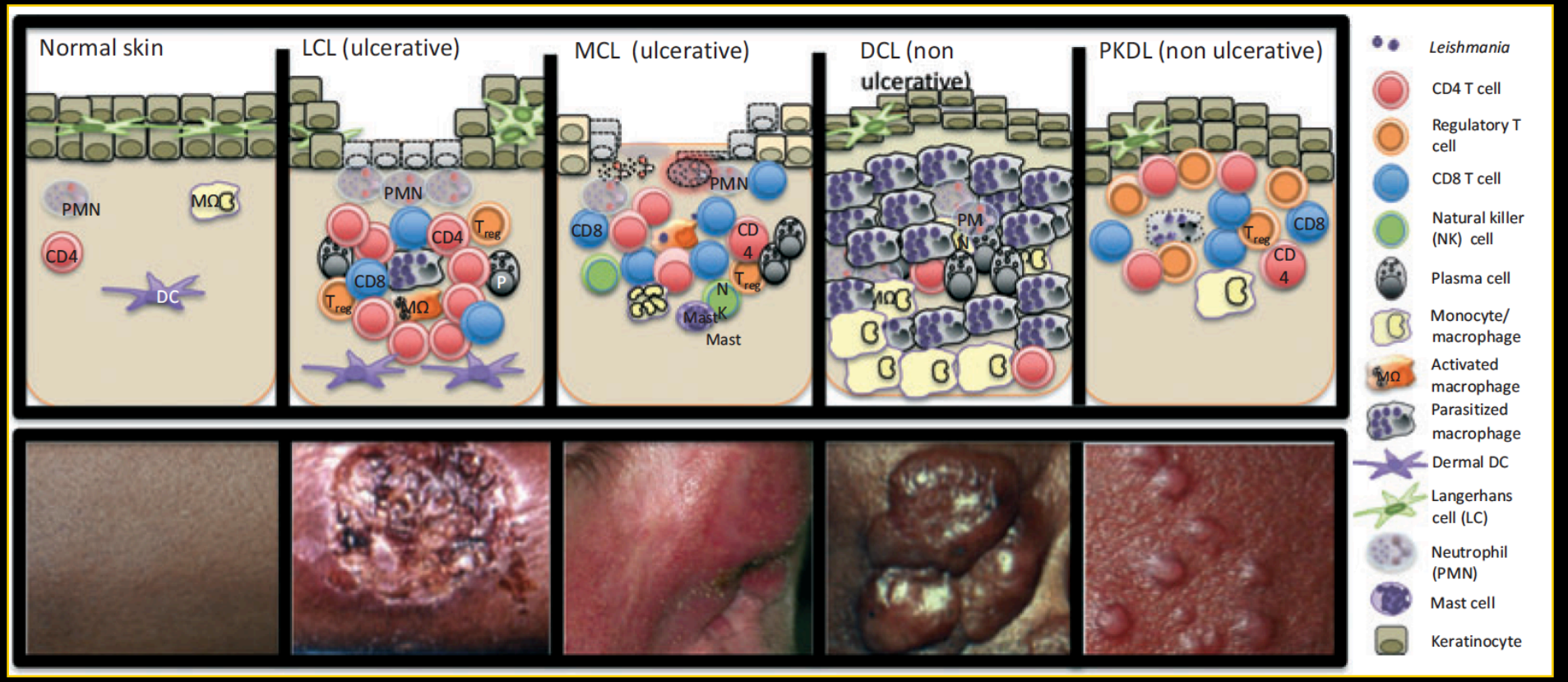
Formas infectivas- específicas funções





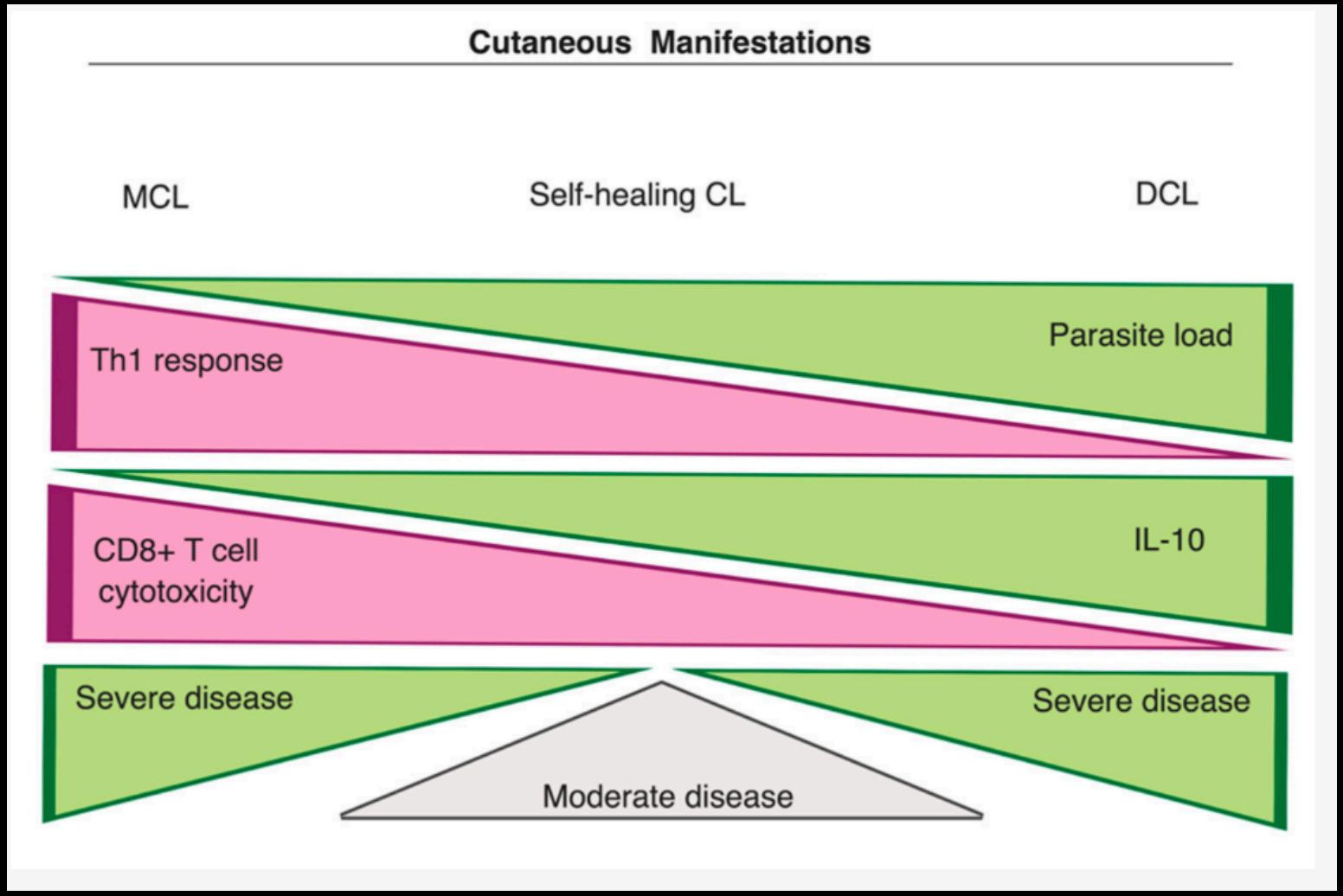


Perfil imunológico– Fatores envolvidos

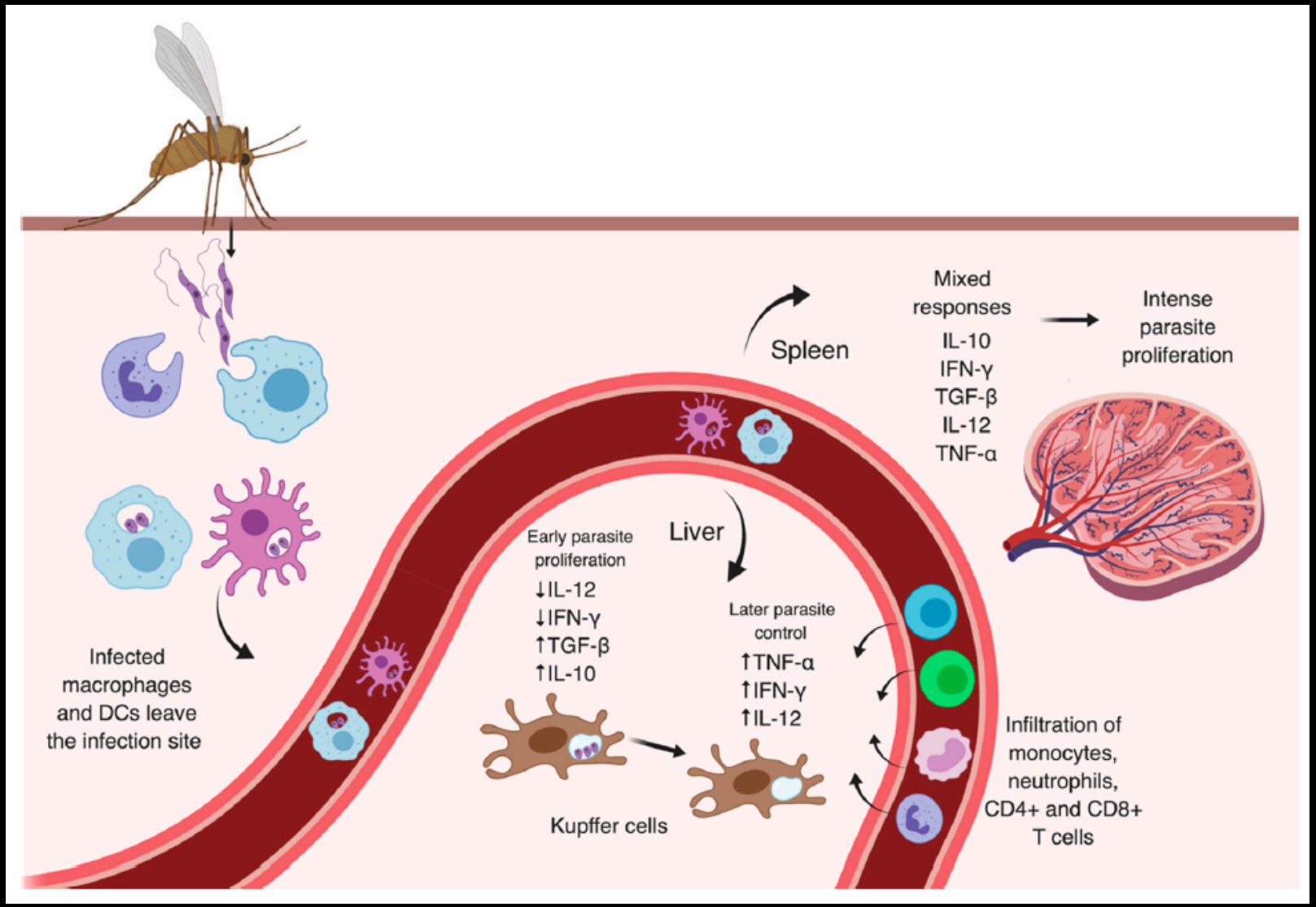


Como explicar a evolução da infecção? Quais são os fatores do parasita e da célula hospedeira que participam no processo

Perfil imunológico– Severidade da doença e moléculas envolvidas

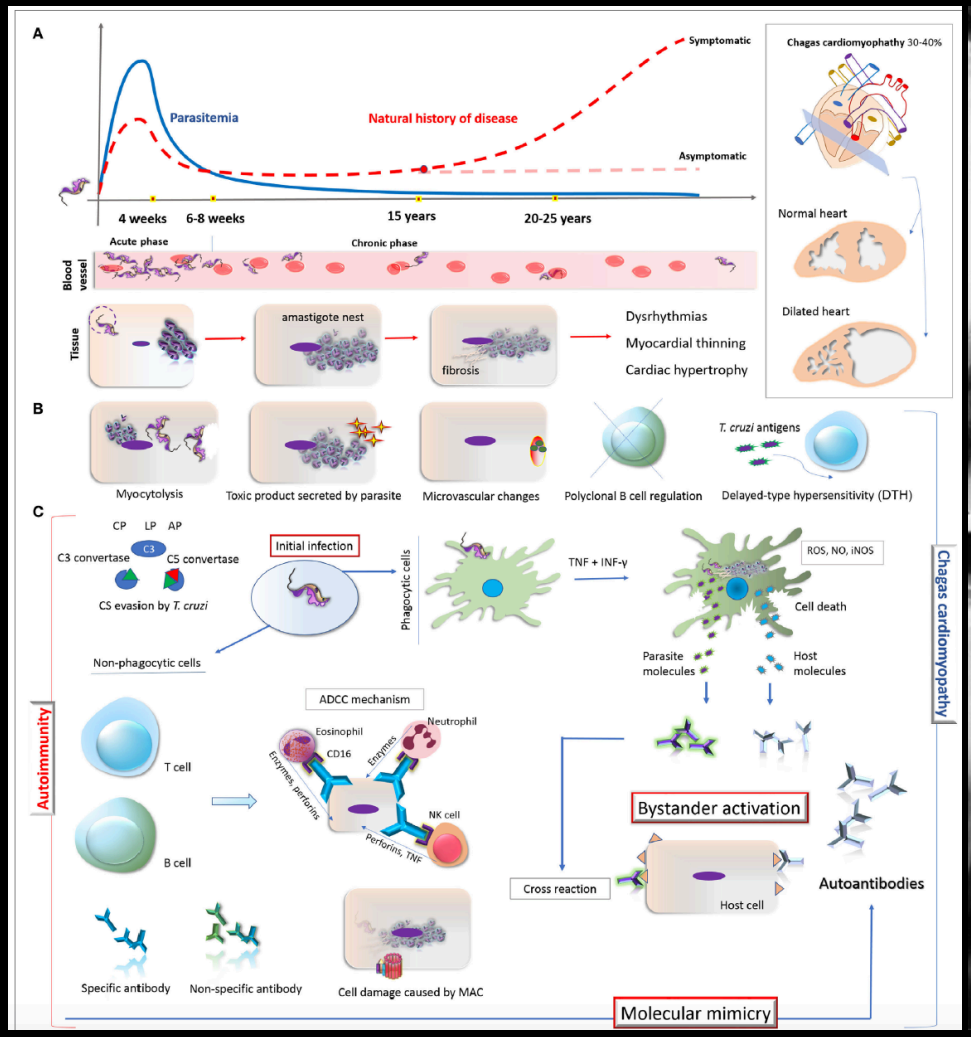


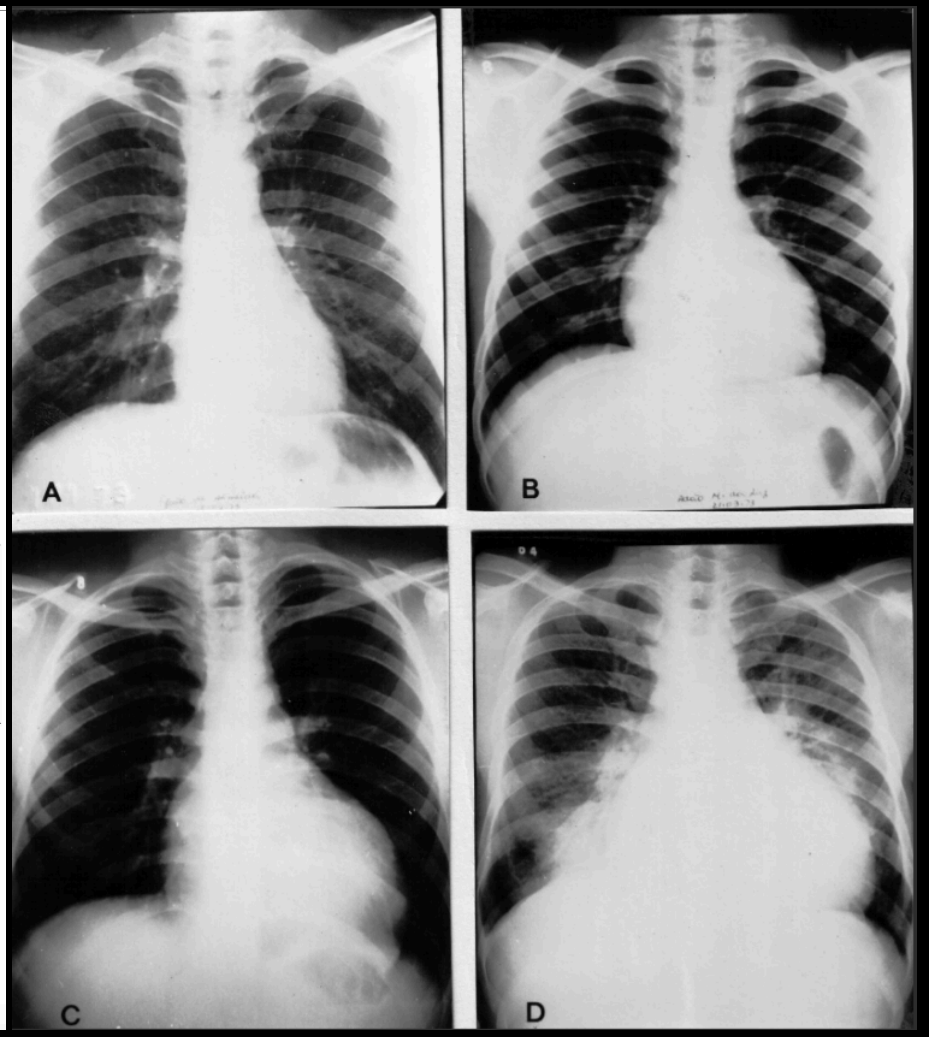
Severidade das doenças de tripanosomatídeos



Dos Santos Meira e Gedamu *et al.* *Immuno*. 2022

Mecanismos envolvidos na severidade da doença

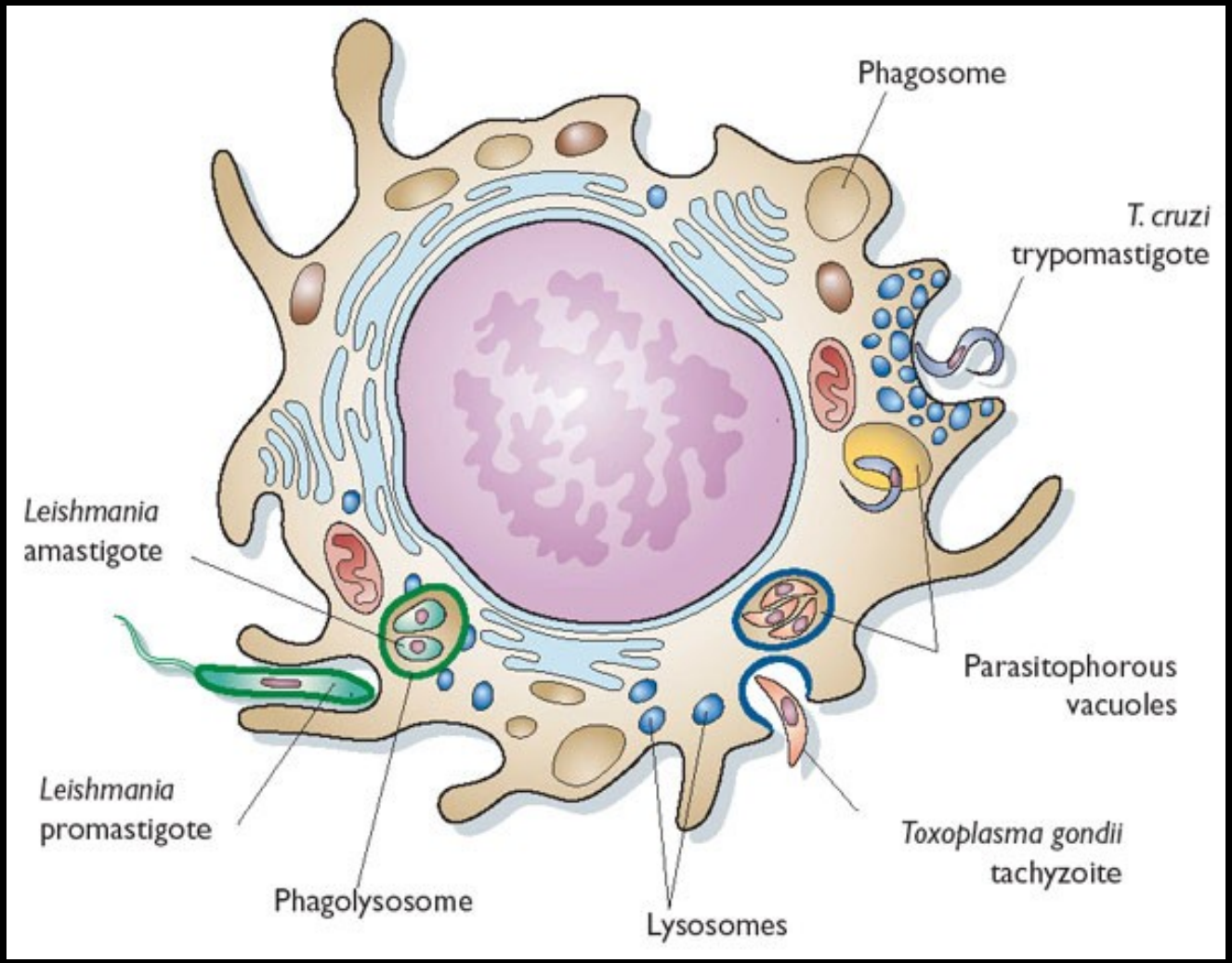




De Bona *et al.* *Immuno*. 2018

Patogenia– Fatores envolvidos

- Evasão do parasita



Patogenia– Fatores envolvidos

JCI insight

RESEARCH ARTICLE

TLR9/MyD88/TRIF signaling activates host immune inhibitory CD200 in *Leishmania* infection

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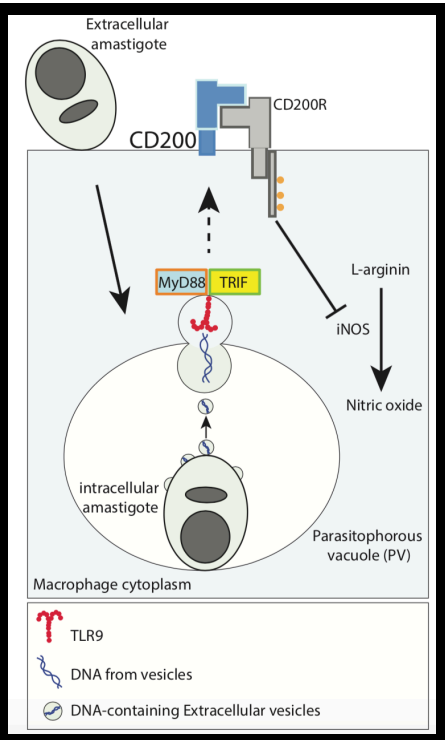

Perguntas e discussão