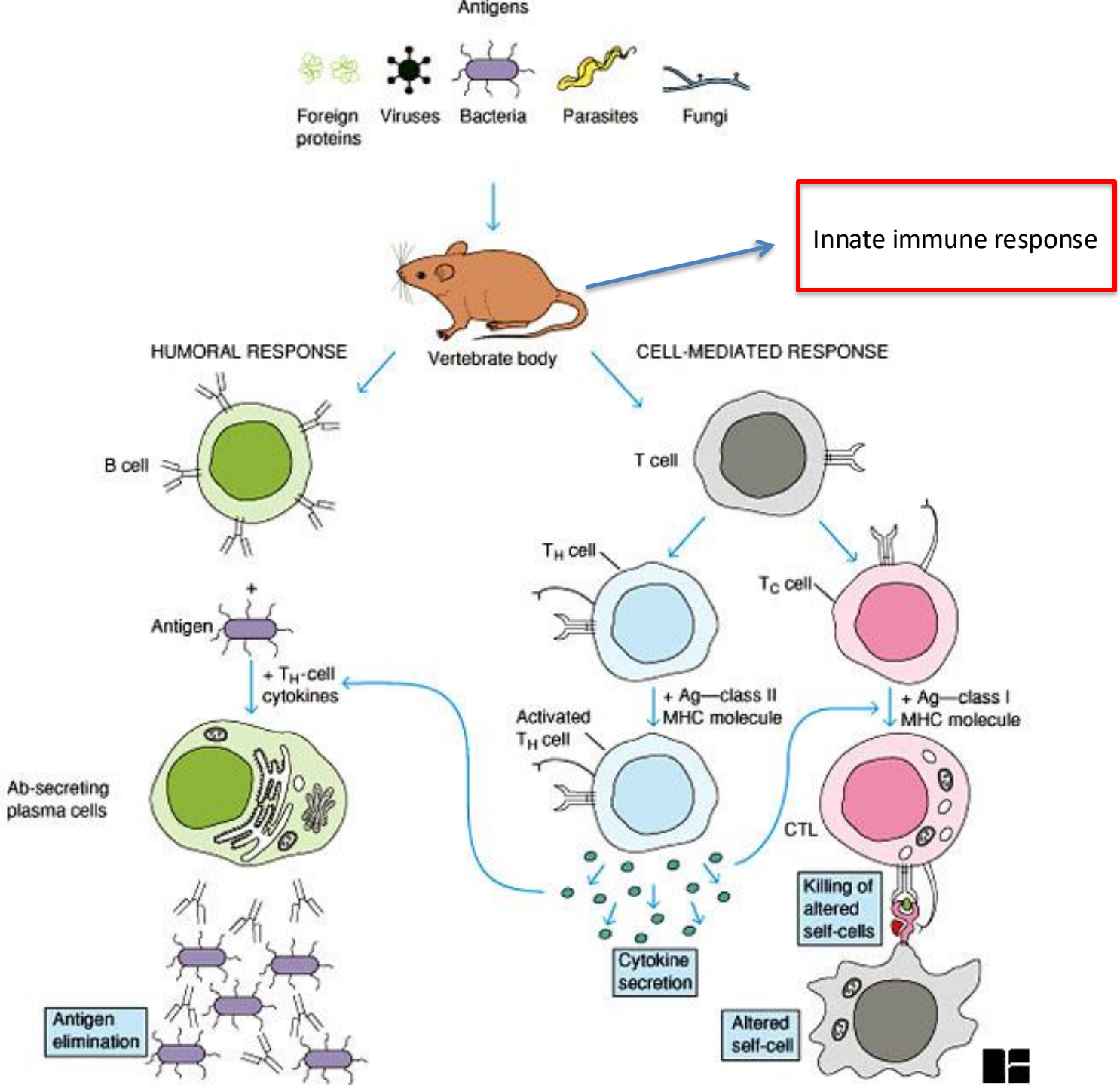
UNIVERSIDADE DE SÃO PAULO
FACULDADE DE CIÊNCIAS FARMACÊUTICAS

RESPOSTA IMUNE E PAREDE CELULAR DOS FUNGOS PATOGÊNICOS

Disciplina BMM 5919: Aspectos Celulares
e Moleculares de Fungos Patogênicos

Prof. Dr. Sandro Rogério de Almeida


Antigens
Foreign proteins
Viruses
Bacteria
Parasites
Fungi
Innate immune response
Vertebrate body
HUMORAL RESPONSE
CELL-MEDIATED RESPONSE
B cell
T cell
T_H cell
T_C cell
Antigen
+ T_H-cell cytokines
+ Ag—class II MHC molecule
+ Ag—class I MHC molecule
Activated T_H cell
Ab-secreting plasma cells
CTL
Killing of altered self-cells
Cytokine secretion
Antigen elimination
Altered self-cell

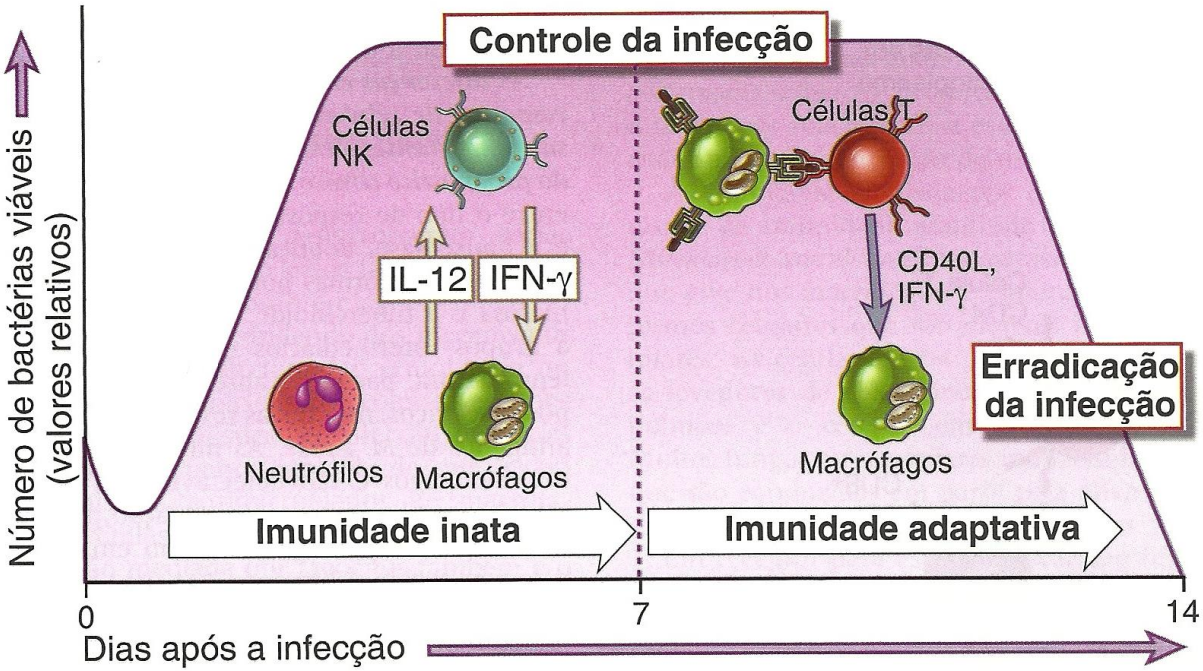
Mecanismos de defesa da imunidade inata

Barreiras

Camadas epiteliais	Evitam entrada do microorganismo
Defensinas	Morte do microorganismo
Linfócitos intraepiteliais	Morte do microorganismo

	PELE	INTESTINO	PULMÕES	OLHOS/NARIZ
MECÂNICA	Células epiteliais unidas pelas junções ocludentes			
	Fluxo longitudinal de ar e fluídos		Movimento do muco	
QUÍMICA	Ácidos graxos	Baixo pH		Enzimas (lisozima)
		pepsina		
	Peptídeos antibacterianos			
MICROBIOLÓGICA	Microbiota normal			

~~Remoção do agente infeccioso~~ → Resposta adaptativa


Controle da infecção
Células NK
IL-12
IFN-γ
Células T
CD40L, IFN-γ
Erradicação da infecção
Neutrófilos
Macrófagos
Macrófagos
Imunidade inata
Imunidade adaptativa
Número de bactérias viáveis (valores relativos)
0
7
14
Dias após a infecção

ESPECIFICIDADE DA INATA X ADAPTATIVA

	INATA	ADAPTATIVA
Receptores	Genoma fixo – não precisa de rearranjo	Rearranjo necessário
Distribuição	Não clonal	Clonal
Reconhecimento	Padrões moleculares conservados (LPS, mananas, glicanas, etc)	Estrutura molecular (proteínas, peptídeos, carboidratos, etc)
Próprio x não Próprio	Perfeito: evolução	Imperfeito: células somáticas
Tempo de ação	Ativação imediata	Ativação tardia
Resposta	Moléculas co-estimuladoras, citocinas (IL-1 β, IL-6) e quimiocinas (IL-8)	Expansão clonal ou anergia, IL-2 e citocinas efetoras (IL-4, IFN-γ)

TEMPO DE RESPOSTA

Imunidade inata (imediata: 0-4 hs)

infecção

↓

Reconhecimento por efetores inespecíficos pré-formados

↓

Remoção do agente infeccioso

Resposta precoce induzida (precoce: 4-96 hs)

infecção

↓

Reconhecimento de padrões moleculares associados aos micro organismos

↓

Inflamação, recrutamento e ativação de células efetoras

↓

Remoção do agente infeccioso

Imunidade adaptativa (tardia: > 96 hs)

infecção

↓

Transporte do antígeno para os órgãos linfóides

↓

Reconhecimento pelas células T e B virgens

↓

Expansão clonal e diferenciação em células efetoras

↓

Remoção do agente infeccioso

Células do sistema imune inato

Célula	Função Principal	Características
Macrófagos	Fagocitose, produção de citocinas, apresentação de antígenos	Derivados de monócitos; residentes nos tecidos
Neutrófilos	Fagocitose e liberação de enzimas antimicrobianas	Primeira célula a chegar na inflamação; vida curta
Células dendríticas	Apresentação de antígenos, ativação de linfócitos T	Ponte entre imunidade inata e adaptativa
Células NK	Destruição de células infectadas ou tumorais	Reconhecem a ausência de MHC I; liberam perforinas e granzimas
Eosinófilos	Combate a parasitas e participação em reações alérgicas	Liberação de grânulos tóxicos; recrutados em infecções helmínticas
Basófilos	Mediação de respostas alérgicas e inflamatórias	Liberação de histamina; circulam no sangue
Mastócitos	Defesa contra parasitas e mediação da alergia	Residem nos tecidos; liberam histamina, heparina e citocinas
Células ILCs	Produção de citocinas, regulação da resposta imune e inflamatória	Não possuem receptores específicos; subdivididas em ILC1, ILC2 e ILC3

Reconhecimento da Imunidade Inata

PAMPs

- produzidos somente por patógenos e não pelo hospedeiro;
- invariáveis;
- Essencial para a sobrevivênvia do patógeno

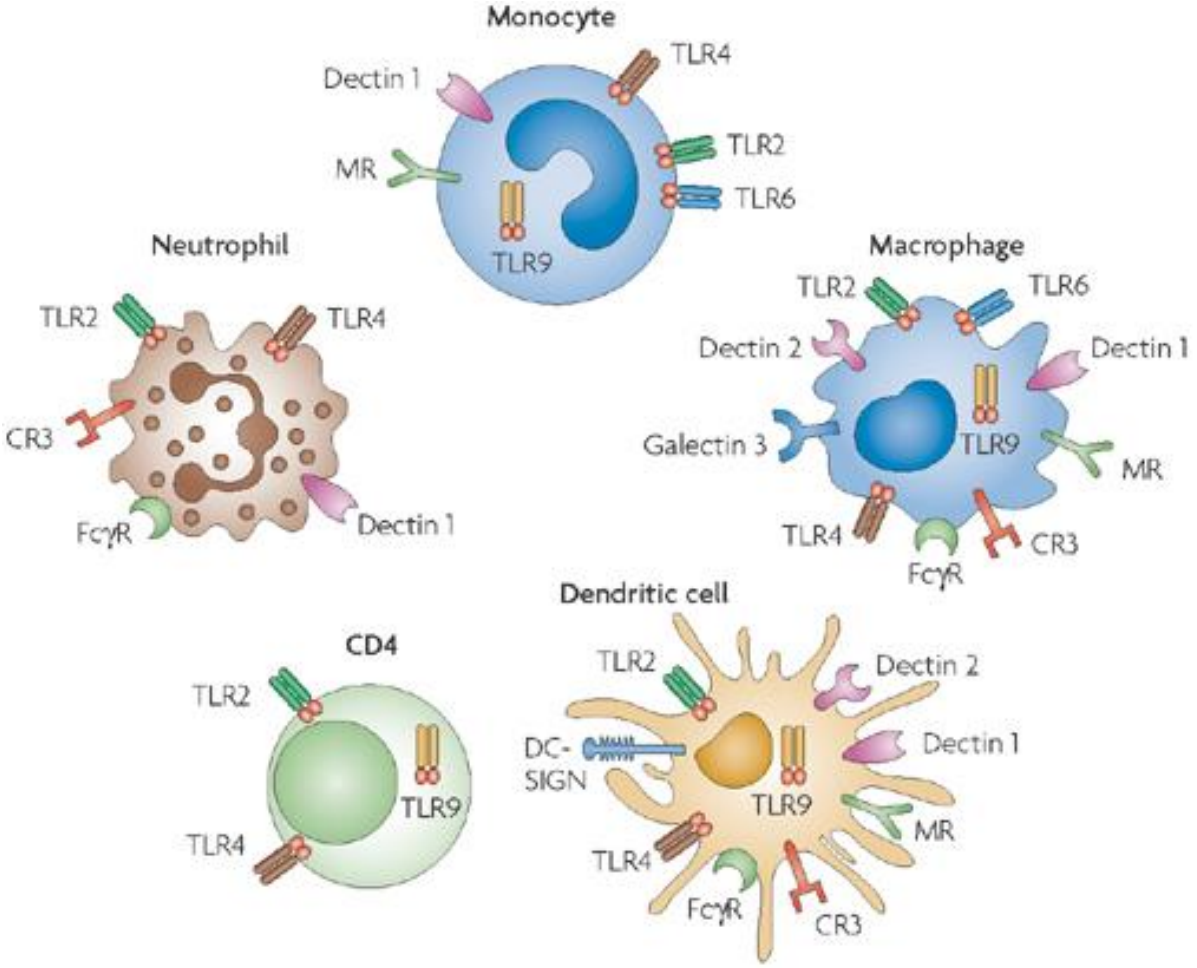
Ex: LPS, ácido lipoteicoico, etc

PRRs

- Sensores da imunidade inata resultando na fagocitose, indução da resposta inflamatória, e ativação da resposta adaptativa

Ex: TLR, Lectinas do tipo C, etc

MO, DC, neutrófilos, células endoteliais e células epiteliais



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PRRs: 4 famílias

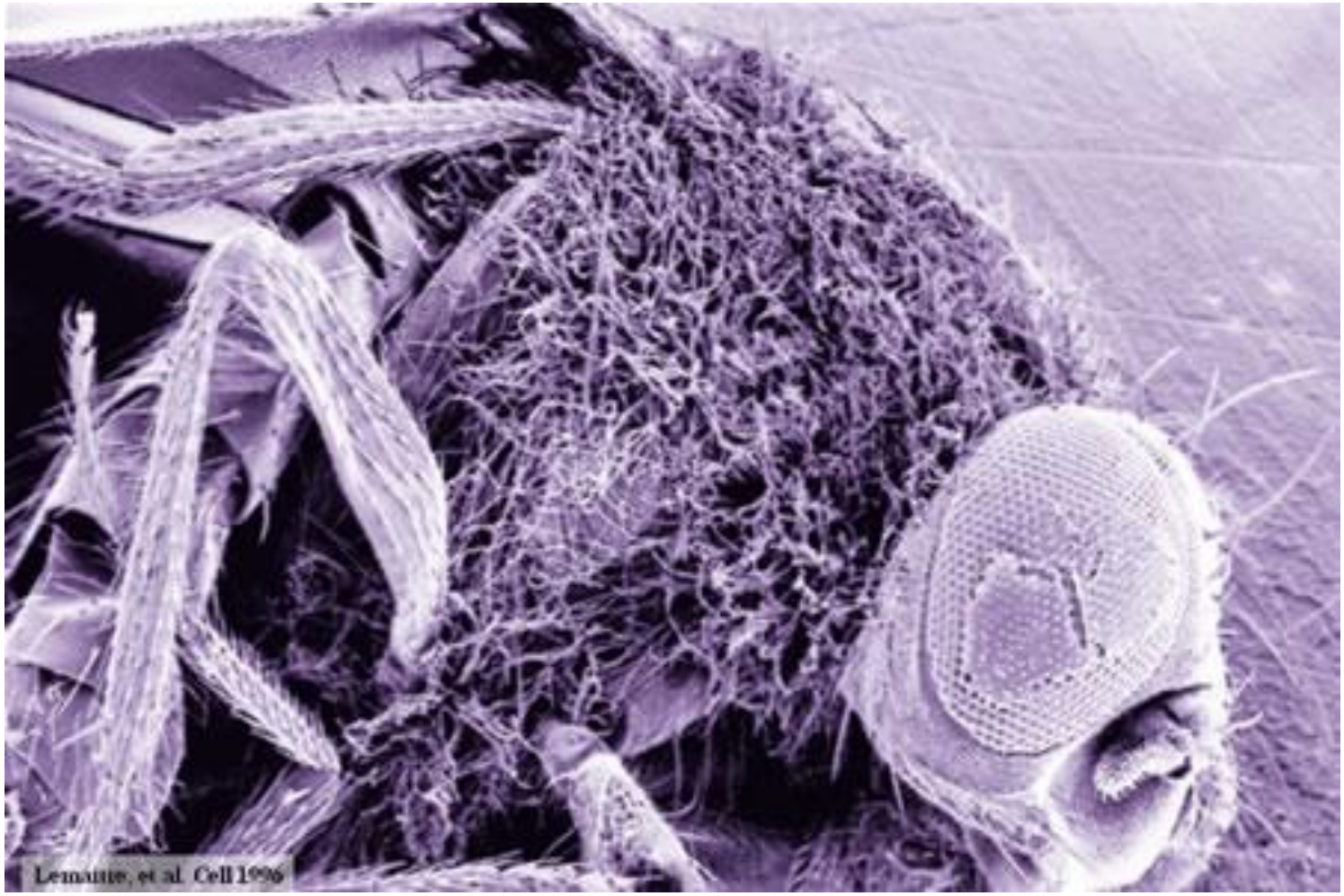
TLRs - Toll-like receptors

CLRs - C-type lectin receptors

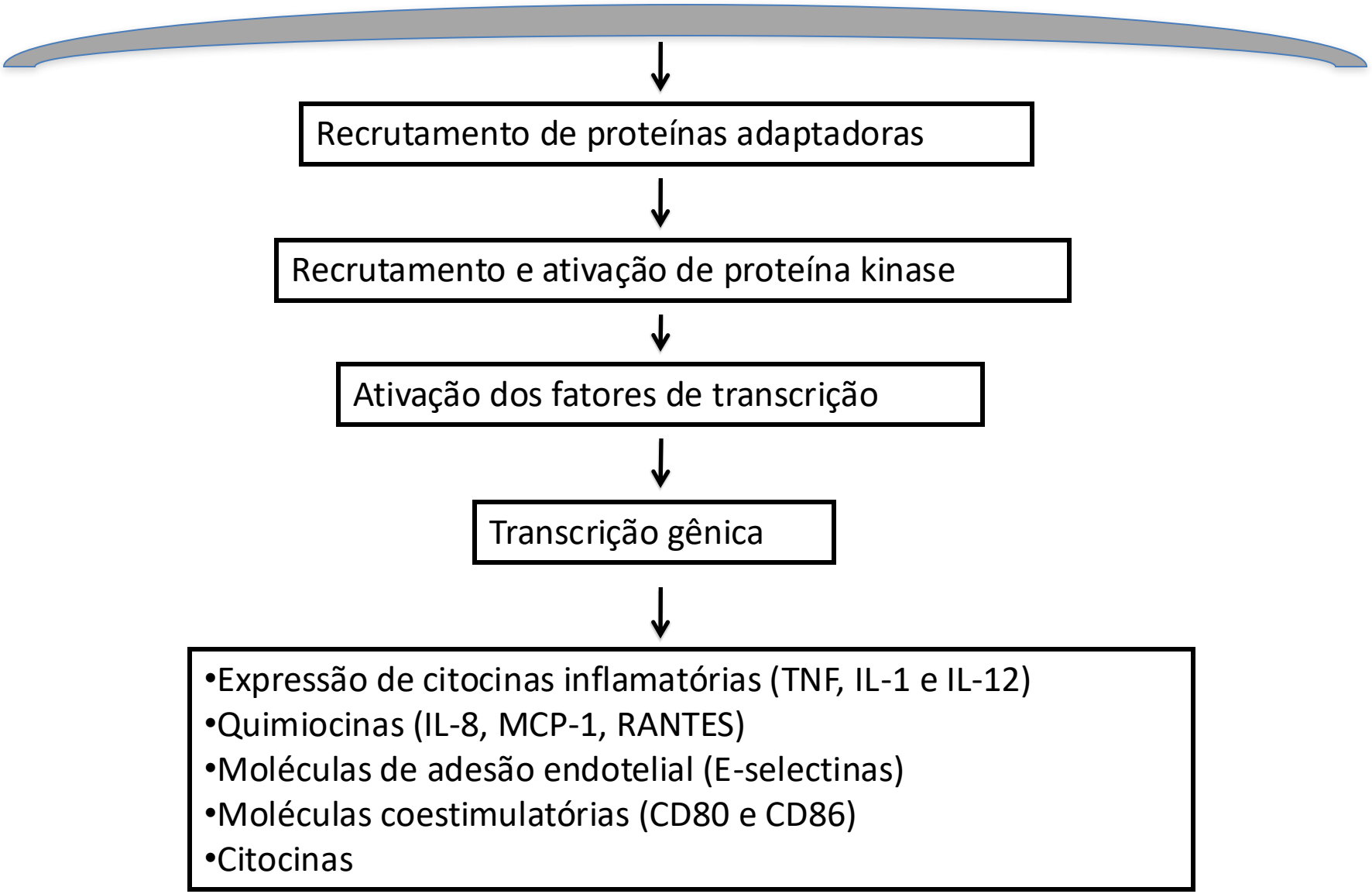
NLRs – NOD (nucleotide binding and oligomerization domain – like receptors)

RIG-1Retinoic acid-inducible gene 1-like receptors

TLRs



PAMPs	Componentes bacterianos	Peptideoglicano, lipoproteínas, etc	mananas, LPS	flagelina
Receptores	TLR1/TLR2	TLR2	TLR4	TLR5



Receptores tipo NOD (NLR) – grupo de proteínas envolvidas no reconhecimento padrão intracelular

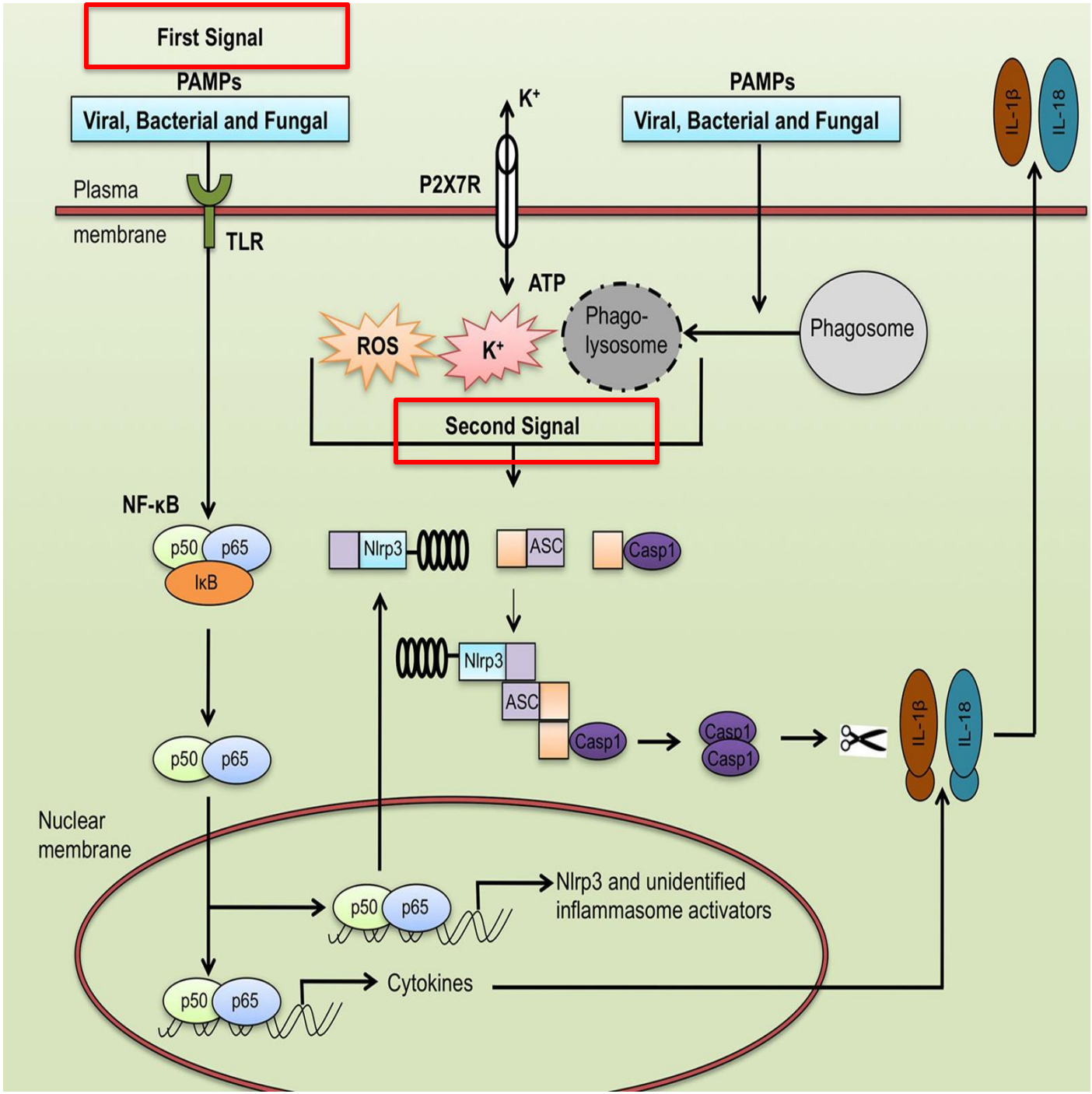
Domínio de ligação a nucleotídeos (NBD)	Região C- terminal rica em leucinas (LRR)	Domínio CARD N-terminal

- reconhecem patógenos intracelulares
- recrutam moléculas efetoras (ex. Pro-caspases e kinases) – processamento de citocinas e ativação de NF-kB
- NODs estão envolvidos na regulação da apoptose e processo inflamatório (caspase 1)

- Os domínios CARD de NOD1 e NOD2 associados com a proteína kinase RIP2 ativam NF-κB

- NOD1 e NOD2 ativam NF-κB em resposta ao LPS, através da ligação com os seus LRRs

Wagner, et al, 2009, Plos One


First Signal
PAMPs
Viral, Bacterial and Fungal
PAMPs
Viral, Bacterial and Fungal
K+
IL-1β
IL-18
Plasma
membrane
TLR
P2X7R
ATP
ROS
K+
Phago-
lysosome
Phagosome
Second Signal
NF-κB
p50
p65
IκB
Nlrp3
ASC
Casp1
Nlrp3
ASC
Casp1
Casp1
Casp1
IL-1β
IL-18
p50
p65
Nuclear
membrane
p50
p65
Nlrp3 and unidentified
inflammasome activators
p50
p65
Cytokines

CLRs- Lectinas do tipo C

Dectin-1

can be detected remotely from the air or from space. We acquired high-spatial-resolution (1 m × 1 m), multispectral images from the air of two reefs in the lagoon of Rangiroa Atoll, French Polynesia, by using a compact spectrographic imager. We carried out this imaging in November 1998 because coral populations had suffered significant mortality after the extreme El Niño/Southern Oscillation that occurred in the austral summer of 1997–98 (ref. 11). At the same

plots of 25 m² each would need to be surveyed by remote sensing, compared with 20 equivalent-sized plots by video camera, to achieve the same level of statistical resolution on the reefs surveyed (that is, similar sample sizes for field and remote methods). However, spectographic images can be acquired over areas that are many times larger than those that can be surveyed underwater.

We anticipate that the application of multispectral remote sensing will signif-

Table 1 Estimates of substrate cover for live and dead reefs

	Cover (%)		Mean disparity	Maximum disparity	Minimal detectable disparity of means (%)
	Field survey	Imagery	(%)	(%)	
Live Porites	11.5 (2.7)	8.8 (2.9)	−2.7	−9	5.6
Recently dead Porites	7.8 (1.6)	6.8 (3.1)	−1.0	18.9	10.6
Dead Pocillopora	32.5 (8.3)	37.2 (12.6)	4.7	28.9	17.3
Red coralline algae	21.9 (2.4)	15.2 (4.8)	6.6	−25.7	14.3
Sand	18.9 (6.0)	26.8 (9.1)	7.9	27.2	12.1
Halimeda	3.9 (1.6)	5.1 (2.1)	1.2	−9.7	8.3

Field and remote estimates of substrate cover are shown for comparison (standard errors shown in parentheses). Results of pairwise *t*-test comparisons for each habitat were non significant ($P < 0.05$). Minimal detectable difference represents the smallest disparity in mean cover between field and image estimates that would result in a significant *t*-test with 90% power. These values provide a worst-case scenario for the accuracy of remote sensing to predict mean habitat cover; actual disparities were considerably lower. Compact airborne spectrographic imager (CASI) data (10 bands) were corrected for depth variation (1–7 m) using image-derived attenuation coefficients. Substrata were predicted from unsupervised classification of spectral data and were categorized using independent field data. Each plot was identified on CASI images by triangulation to white plastic markers (4 m²) and mapped *in situ* with a resolution of 0.01 m².

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Immune recognition

A new receptor for β-glucans

The carbohydrate polymers known as β-1,3-glucans present in yeast affect the immune system — stimulating antitumour and antimicrobial activity, for example — by binding to receptors on macrophages and other white blood cells and activating them. Although β-glucans are known to bind to receptors, such as complement receptor 3 (ref. 1), there is evidence that another β-glucan receptor is present on macrophages. Here we identify this unknown receptor as dectin-1 (ref. 2), a finding that provides new insights into the innate immune recognition of β-glucans.

We screened a RAW264.7 complementary DNA retroviral expression library using the β-glucan-rich particle zymosan[3] and isolated a single receptor that bound to zymosan. The DNA sequence identified the receptor as dectin-1, a small (relative molecular mass about 28,000) type-II membrane receptor with an extracellular C-type lectin-like domain fold and a cytoplasmic domain with an immunoreceptor tyrosine-based activation motif[2]. In contrast to its reported specificity for dendritic cells[2], we found that dectin-1 was expressed in every macrophage population we examined and in more tissues than was previously reported, with the highest expression being in the liver, lung and thymus (results not shown).

By assaying the ability of different carbohydrates to block the binding of zymosan to NIH3T3 cells expressing dectin-1, we found dectin-1 to be a pattern-recognition receptor that recognizes a variety of β-1,3-linked and β-1,6-linked glucans from fungi and plants (Fig. 1a). Dectin-1 did not recognize monosaccharides (data not shown) or carbohydrates with different linkages. Laminarin and glucan phosphate, a structurally defined, immunologically active β-glucan[4], were the most effective inhibitors; both bind to the β-glucan receptor on monocytes and macrophages[5,6]. The ability of dectin-1 transfectants to bind to zymosan was trypsin-sensitive, a well-known feature of the β-glucan receptor[7].

The C-type lectin-like fold of dectin-1 is similar to those of natural-killer T-cell C-type lectin domains, which lack the residues that are involved in calcium coordination and are required for carbohydrate binding in classic Ca^{2+}-dependent C-type lectins[8]. This is consistent with our finding that binding of dectin-1 to zymosan is independent of metal ions (results not shown).

Soluble, recombinant dectin-1 also stimulates the proliferation of T lymphocytes[2]. In a whole-cell binding assay, binding of T cells to NIH3T3 cells expressing dectin-1 was not inhibited by β-glucans (results not shown). We conclude that dectin-1 has two ligand-binding sites: one that recognizes an endogenous ligand on T cells[2], and another for exogenous carbohydrates.

The β-glucan receptor has also been implicated in the recognition and phagocytosis of intact *Saccharomyces cerevisiae*[9] and of the fungal pathogen *Candida albicans*[10]. Both of these organisms were bound to by dectin-1 transductants in a β-glucan-dependent manner (Fig. 1b), consistent with the presence of β-1,3-linked and β-1,6-linked glucans within their cell walls[11]. Dectin-1 also mediates actin-dependent phagocytosis of zymosan, an activity that requires the cytoplasmic tail of this receptor (results not shown). Furthermore, *C. albicans* conidia were internalized (Fig. 1c), showing that dectin-1 can mediate non-opsonic phagocytosis of this opportunistic pathogen.

A human homologue of dectin-1 (GenBank accession number, AY009090) is similar to the murine receptor, except that it lacks an extracellular stalk region and has no sites for *N*-linked glycosylation. Binding of zymosan and *C. albicans* by the human receptor is also dependent on β-glucan (results not shown), indicating that it may be the functional equivalent of dectin-1. Our identification of dectin-1 as the elusive macrophage receptor for β-glucan resolves a long-standing mystery and will open up new opportunities to exploit the effects of β-glucans.

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Volume 196, Issue 3
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Brief Definitive Report | July 29 2002

Dectin-1 Is A Major β-Glucan Receptor On Macrophages

Gordon D. Brown, Philip R. Taylor, Delyth M. Reid, Janet A. Willment, David L. Williams, Luisa Martinez-Pomares, Simon Y.C. Wong, Siamon Gordon

+ Author and Article Information

J Exp Med (2002) 196 (3): 407–412. | https://doi.org/10.1084/jem.20020470 | Article history

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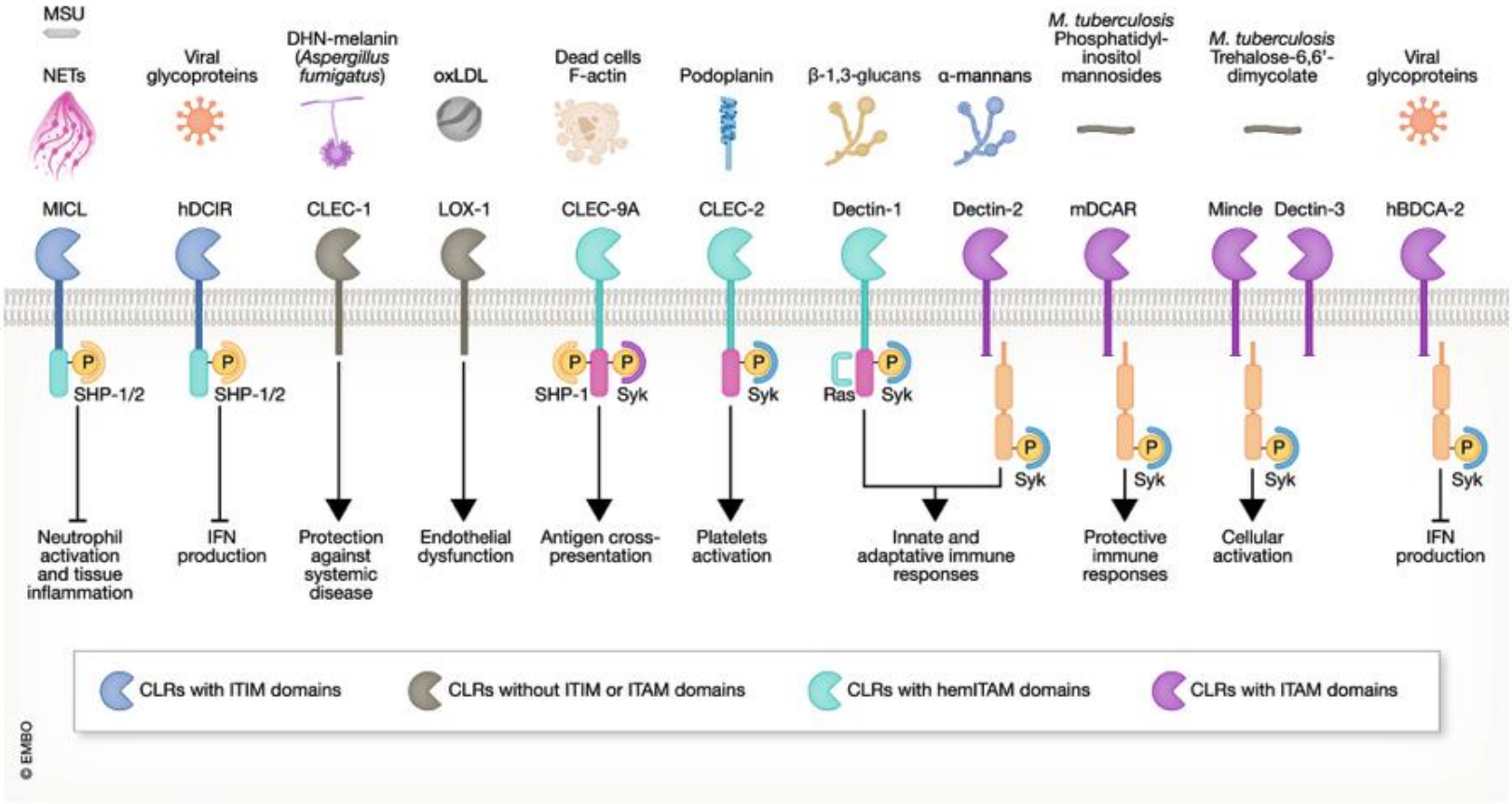
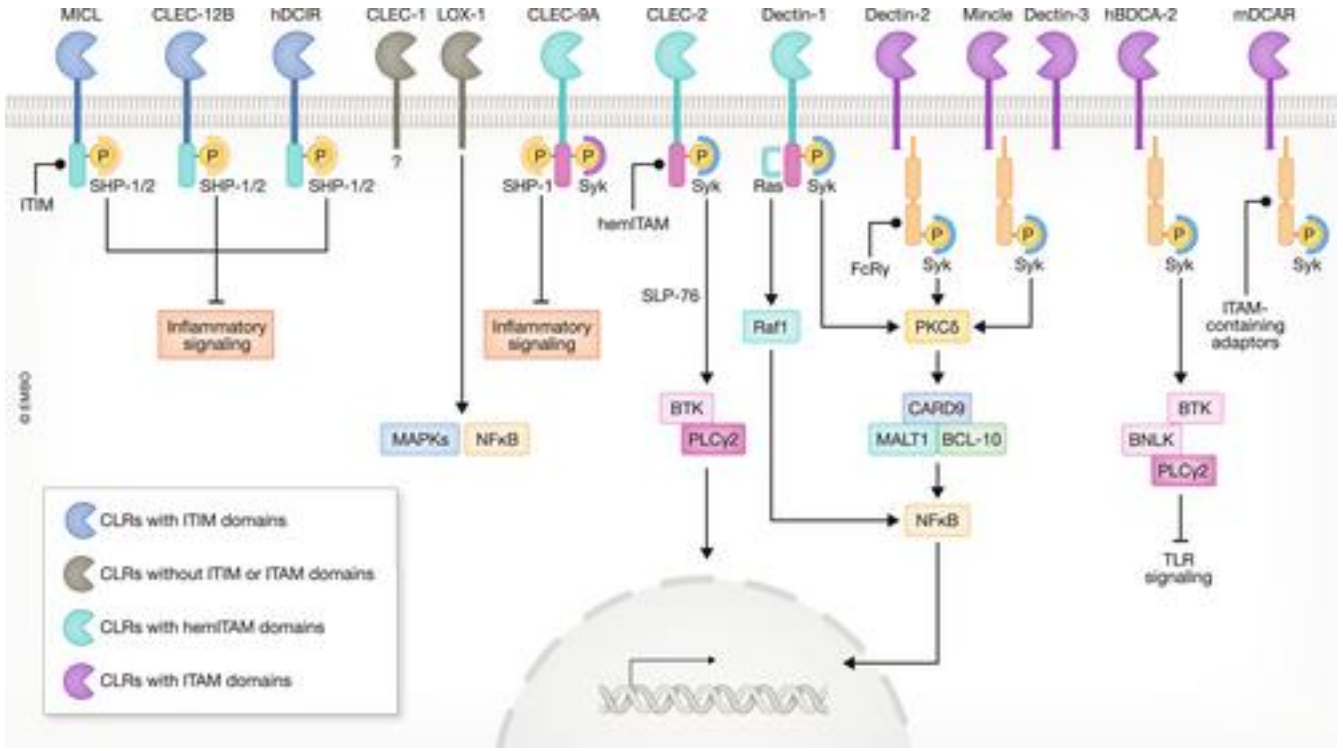
Zymosan is a β-glucan– and mannan-rich particle that is widely used as a cellular activator for examining the numerous responses effected by phagocytes. The macrophage mannose receptor (MR) and complement receptor 3 (CR3) have historically been considered the major macrophage lectins involved in the nonopsonic recognition of these yeast-derived particles. Using specific carbohydrate inhibitors, we show that a β-glucan receptor, but not the MR, is a predominant receptor involved in this process. Furthermore, nonopsonic zymosan binding was unaffected by genetic CD11b deficiency or a blocking monoclonal antibody (mAb) against CR3, demonstrating that CR3 was not the β-glucan receptor mediating this activity. To address the role of the recently described β-glucan receptor, Dectin-1, we generated a novel anti–Dectin-1 mAb, 2A11. Using this mAb, we show here that Dectin-1 was almost exclusively responsible for the β-glucan–dependent, nonopsonic recognition of zymosan by primary macrophages. These findings define Dectin-1 as the leukocyte β-glucan receptor, first described over 50 years ago, and resolves the long-standing controversy regarding the identity of this important molecule. Furthermore, these results identify Dectin-1 as a new target for examining the immunomodulatory properties of β-glucans for therapeutic drug design.

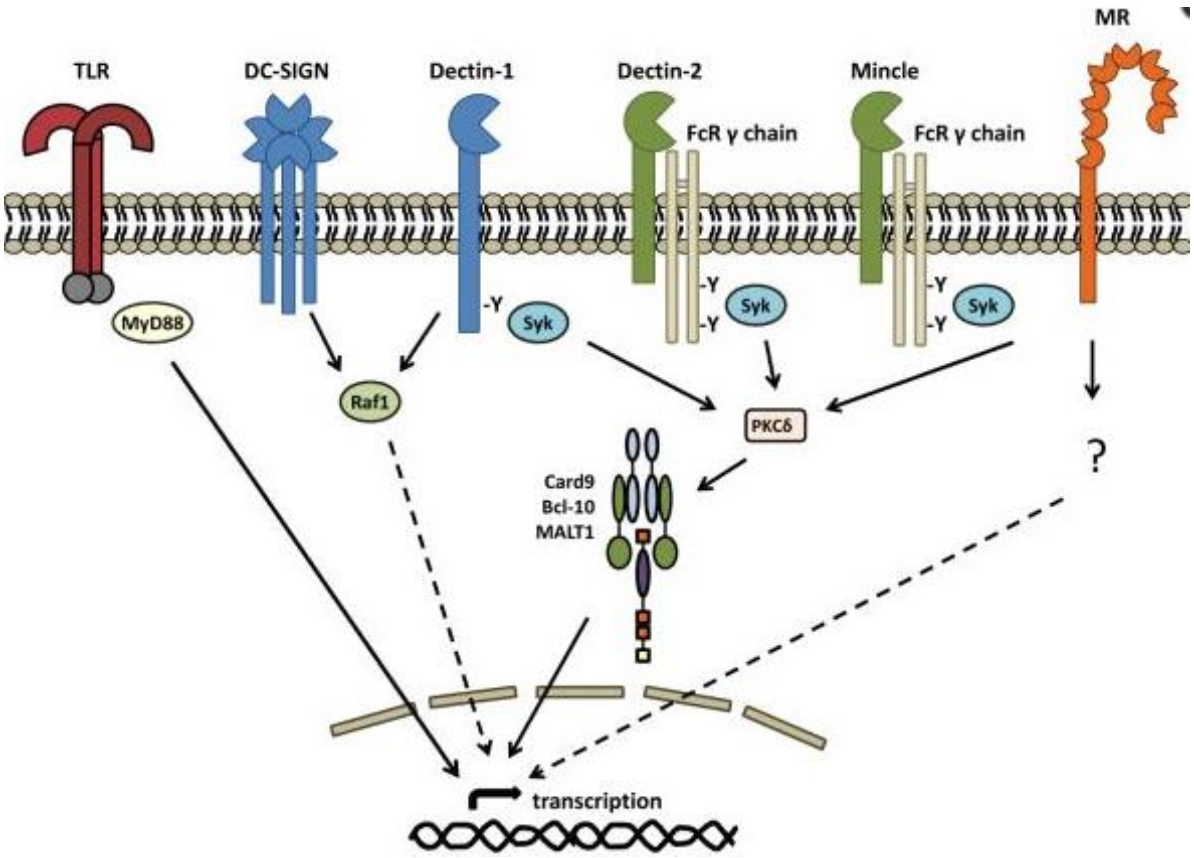
CLRs- Lectinas do tipo C

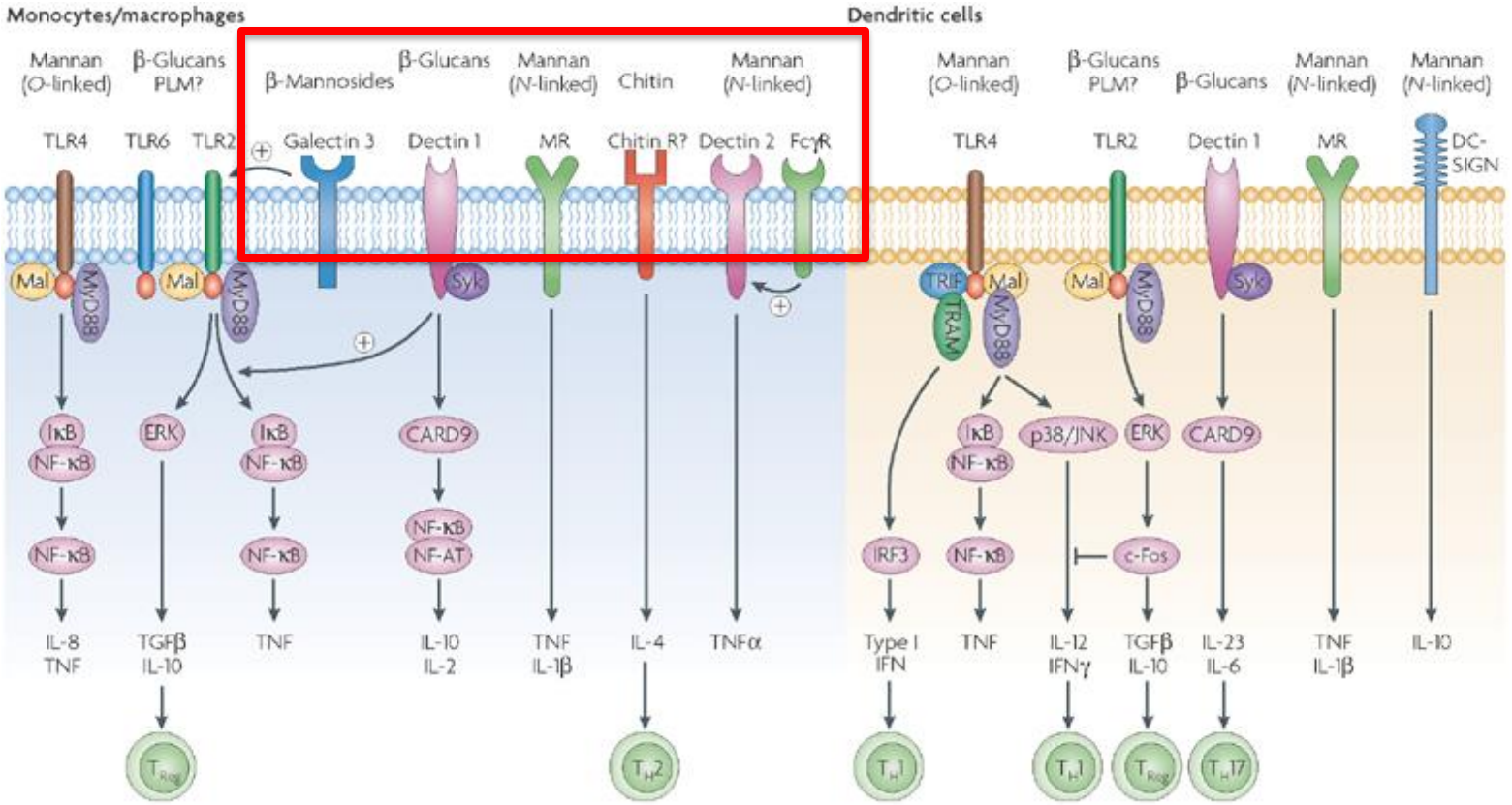


The Dectin-1 and Dectin-2 clusters: C-type lectin receptors with fundamental roles in immunity



CLRs- Lectinas do tipo C





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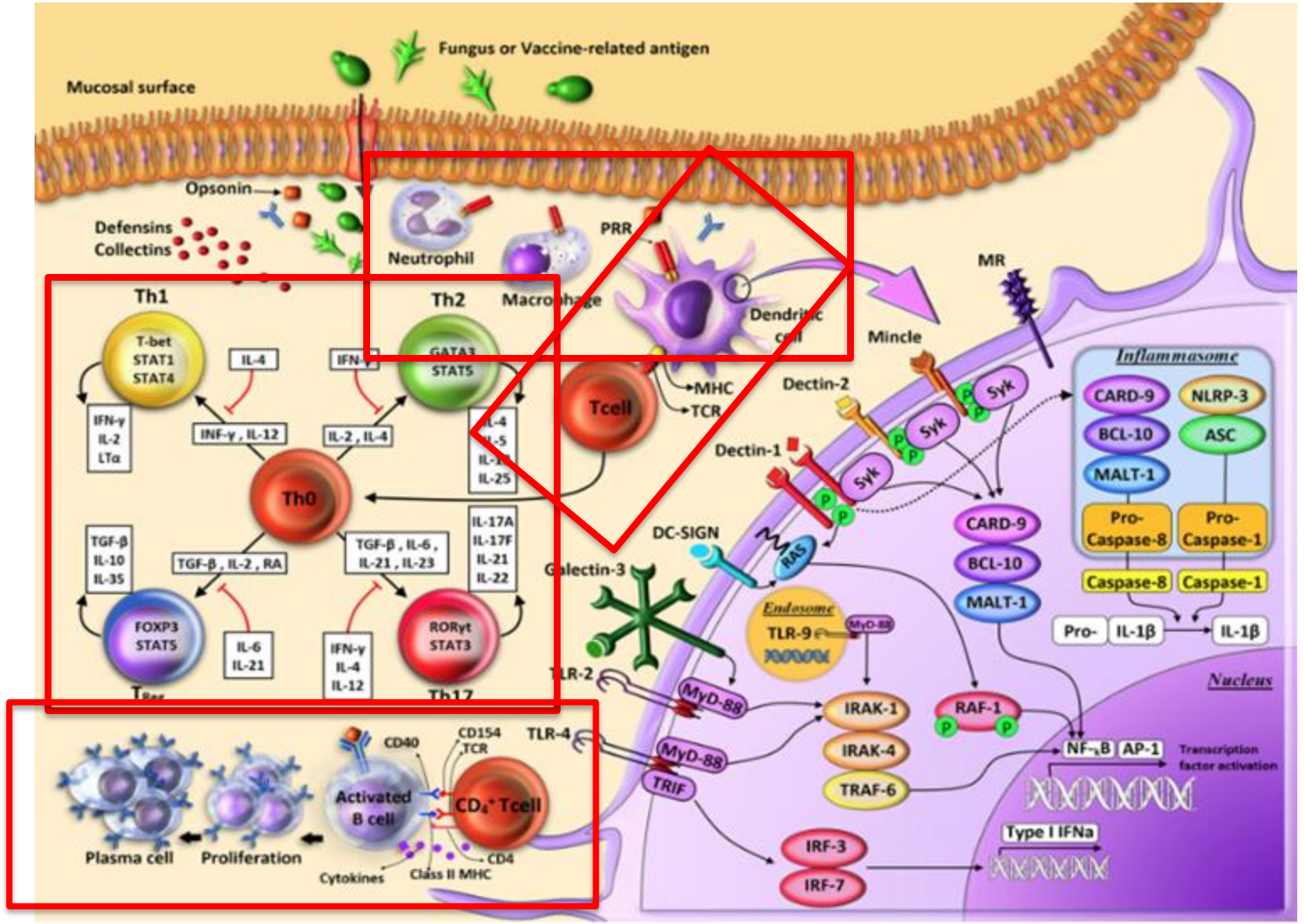
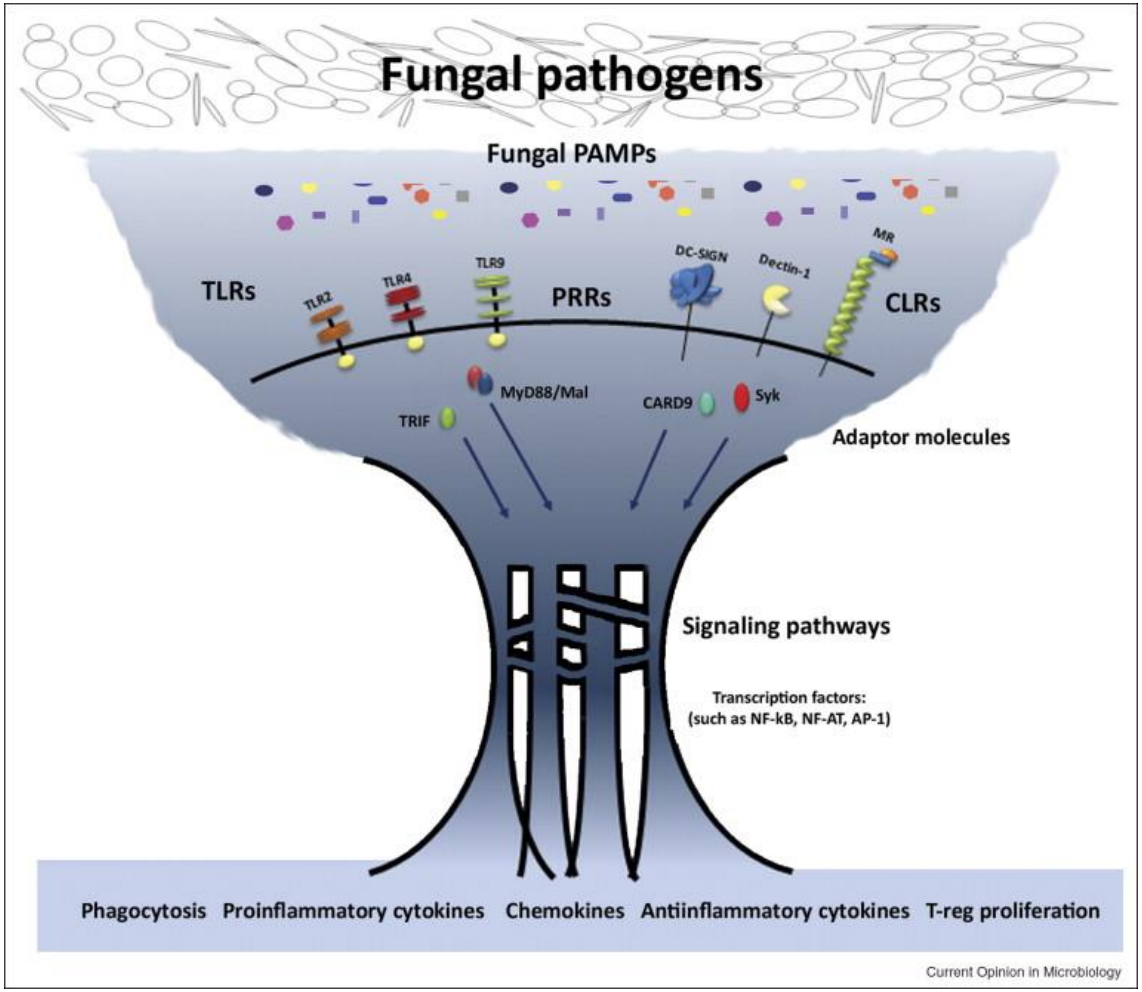
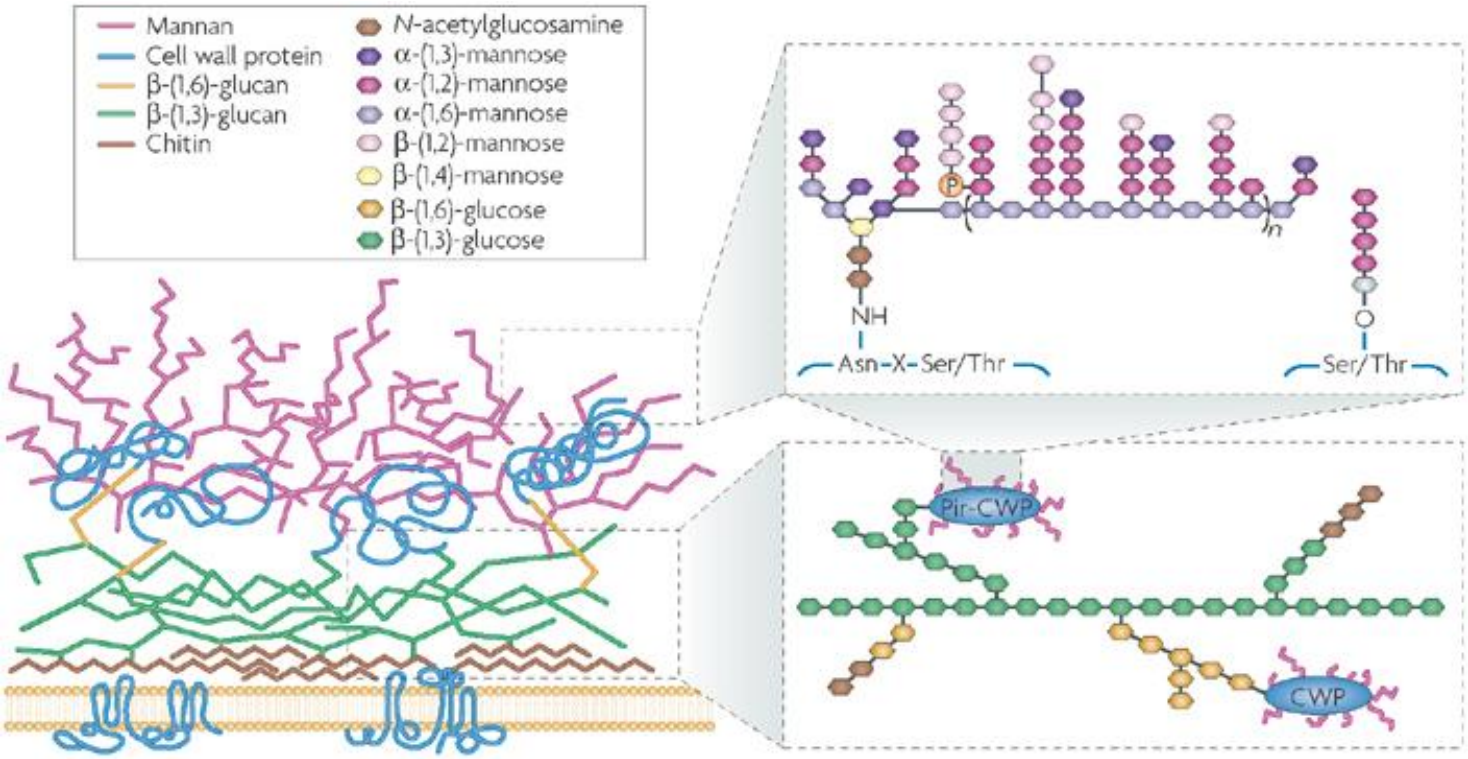
Resposta imunológica- Infecção fúngica



S. Nami et al. Biom. Pharm. 2019


Fungal pathogens
Fungal PAMPs
TLRs
TLR2
TLR4
TLR9
PRRs
DC-SIGN
Dectin-1
MR
CLRs
MyD88/Mal
TRIF
CARD9
Syk
Adaptor molecules
Signaling pathways
Transcription factors:
(such as NF-kB, NF-AT, AP-1)
Phagocytosis
Proinflammatory cytokines
Chemokines
Antiinflammatory cytokines
T-reg proliferation
Current Opinion in Microbiology

Location	PRR	PAMP(s)
Soluble	SP-A	mannan
	SP-D	mannan
	Galectin-3	β1,2-mannan
Membrane	TLR2	phospholipomannan
	TLR4	O-mannan
	Dectin-1	β-glucan
	CR3	β-glucan, mannan
	DC-SIGN	mannan
	mannose receptor	N-mannan
	CD14	mannan
	?	chitin
	MINCLE	mannan
	Dectin-2	hyphal mannan
	scavenger receptors	β-glucan
Intracellular	TLR9	DNA



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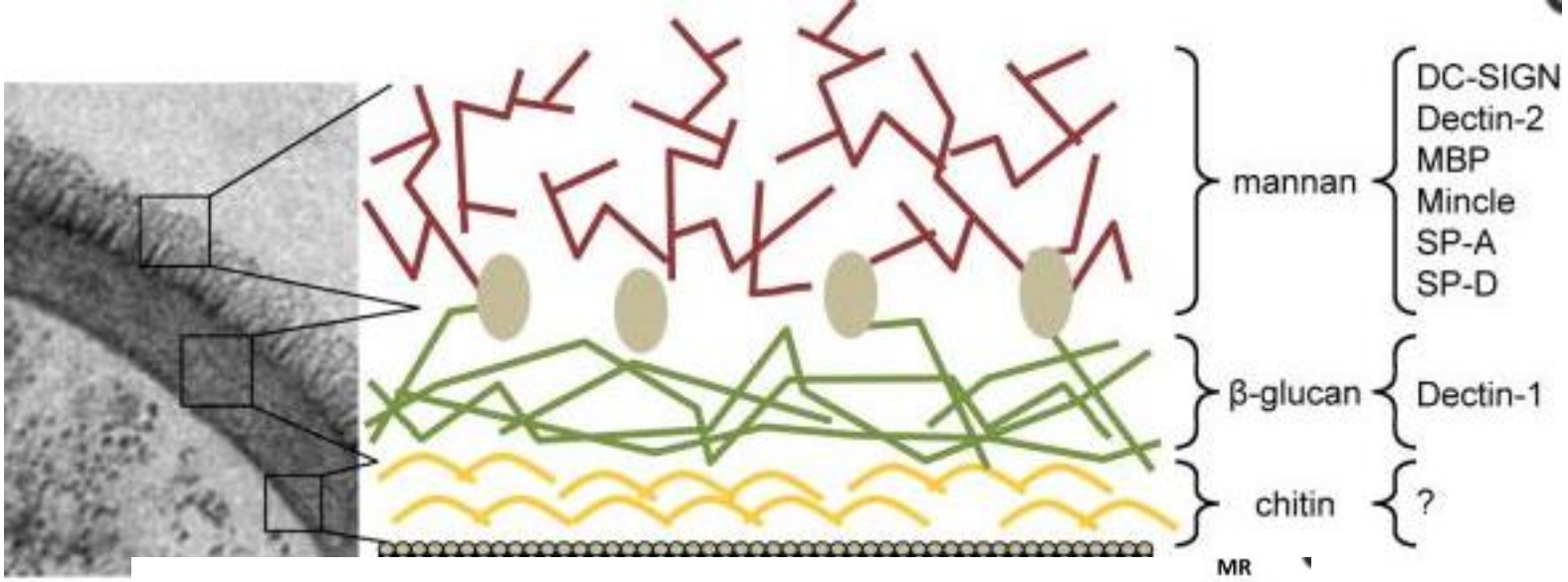
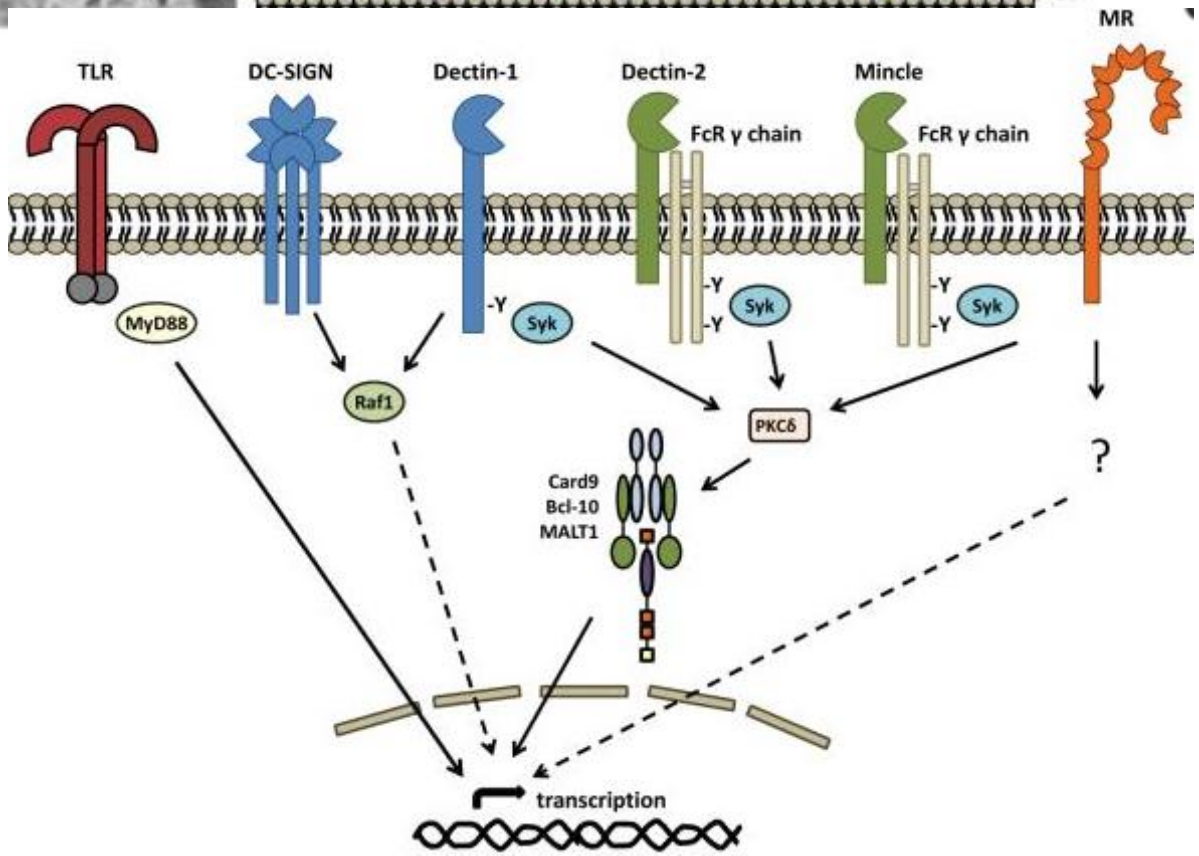
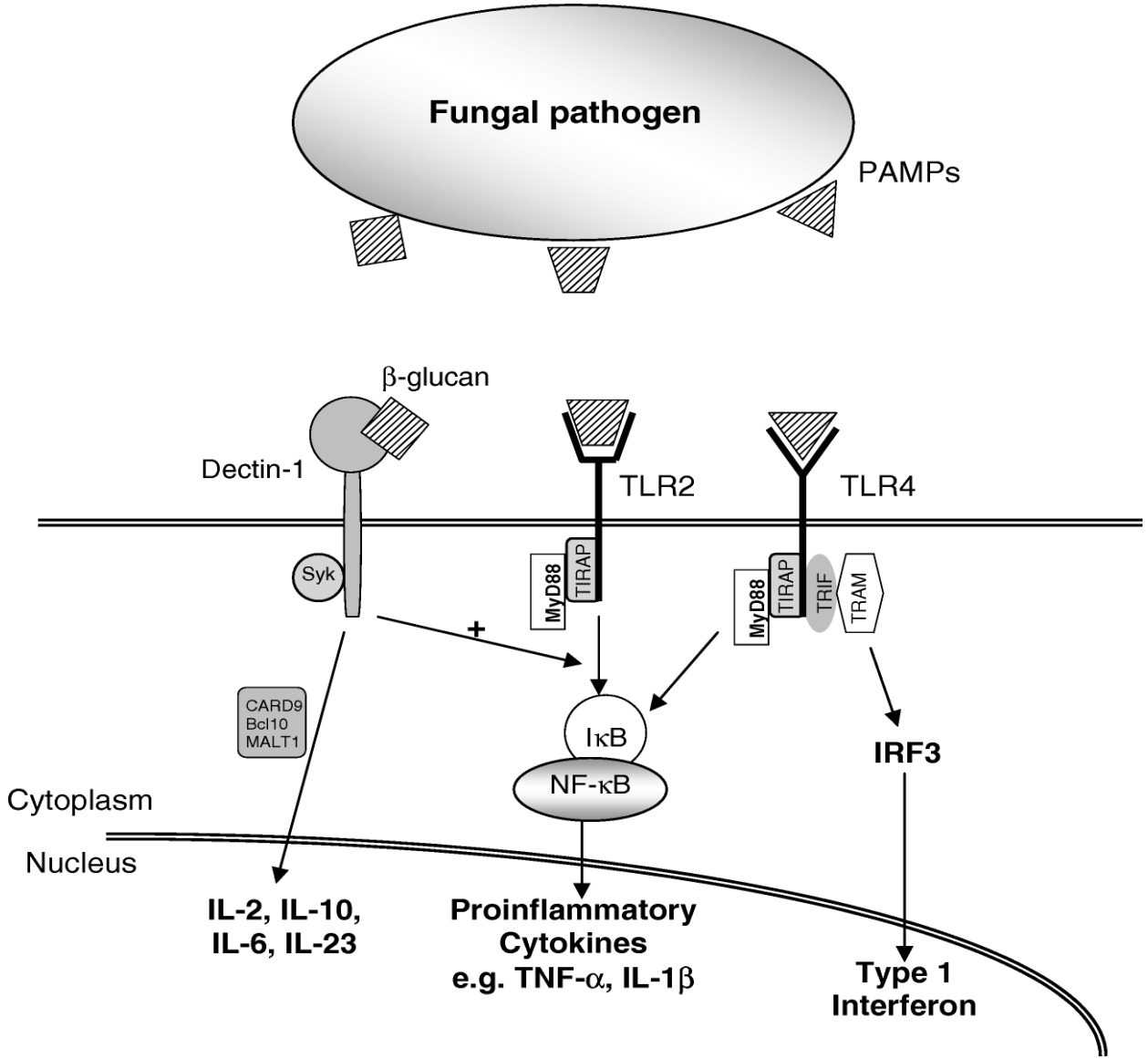
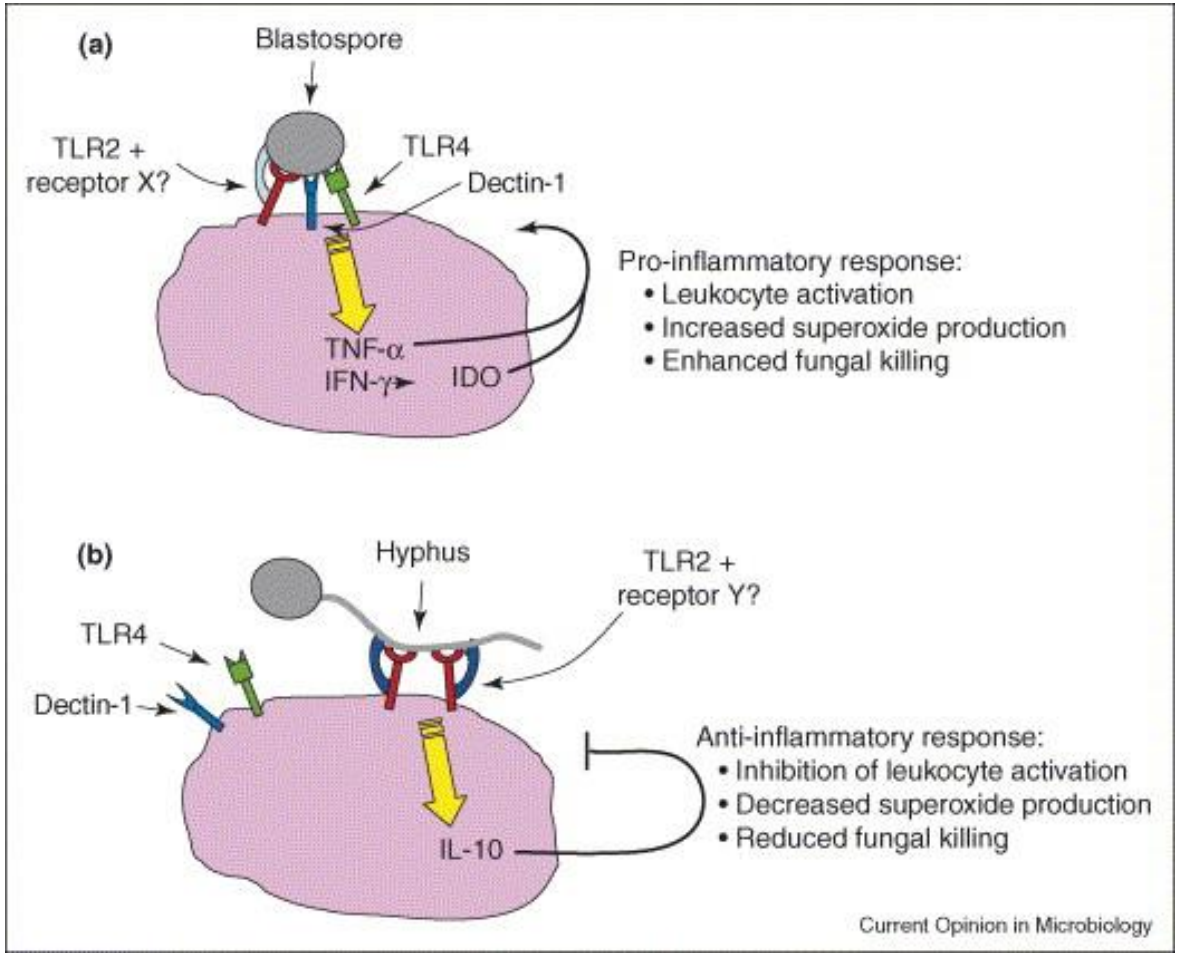
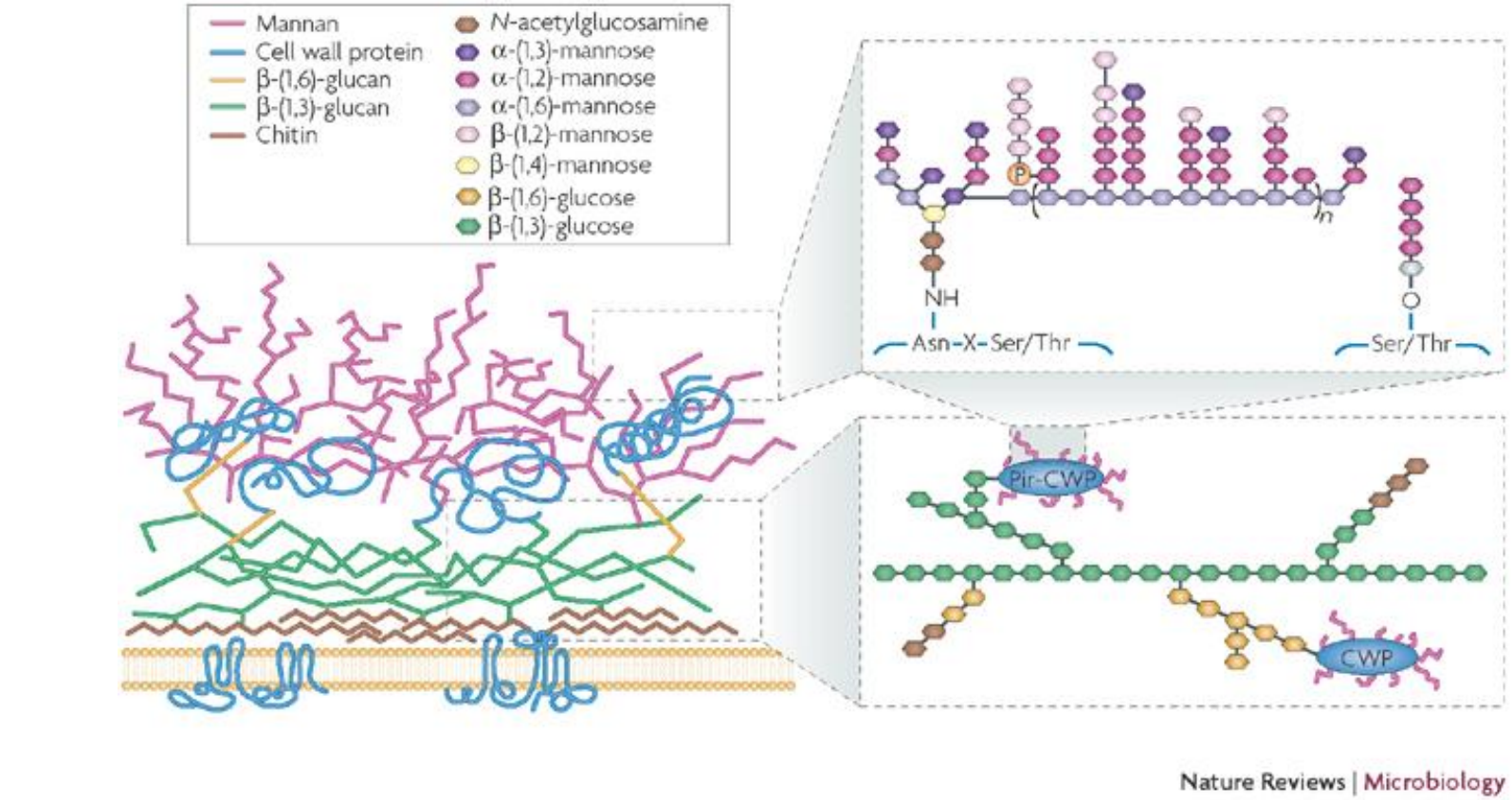

mannan
DC-SIGN
Dectin-2
MBP
Mincle
SP-A
SP-D
β-glucan
Dectin-1
chitin
?

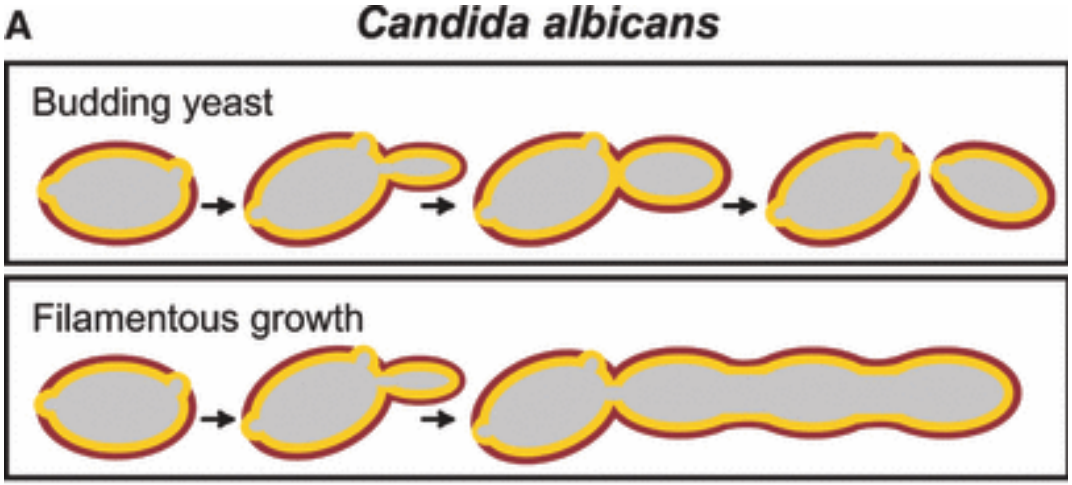

TLR
DC-SIGN
Dectin-1
Dectin-2
Mincle
MR
FcR γ chain
FcR γ chain
MyD88
-Y
Syk
-Y
-Y
Syk
-Y
-Y
Syk
Raf1
PKCδ
?
Card9
Bcl-10
MALT1
transcription


Fungal pathogen
PAMPs
β-glucan
Dectin-1
TLR2
TLR4
Syk
MyD88
TIRAP
MyD88
TIRAP
TRIF
TRAM
+
CARD9
Bcl10
MALT1
IκB
NF-κB
IRF3
Cytoplasm
Nucleus
IL-2, IL-10,
IL-6, IL-23
Proinflammatory
Cytokines
e.g. TNF-α, IL-1β
Type 1
Interferon

Produção de citocinas
pro-inflamatórias X anti-inflamatórias

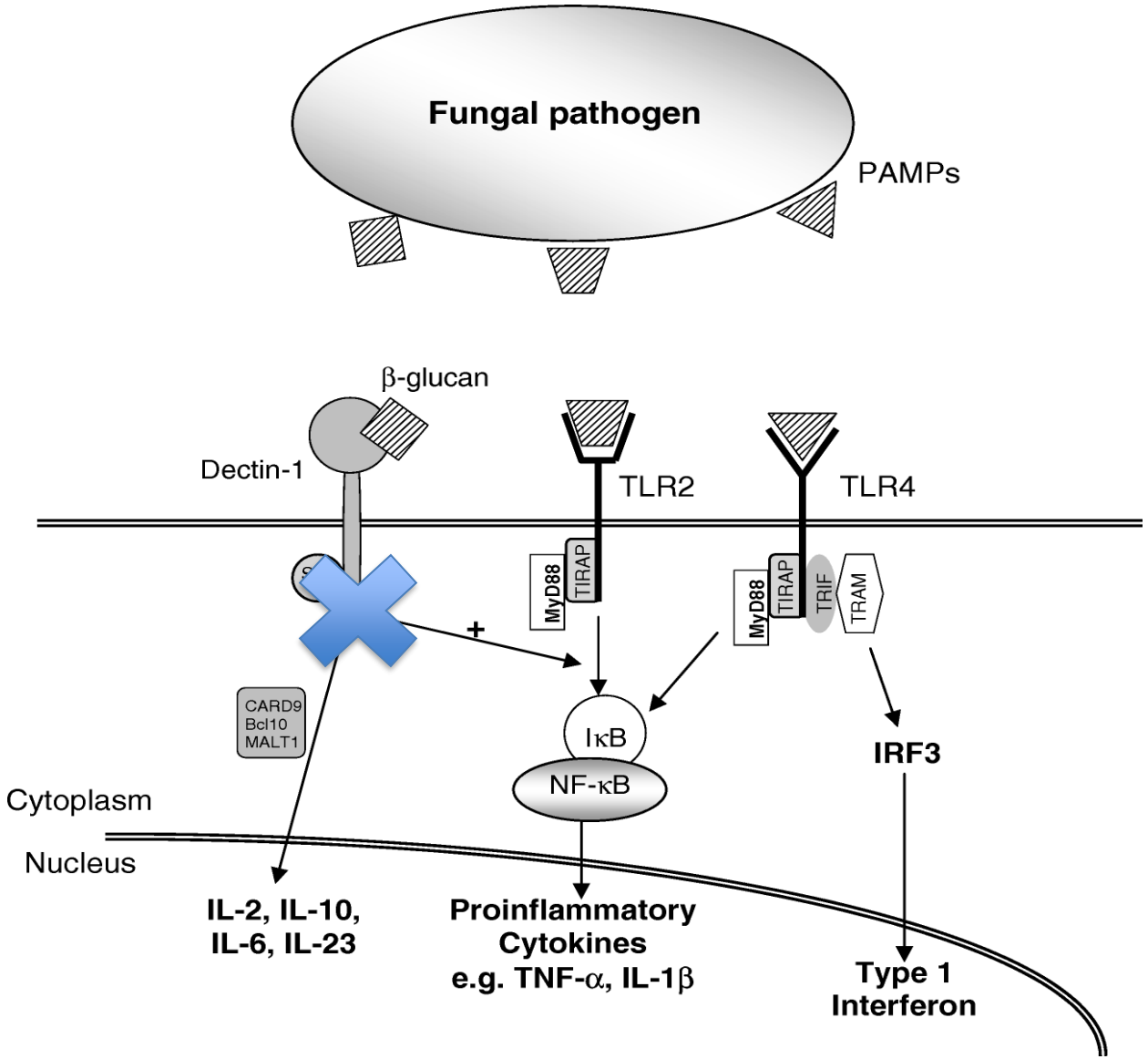




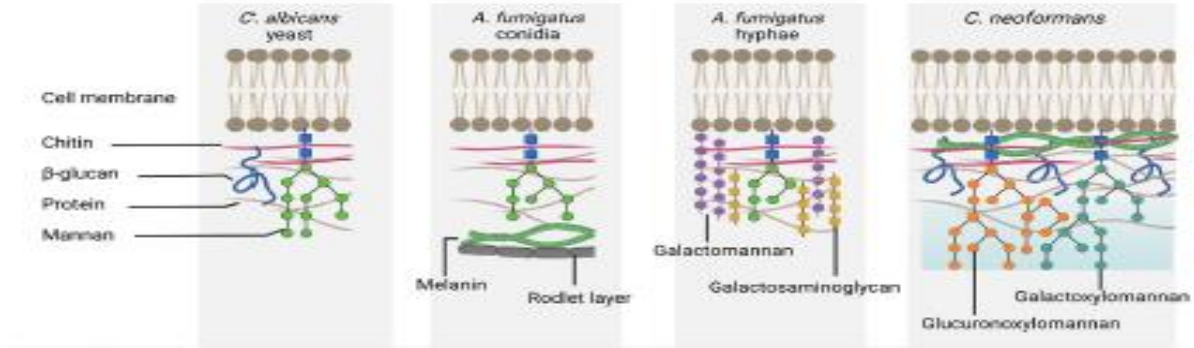


Vermelho: Manana

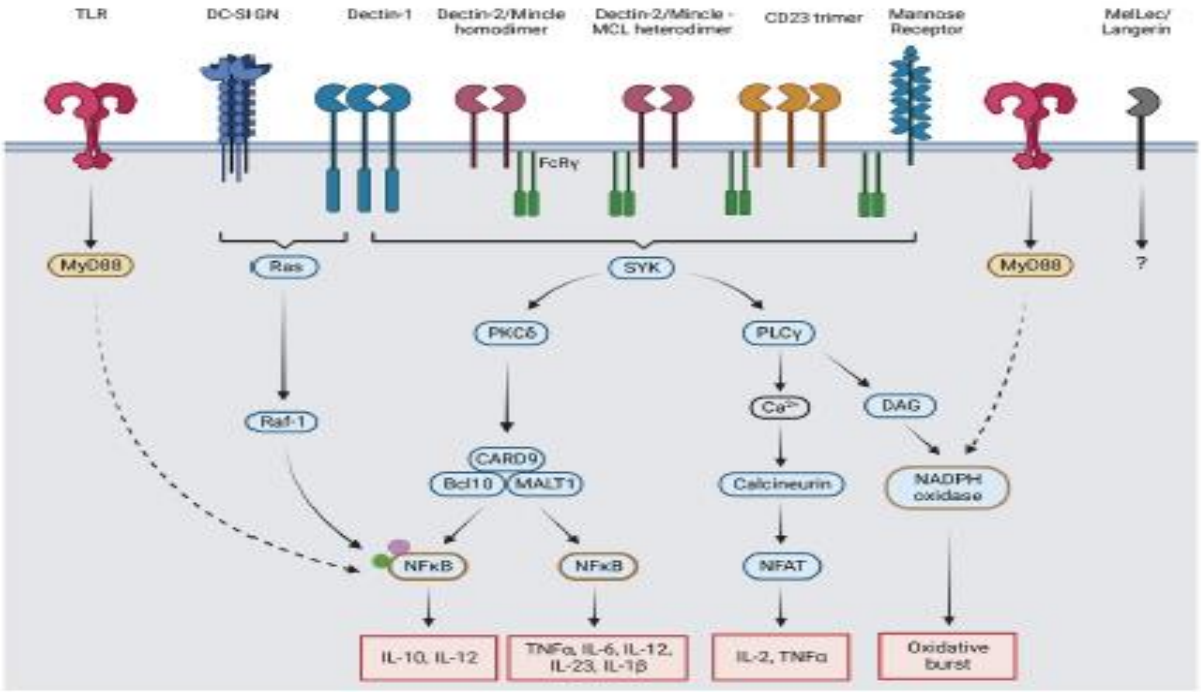
Amarelo: Glucana



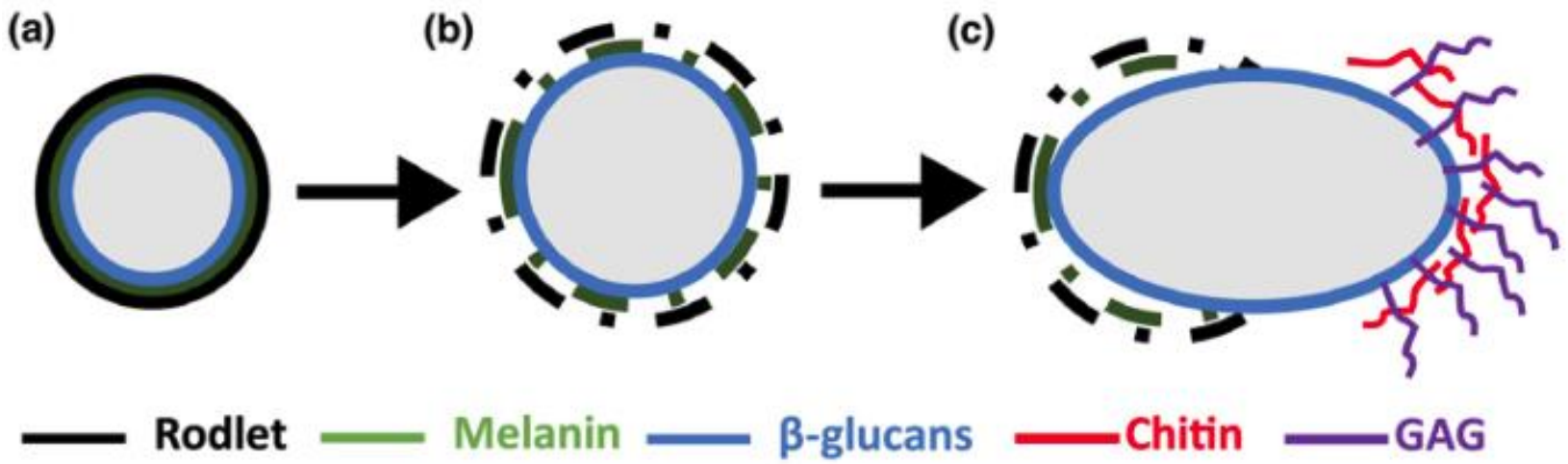
Candidíase crônica



CLR	Ligand			
DC-SIGN	Mannose	Mannose	Mannose	
Dectin-1	β-glucan	β-glucan*	β-glucan	β-glucan
Dectin-2	α-mannans	α-Mannans*	Galactomanann	
Mincle	X			X*
MCL	α-mannans			
Mannose receptor	Chitin*, mannose	Chitin*, mannose*	Chitin*, mannose*	Chitin*, mannoproteins*
CD23	α-mannan, β-glucan	α-mannan, β-glucan	α-mannan, β-glucan	
MelLec		DHN-melanin*		
Langerin	β-glucan, mannans			



Aspergillus

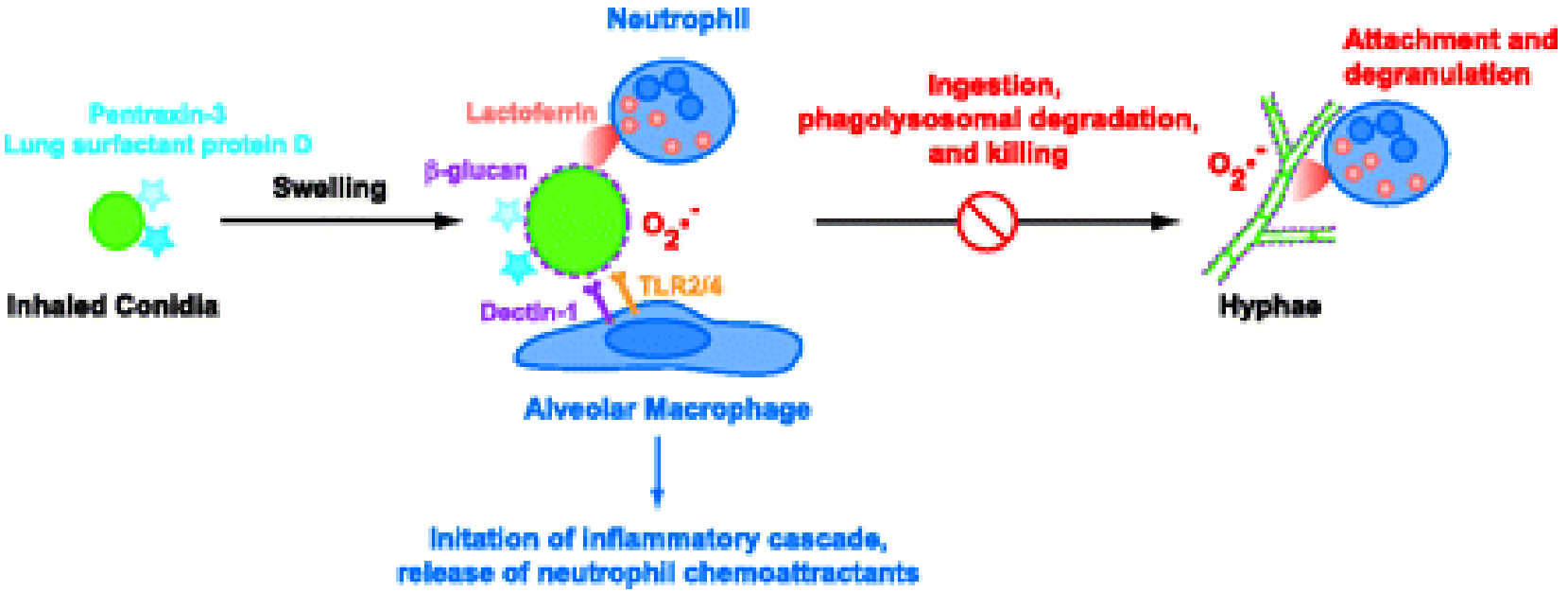


Innate immune defense against the different phenotypes of *Aspergillus fumigatus*.

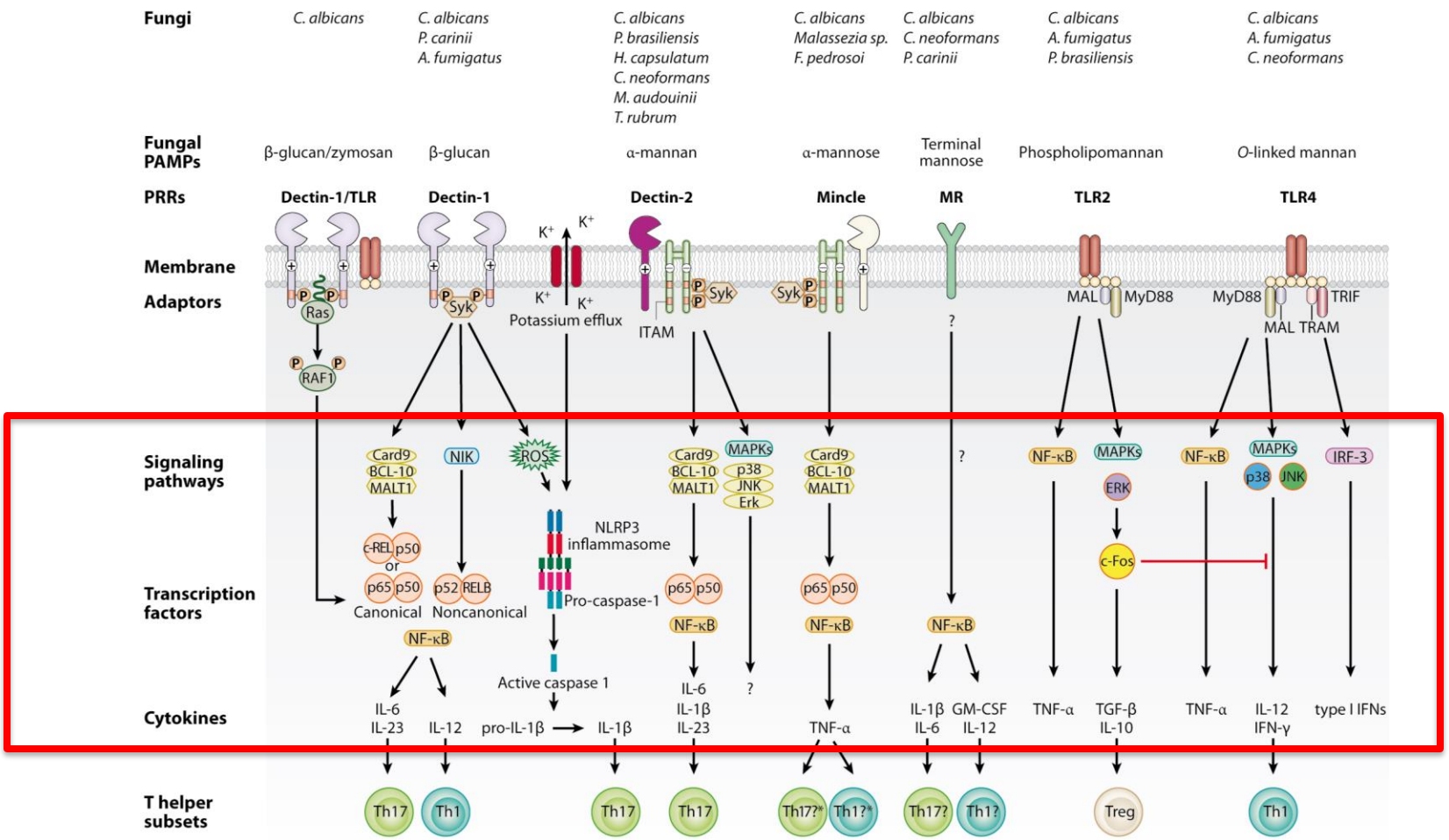
	resting	*swollen*	*germling*	*hyphae*
Recognition	DC-SIGN?	Dectin-1 TLR2 TLR4 DC-SIGN	Dectin-1 TLR2 TLR4	Dectin-1 TLR2 TLR4
Phagocytosis	AM PMN EC	AM PMN		
Intracellular killing		AM PMN EC?		
Extracellular killing			PMN	PMN

AM, alveolar macrophage; PMN, polymorphonuclear neutrophil; EC, epithelial cell; TLR, Toll-like receptor.

Aspergillus



Importância das moléculas adaptadoras



Wüthrich M, et al. 2012.
Annu. Rev. Immunol. 30:115–48

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Deep Dermatophytosis and Inherited CARD9 Deficiency

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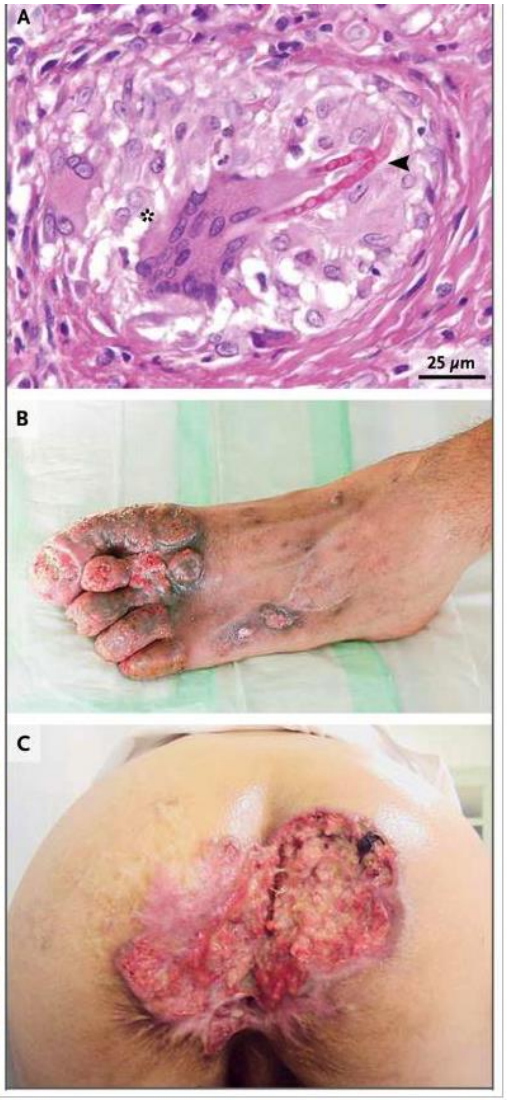
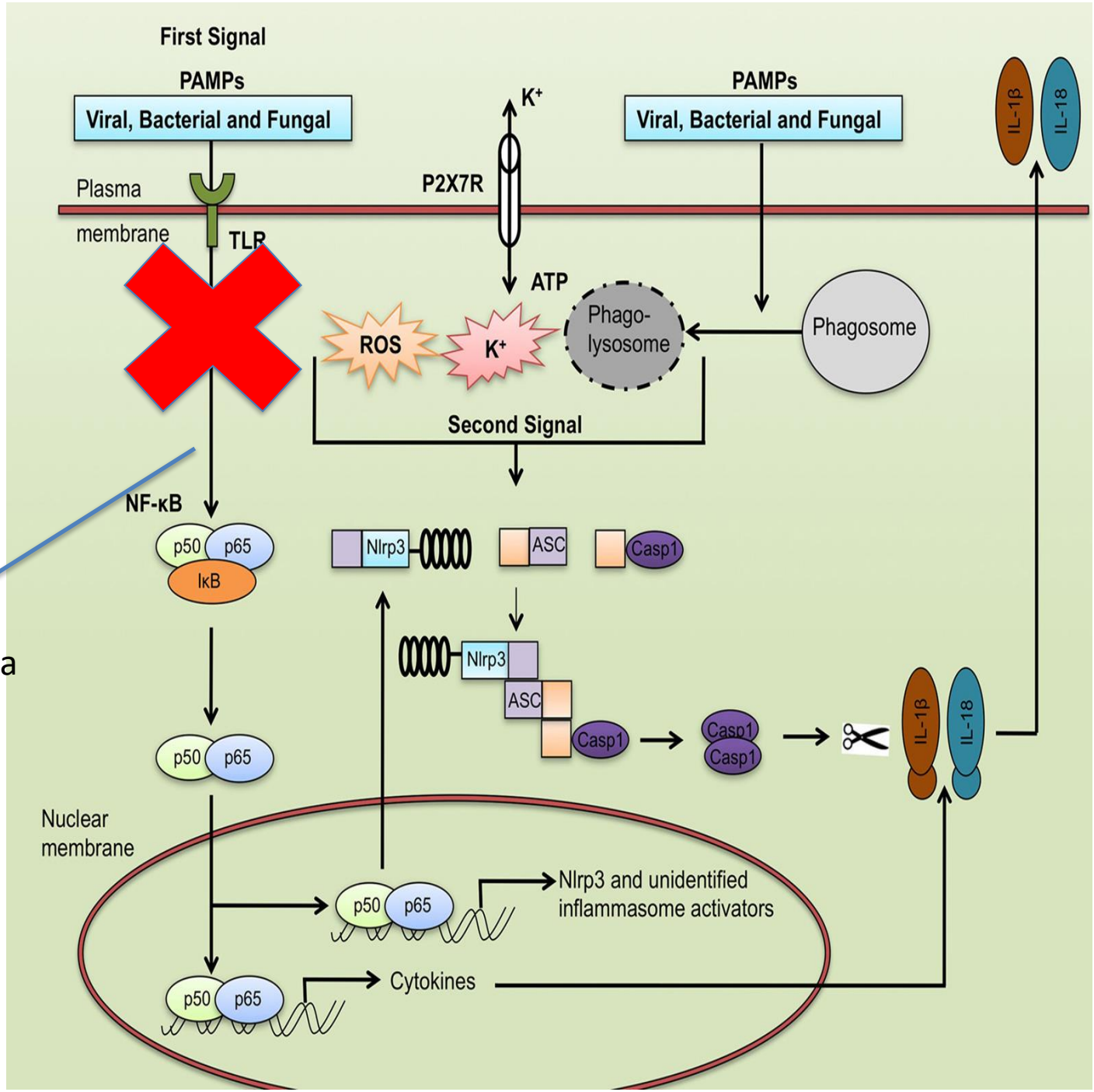
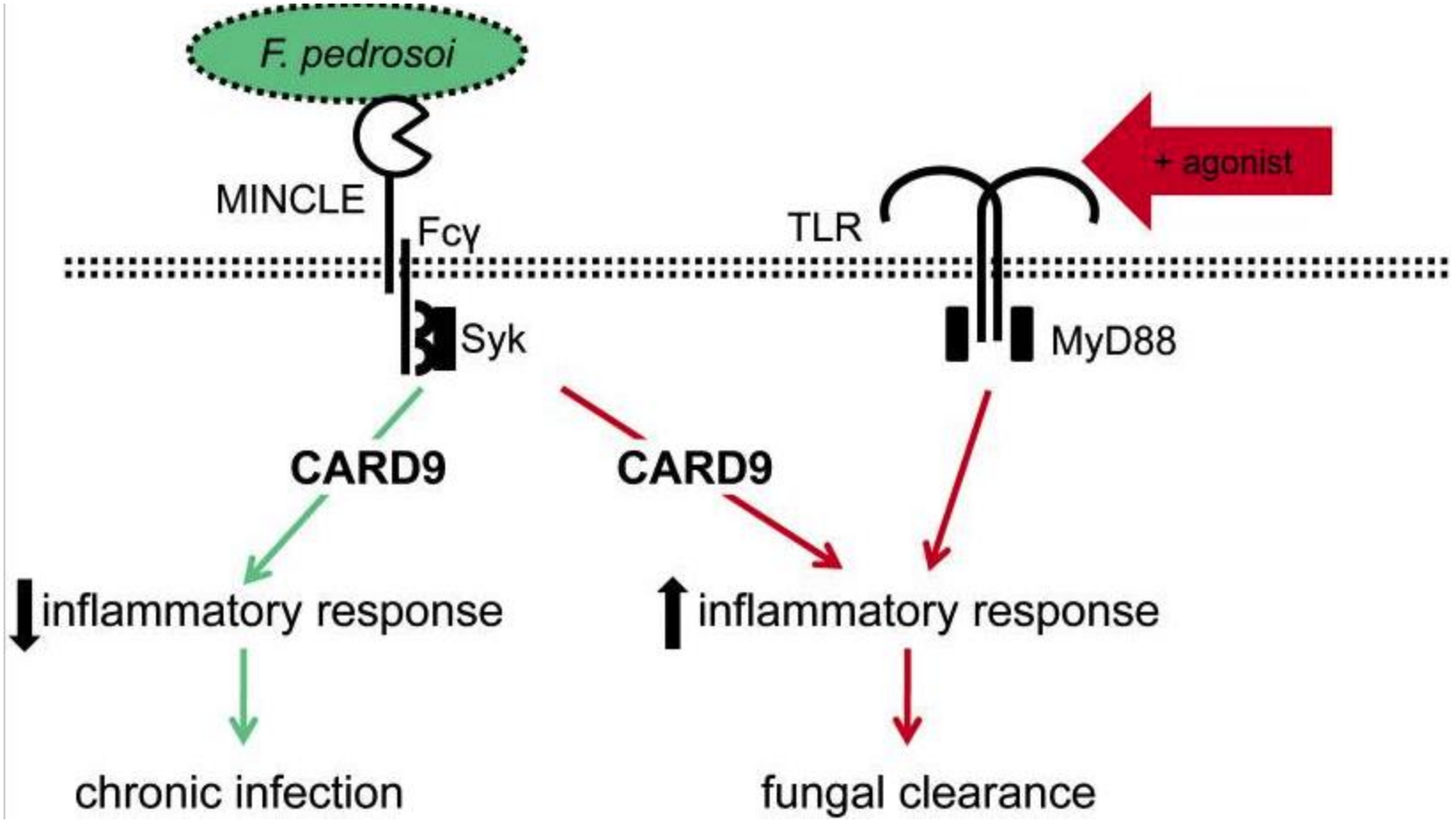


Clinical and Histologic Features of Patients with CARD9 Deficiency



Infecção crônica

F. pedrosoi



Sousa Mda G, Reid DM, Schweighoffer E, Tybulewicz V, Ruland J, Langhorne J, Yamasaki S, Taylor PR, Almeida SR, Brown GD. Restoration of pattern recognition receptor costimulation to treat chromoblastomycosis, a chronic fungal infection of the skin. Cell Host Microbe. 2011 May 19;9(5):436-43

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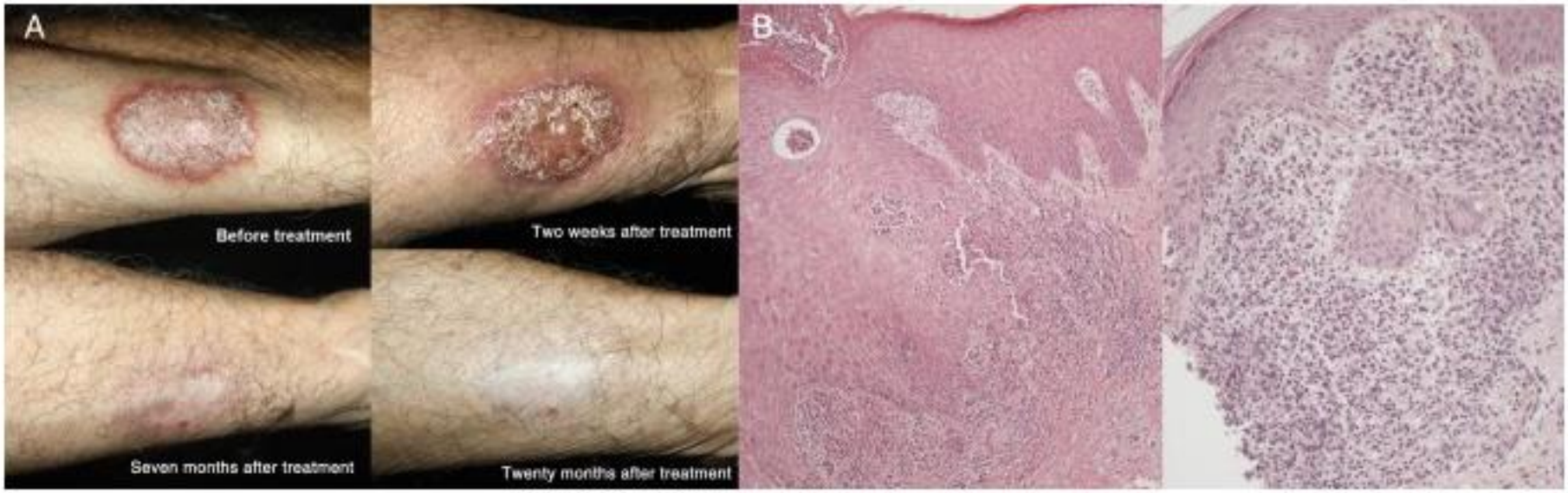
PMCID: PMC4036686

Topical Application of Imiquimod as a Treatment for Chromoblastomycosis

Maria da Glória Teixeira de Sousa,[1,2,a] Walter Belda, Jr,[3,a] Ricardo Spina,[3] Priscila Ramos Lota,[3] Neusa Sakai Valente,[3] Gordon D. Brown,[4] Paulo Ricardo Criado,[3] and Gil Benard[1,2]



Relembrando.....

- ✓ **PAMPs (Padrões Moleculares Associados a Patógenos)**
- ✓ A parede celular fúngica contém **PAMPs**, como:
  - **β-glucanas** (β-1,3-glucana e β-1,6-glucana)
  - **Mananas** e **manoproteínas**
  - **Quitina**
- ✓ Esses PAMPs são detectados por **receptores de reconhecimento padrão (PRRs)** em células do sistema imune inato.

PAMP fúngico	**PRR (Receptor do hospedeiro)**	**Células envolvidas**
β-glucanas	Dectin-1, CR3	Macrófagos, células dendríticas
Mananas	Dectin-2, DC-SIGN, MMR	Macrófagos, células dendríticas
Quitina	Receptores menos definidos (NOD2, TLRs)	Macrófagos, eosinófilos
Diversos PAMPs	TLR2, TLR4	Macrófagos, neutrófilos, DCs

Consequências do reconhecimento:

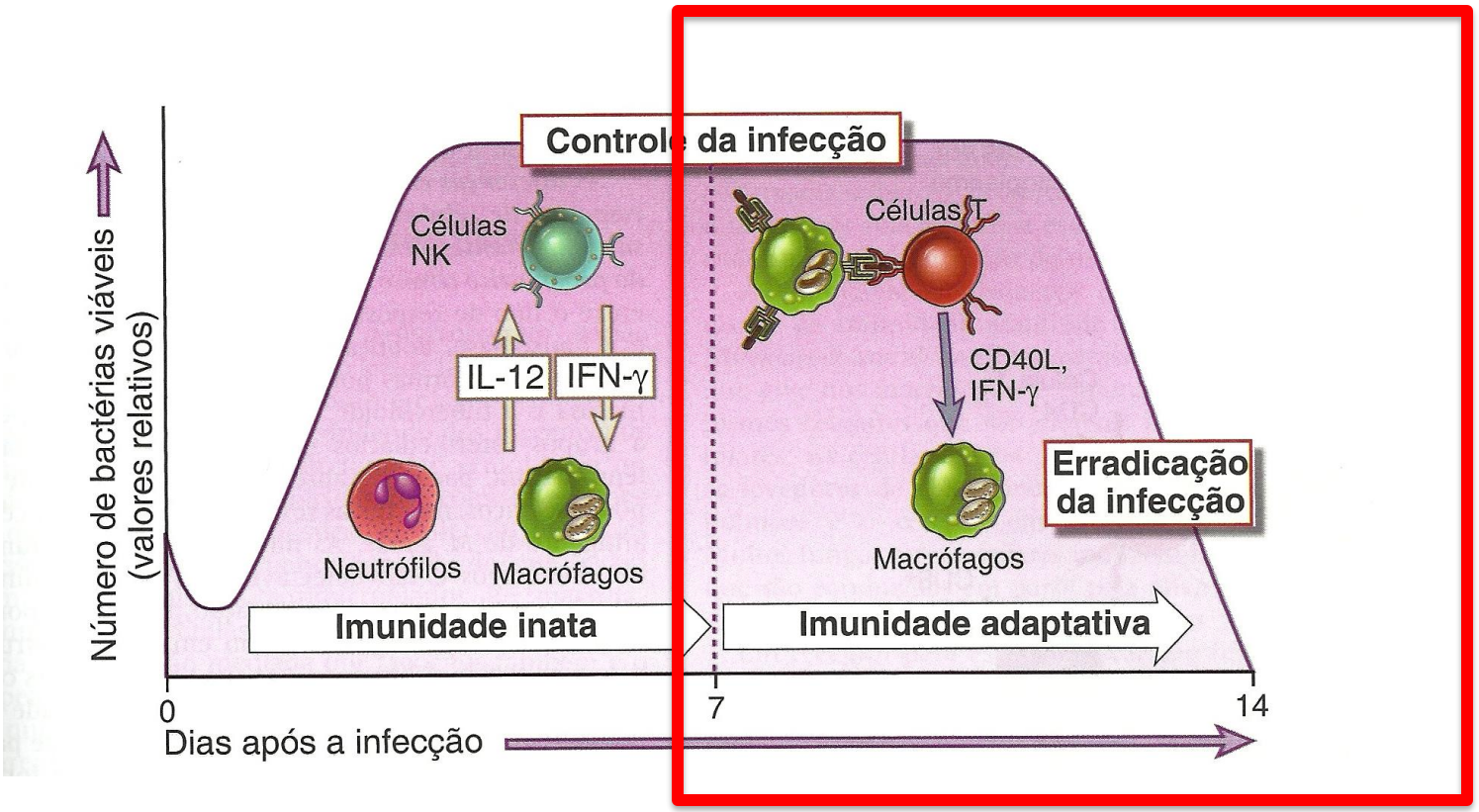
- Ativação de **vias de sinalização intracelular** (como NF-κB)
- Produção de **citocinas pró-inflamatórias** (ex: TNF-α, IL-1β, IL-6)
- Recrutamento de outras células do sistema imune
- Ativação de **respostas antifúngicas**, como:
  - Fagocitose
  - Produção de espécies reativas de oxigênio (ROS)
  - Formação de NETs (neutrófilos)
  - Ativação da resposta imune adaptativa

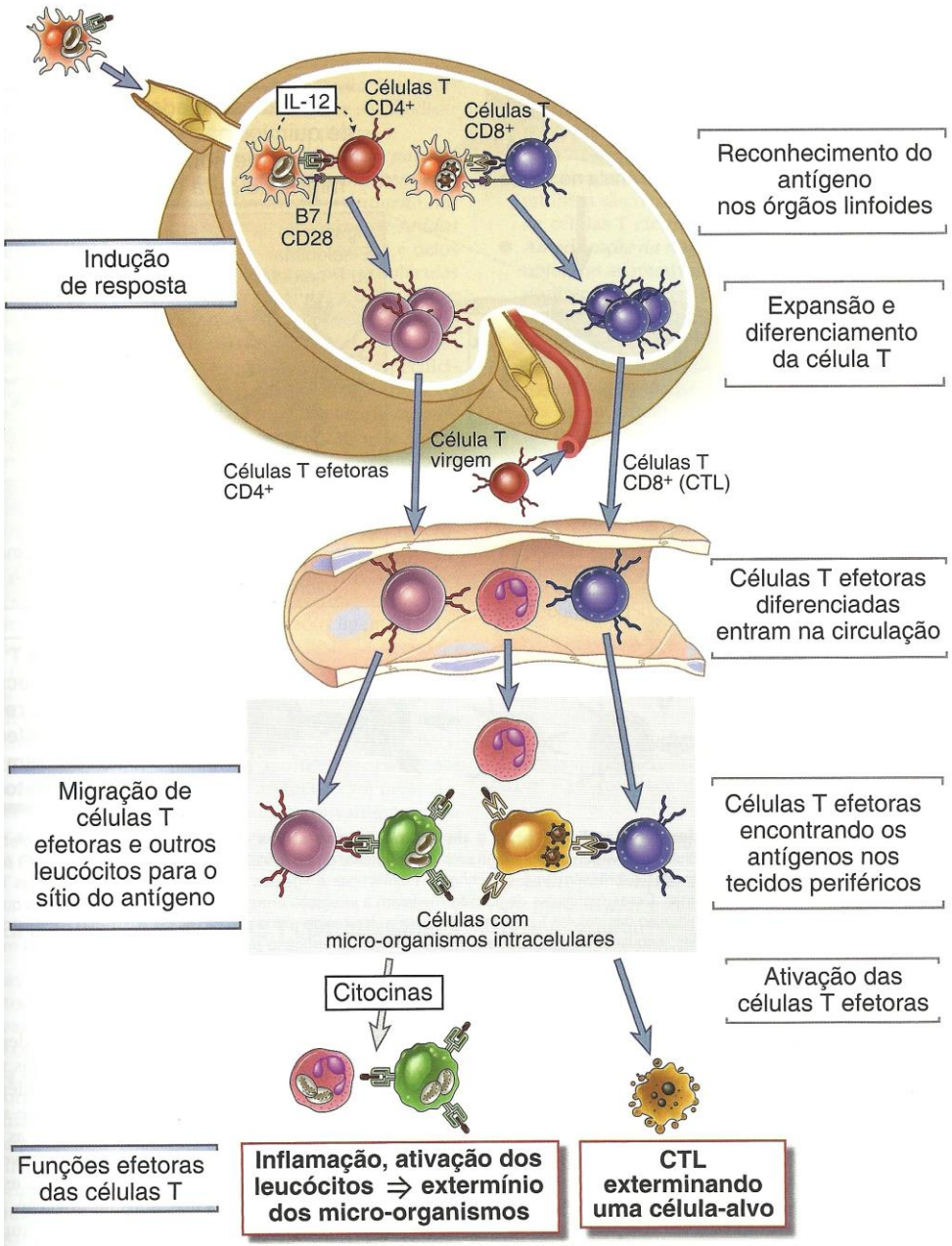
Resumo:

A **parede celular dos fungos é essencial para a detecção pelo sistema imune inato**, funcionando como uma "assinatura" microbiana. Sua composição rica em **carboidratos complexos** é fundamental para a ativação de receptores imunológicos e para o desencadeamento de uma resposta eficiente contra infecções fúngicas.

TEMPO DE RESPOSTA

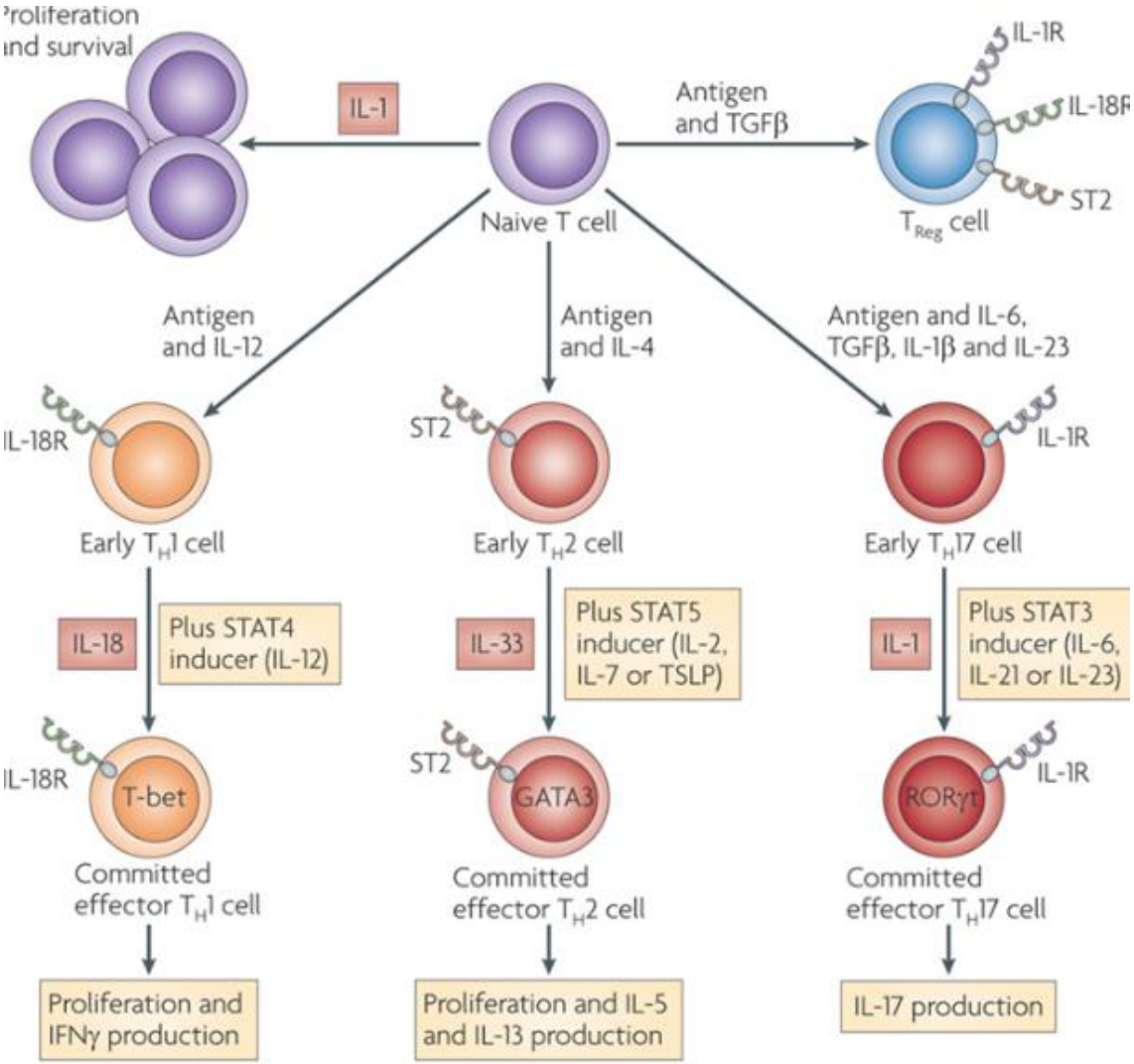
IMUNIDADE ADAPTATIVA

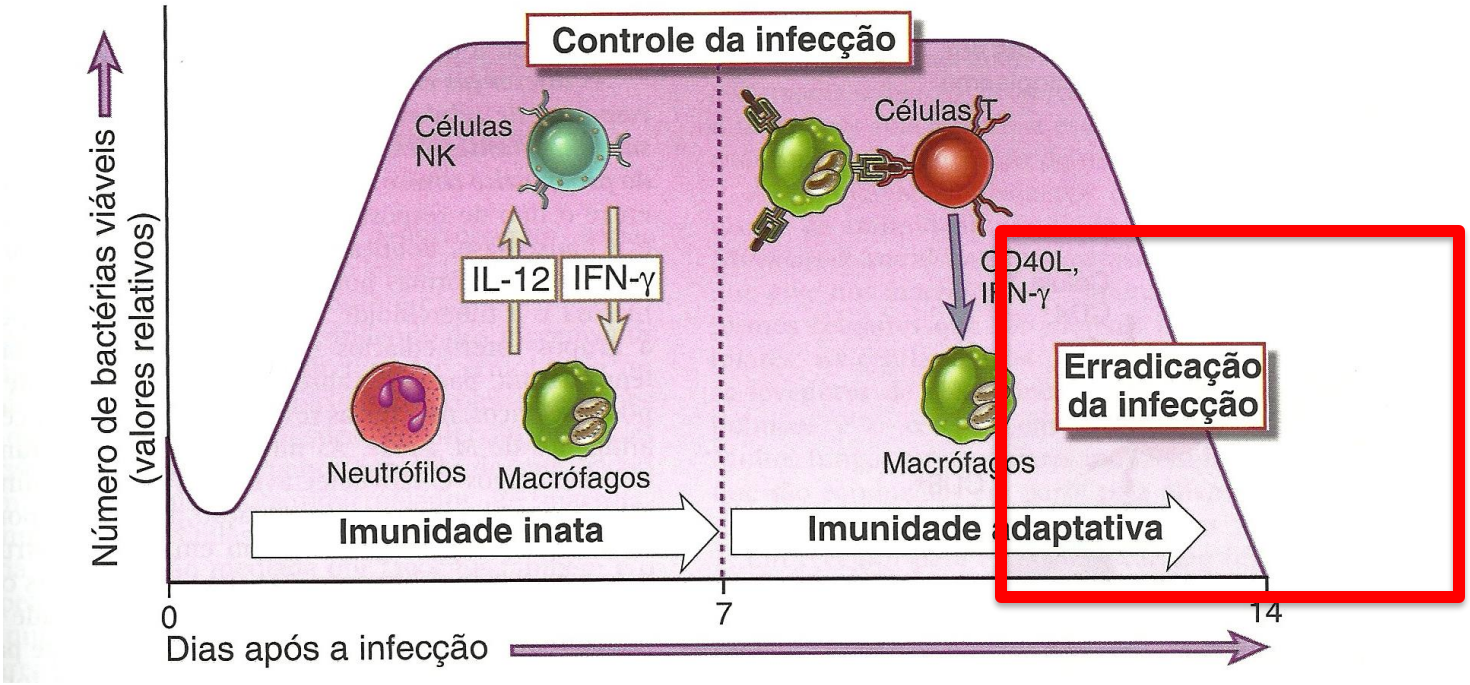


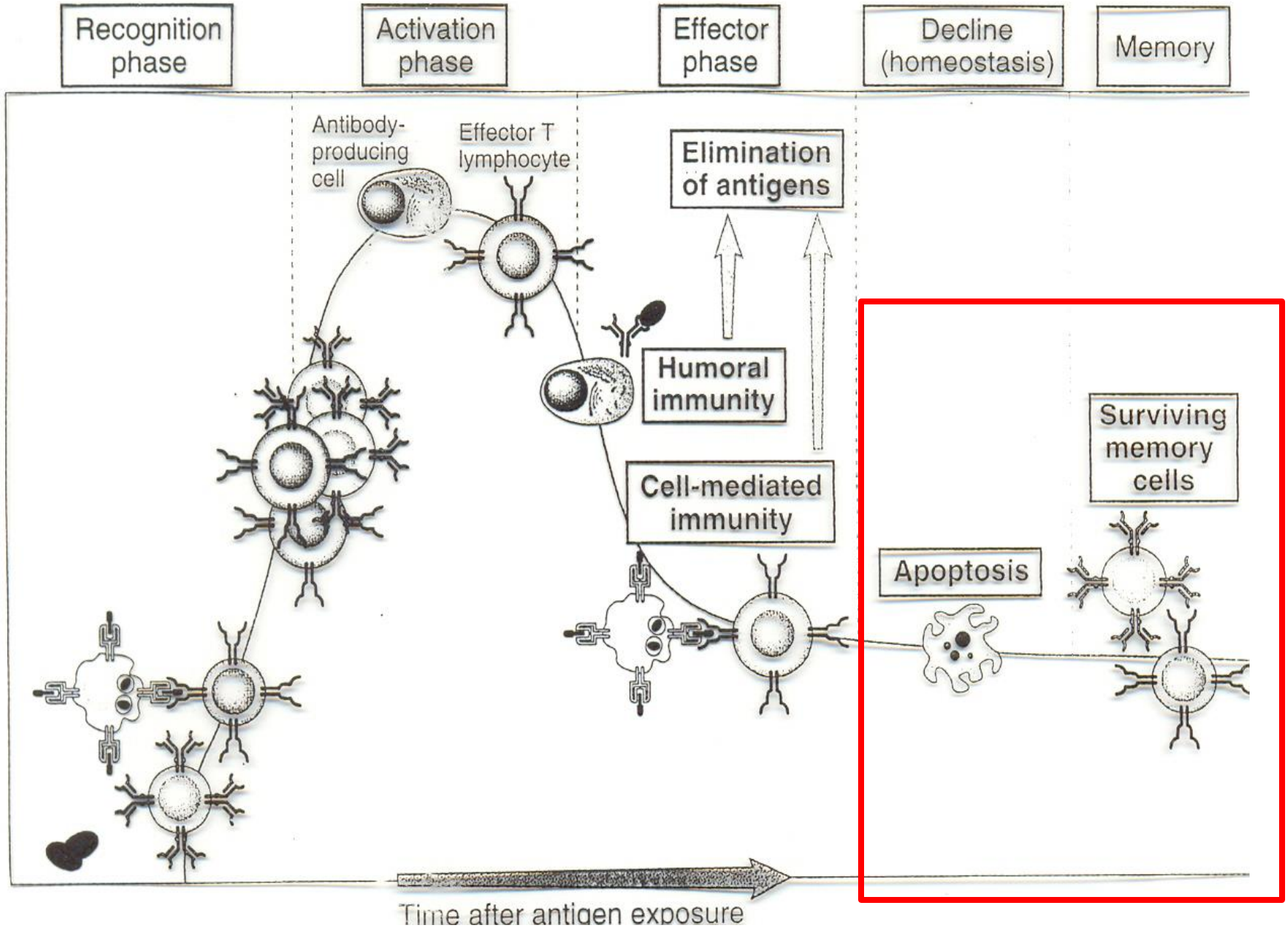


10-2 A indução e as fases efetoras da imunidade mediada por células.

As células T CD4+ e as células T CD8+ reconhecem os peptídeos que são derivados dos antígenos de proteínas e apresen-


Proliferation and survival
IL-1
Naive T cell
Antigen and TGFβ
IL-1R
IL-18R
ST2
T_{Reg} cell
Antigen and IL-12
Antigen and IL-4
Antigen and IL-6, TGFβ, IL-1β and IL-23
IL-18R
ST2
IL-1R
Early T_H1 cell
Early T_H2 cell
Early T_H17 cell
IL-18
Plus STAT4 inducer (IL-12)
IL-33
Plus STAT5 inducer (IL-2, IL-7 or TSLP)
IL-1
Plus STAT3 inducer (IL-6, IL-21 or IL-23)
IL-18R
T-bet
ST2
GATA3
RORγt
IL-1R
Committed effector T_H1 cell
Committed effector T_H2 cell
Committed effector T_H17 cell
Proliferation and IFNγ production
Proliferation and IL-5 and IL-13 production
IL-17 production


Controle da infecção
Células NK
Células T
IL-12
IFN-γ
CD40L,
IFN-γ
Erradicação da infecção
Neutrófilos
Macrófagos
Macrófagos
Imunidade inata
Imunidade adaptativa
Número de bactérias viáveis (valores relativos)
0
7
14
Dias após a infecção


Recognition phase
Activation phase
Effector phase
Decline (homeostasis)
Memory
Antibody-producing cell
Effector T lymphocyte
Elimination of antigens
Humoral immunity
Cell-mediated immunity
Apoptosis
Surviving memory cells
Time after antigen exposure

Obrigado!

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