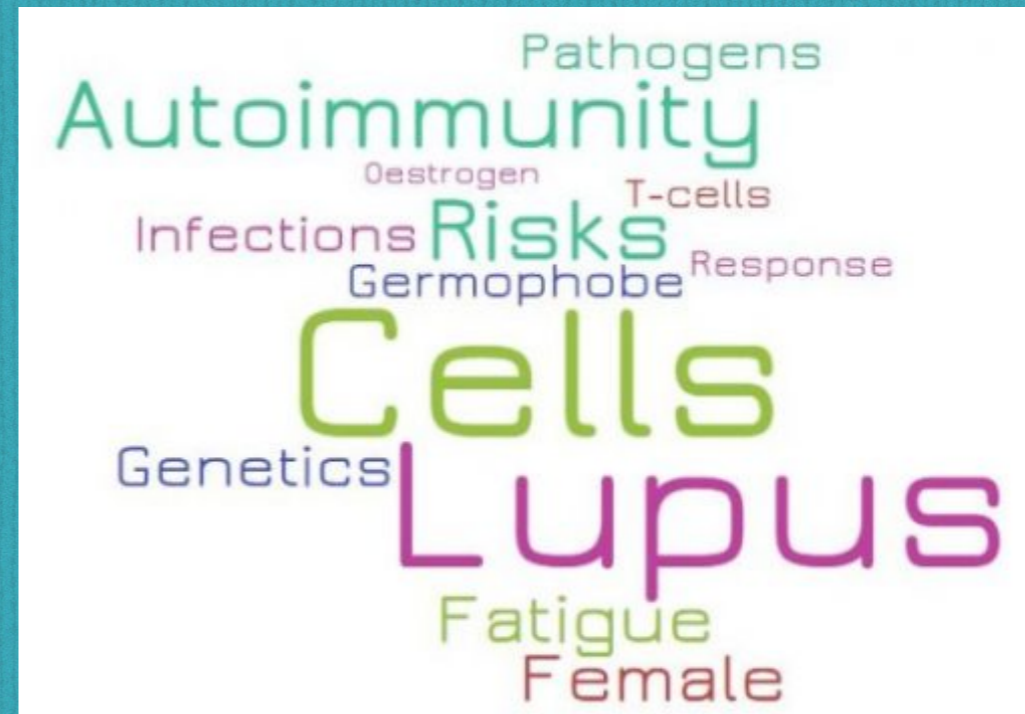


Curso de Farmacia
Disciplina BMI0165 - Imunologia Basica



Tolerância e autoimunidade

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Lab. Imunogenetica/Dep. Imunologia/ICB/USP

Tolerancia imunologica & Homeostasia

A maior função das células do SI é

- o reconhecimento e eliminação de patógenos/dano
- distinguir o "próprio (self)" do "non-próprio (non-self)"
- distinguir o "non patogênico" do "patogênico"

A resposta imune prevê uma fase de ativação e uma de desativação para voltar a homeostasia (mecanismos efetores vs regulatórios)

Temos **evidências** que o SI tolera

- Ag próprios
- Ag alimentares
- Ag ambientais
- microbiota

Porque em **ausência de tolerância**:

- doenças autoimunes (mas tbm rejeição transplante & cia.)
- reações alérgicas a alimentos
- reações alérgicas a Ag ambientais
- doença inflamatória intestinal

Tolerancia imunologica & Homeostasia

Tolerância imunológica é a não resposta a um Ag,
induzida pela exposição previa a este Ag

Sabemos que: é um processo

ATIVO

Ag-especifico

Individual (multifatorial)

Não sabemos todos os
mecanismos e detalhes

Fatores que promovem tolerancia

- Contexto (baixo nível de co-estimulação e citocinas) (**Ag próprio e non**)
- Elevada persistencia/dose do Ag (**Ag próprio e non**)
- Algumas vias de entradas (mucosa, intravenosa) (**Ag non próprios**)
- Ausência de adjuvantes (**Ag non próprios**)

Tolerância a Ag próprios

- Não resposta a Ag “próprios”
- Tolerância a Ag próprios é um estado imunitário mantido por mecanismos de **tolerância central**: eliminação de linfócitos auto-reativos por **deleção clonal** (Timo e MO)
- Os linfócitos que escapam á tolerância central nos órgãos linfóides primários são eliminados ou inibido nos órgãos linfóides periféricos, através de mecanismos de **tolerância periférica**

Tolerância a Ag próprios

Algumas considerações

- O processo que gera o repertório de BCR/Ig e TCR é aleatório e independente do Ag —> *ha o risco dos linfócitos reagirem contra as células e tecidos próprios!*
- A tolerância central pode falhar:
- ✓ Não todos os Ag próprios são apresentados nos OL1
- ✓ A deleção é induzida quando a afinidade entre REC/Ag próprio é elevada, e quando não atinge o limiar?
- A tolerância é Ag-específica!
- Alguns Ag próprios podem ser ignorados pelo S.I. (Ag isolados do S.I.)

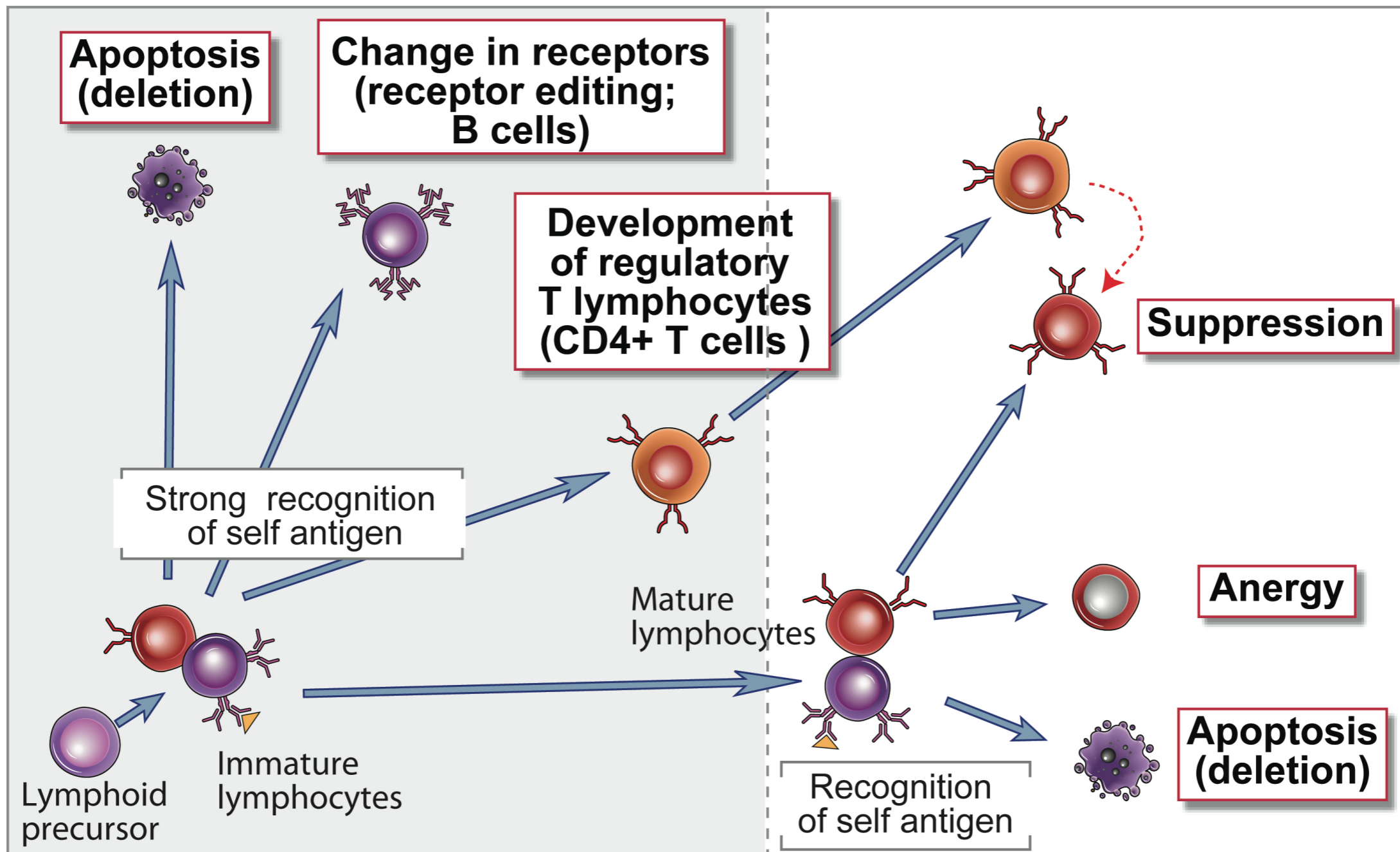
Tolerância a Ag próprios

- ✓ Deleção
- ✓ Edição (B)
- ✓ desenvolv. Treg

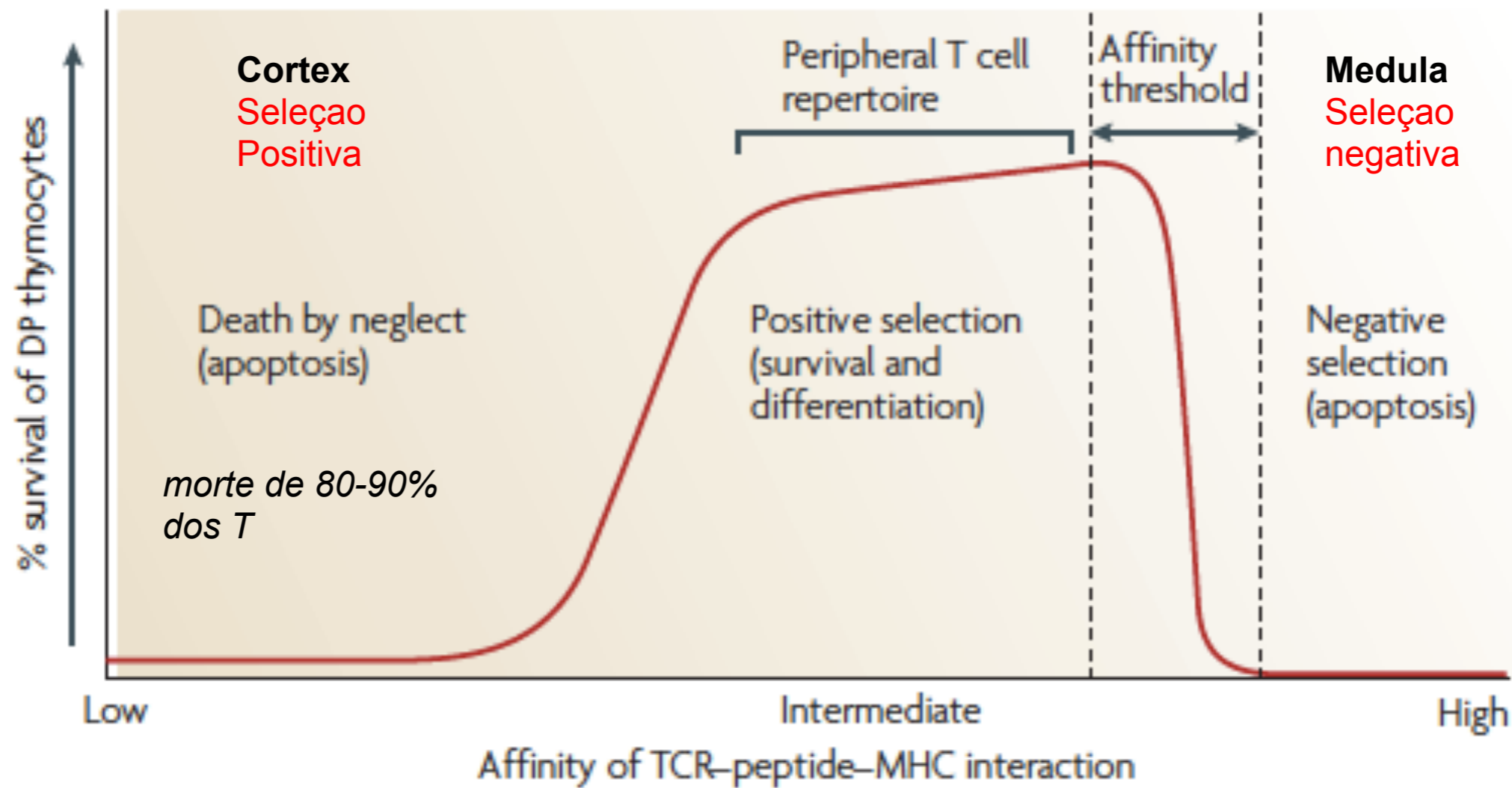
CENTRAL
(M.O., timo)

PERIFERICA
(tecidos perifericos)

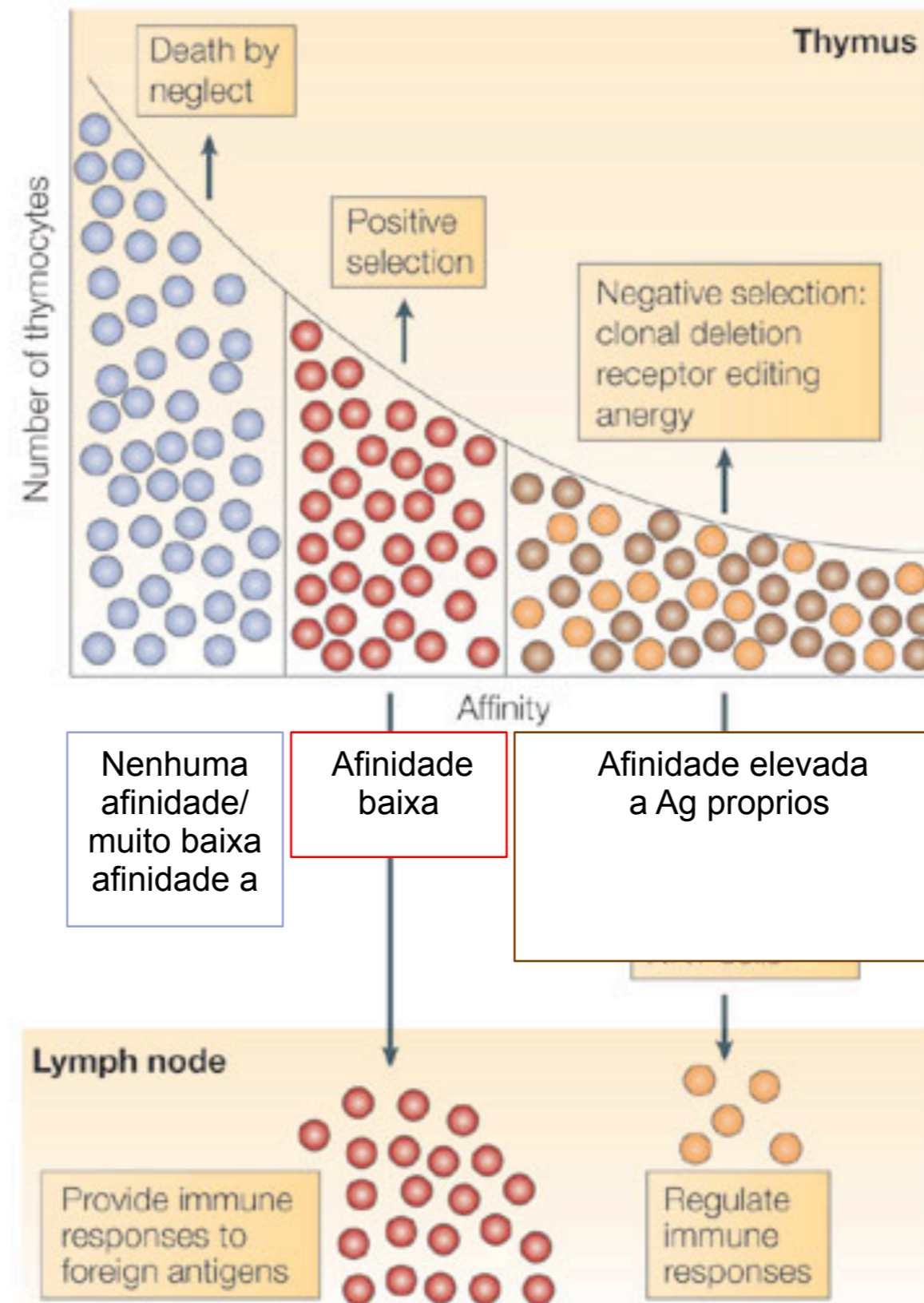
- ✓ Deleção
- ✓ Anergia
- ✓ Sopressao



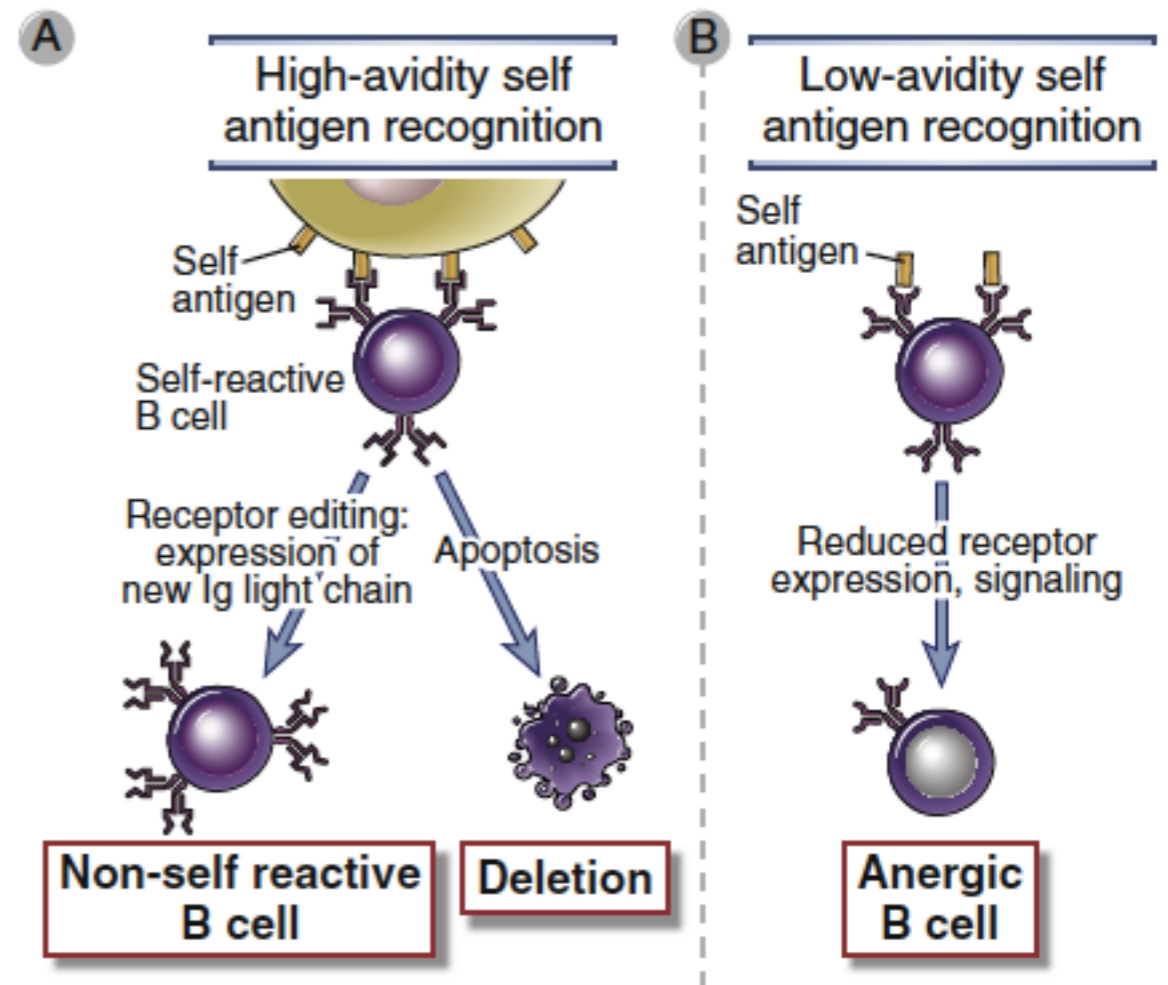
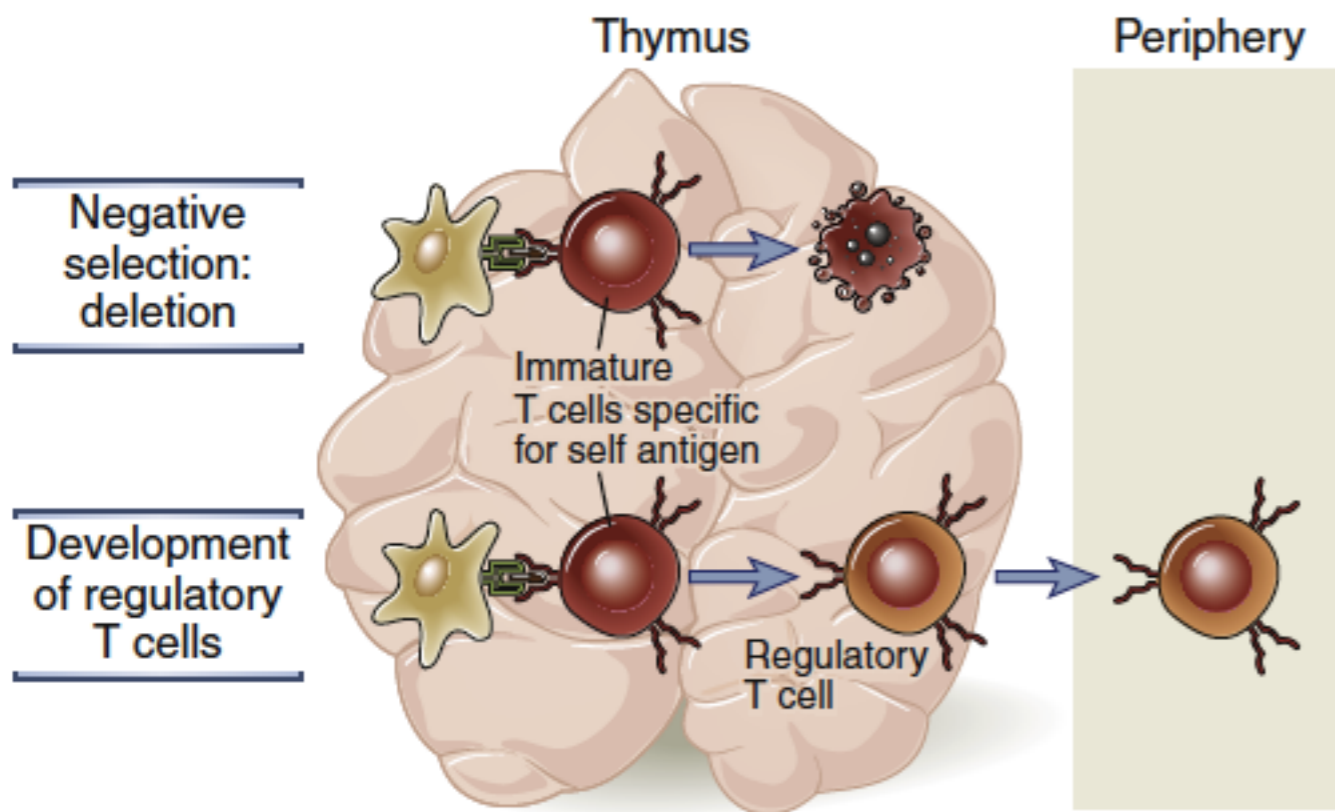
Tolerância central



Tolerância central



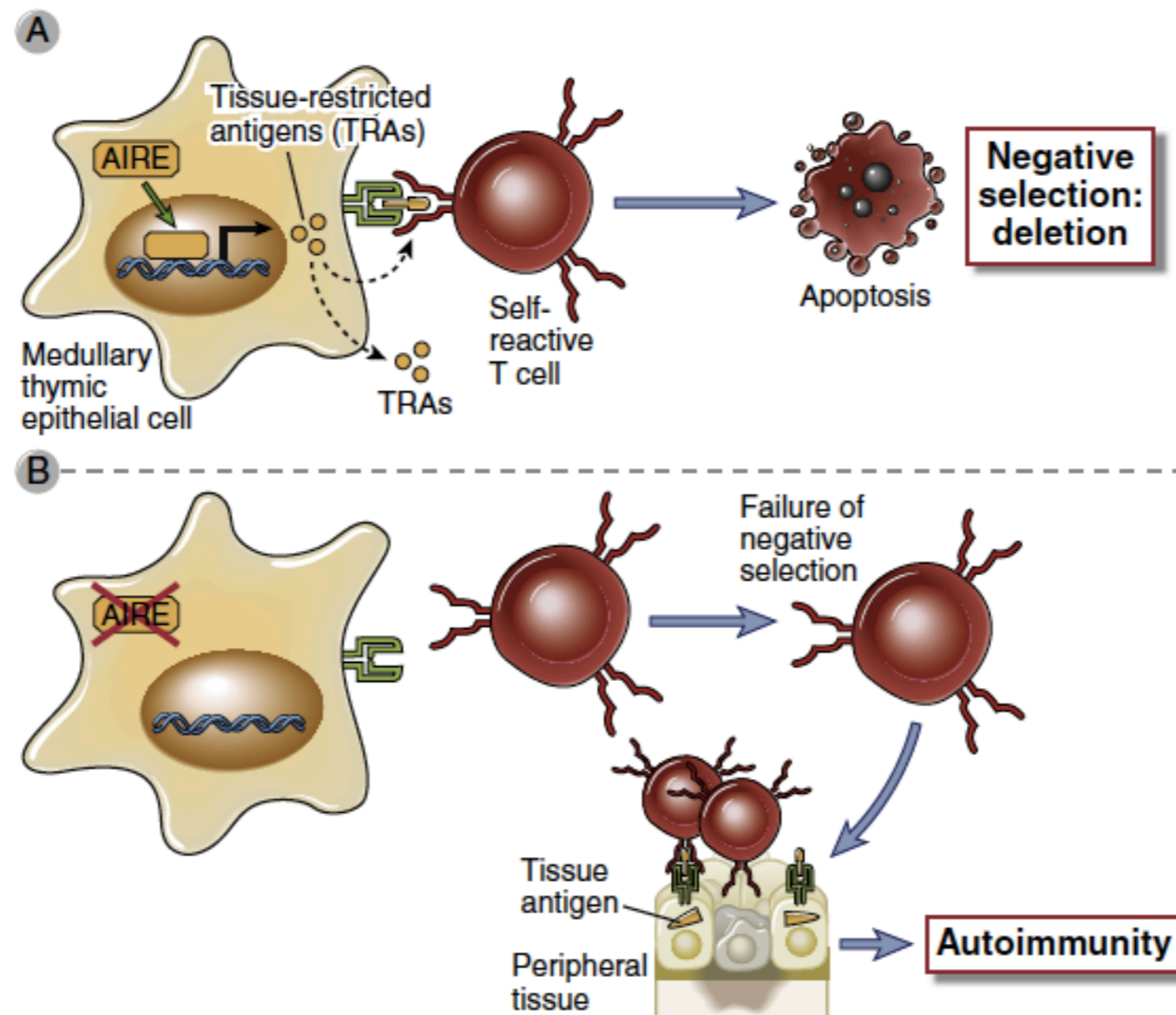
Tolerância central



Tolerância a Ag próprios: como “educar” no Timo?

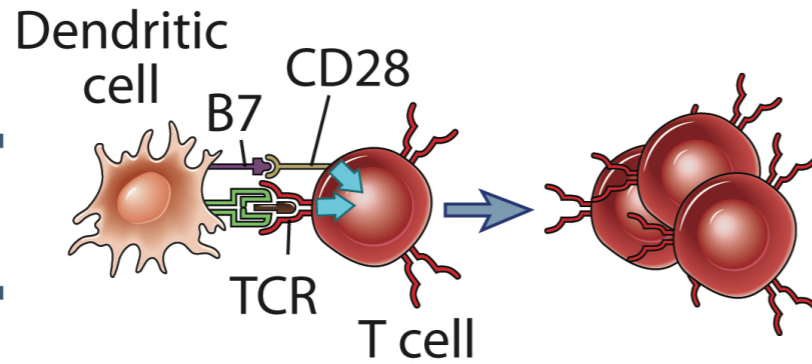
Algumas considerações:

- como posso educar os linfócitos a tolerar TODOS os Ag próprios no Timo?
- tem proteínas que tem expressão tecido/órgão específica



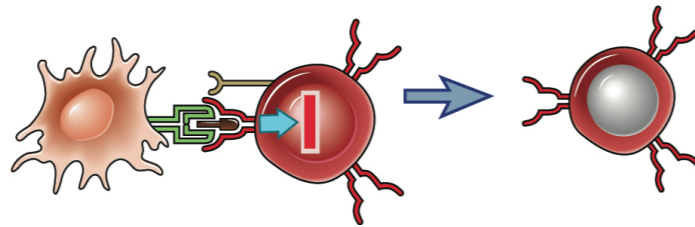
Tolerância periférica dos T

Normal T cell response



Effector and memory T cells

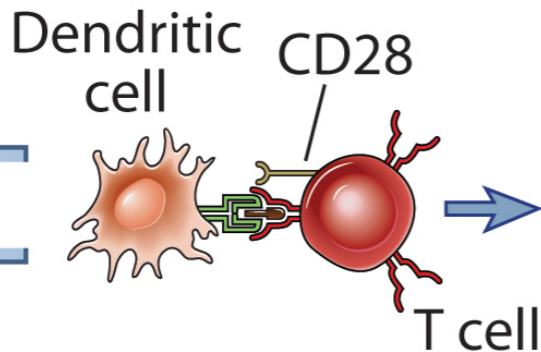
Anergy



Functional unresponsiveness

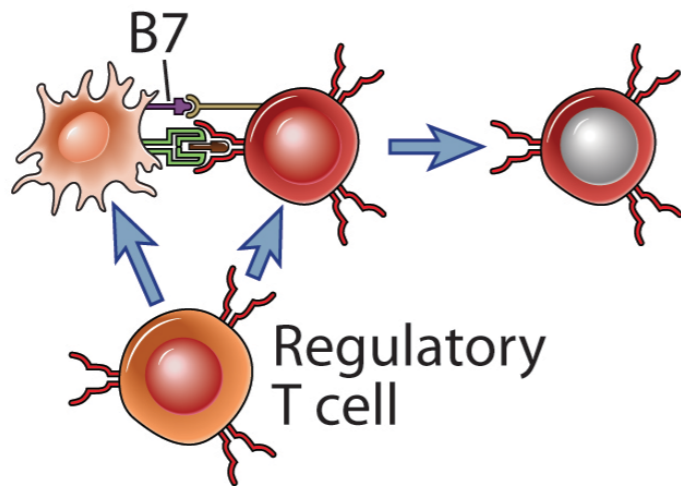
Sem moléculas co-estimuladoras

Deletion



Apoptosis (activation-induced cell death)

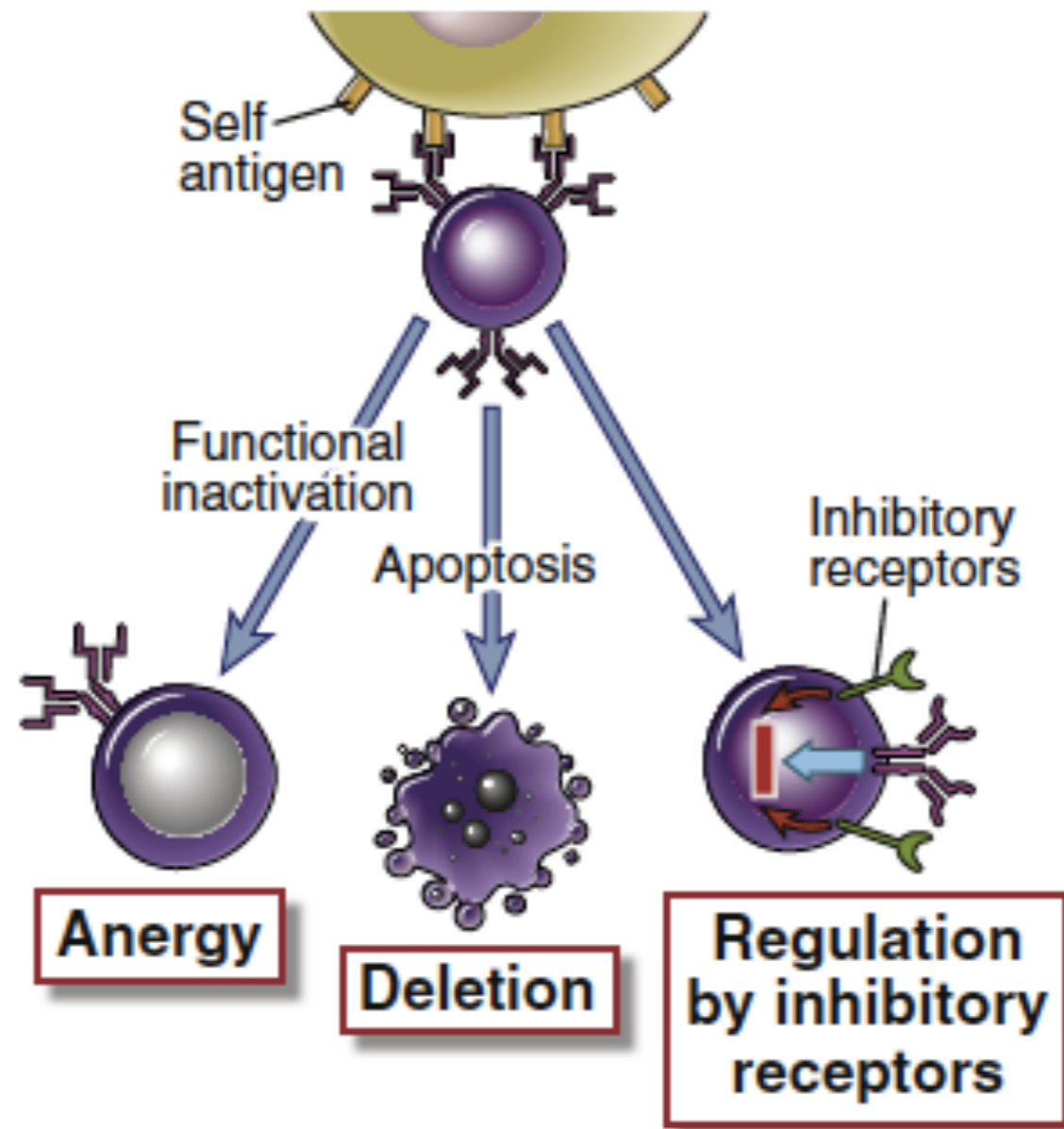
Suppression



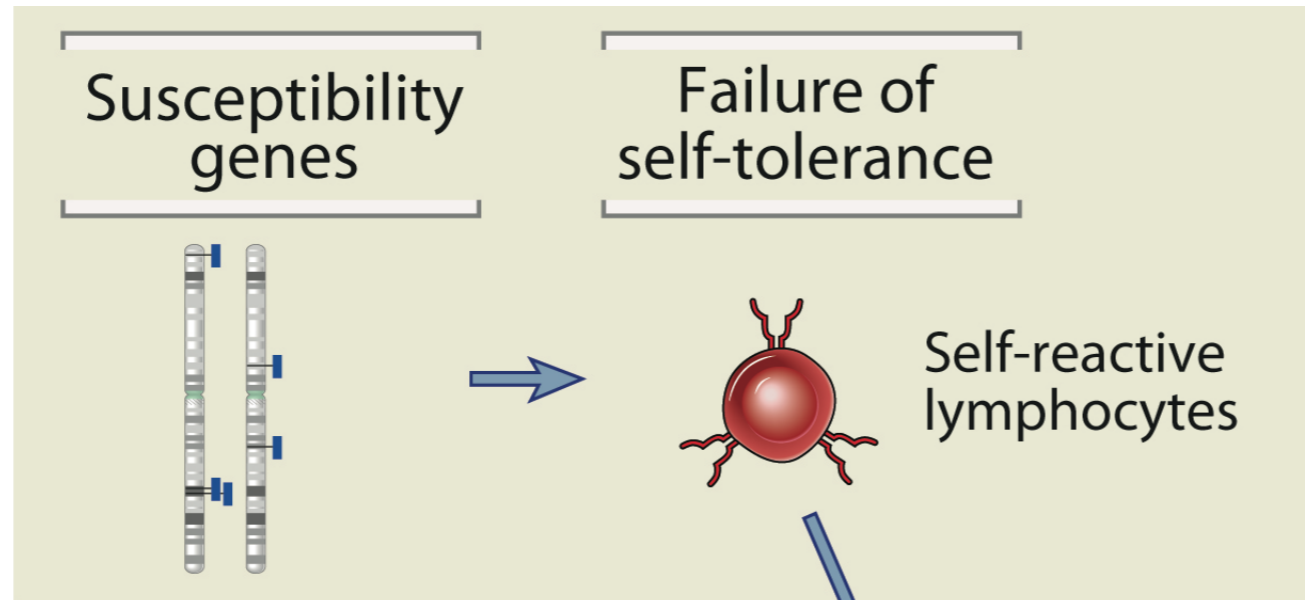
Block in activation

Inibição por Treg

Tolerância periférica dos B

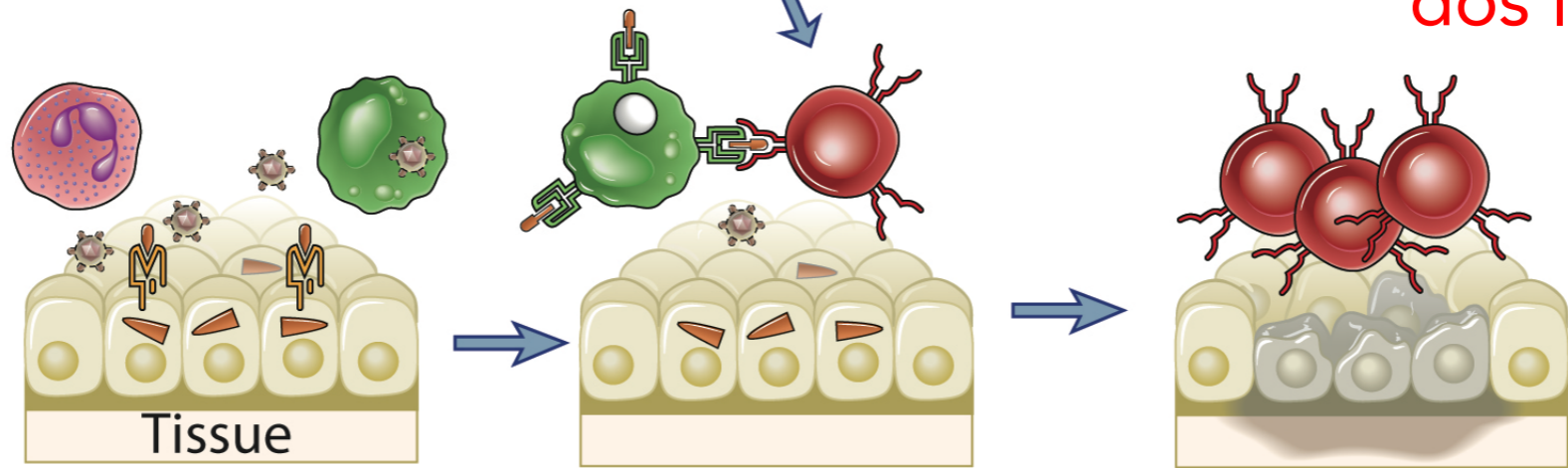


Autoimunidade



- ✓ Perda de tolerancia a Ag propios
- ✓ Falha nos mecanismos de tolerancia (educação dos linfocitos)

Infection, injury



Infections, tissue injury

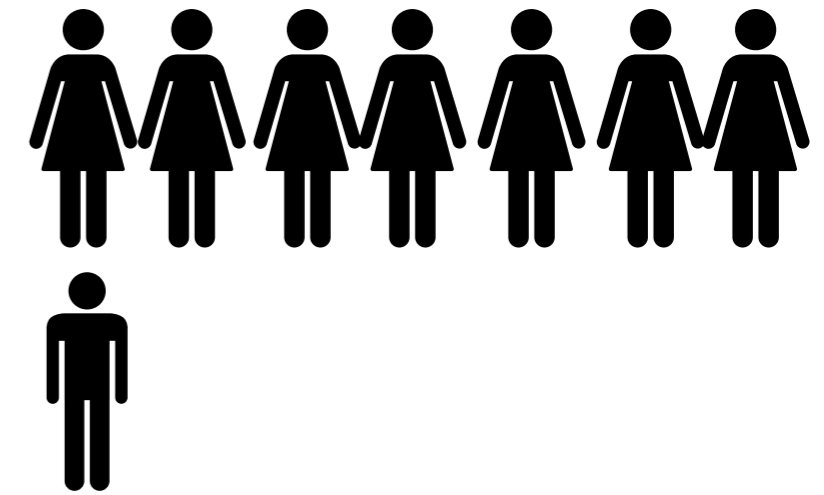
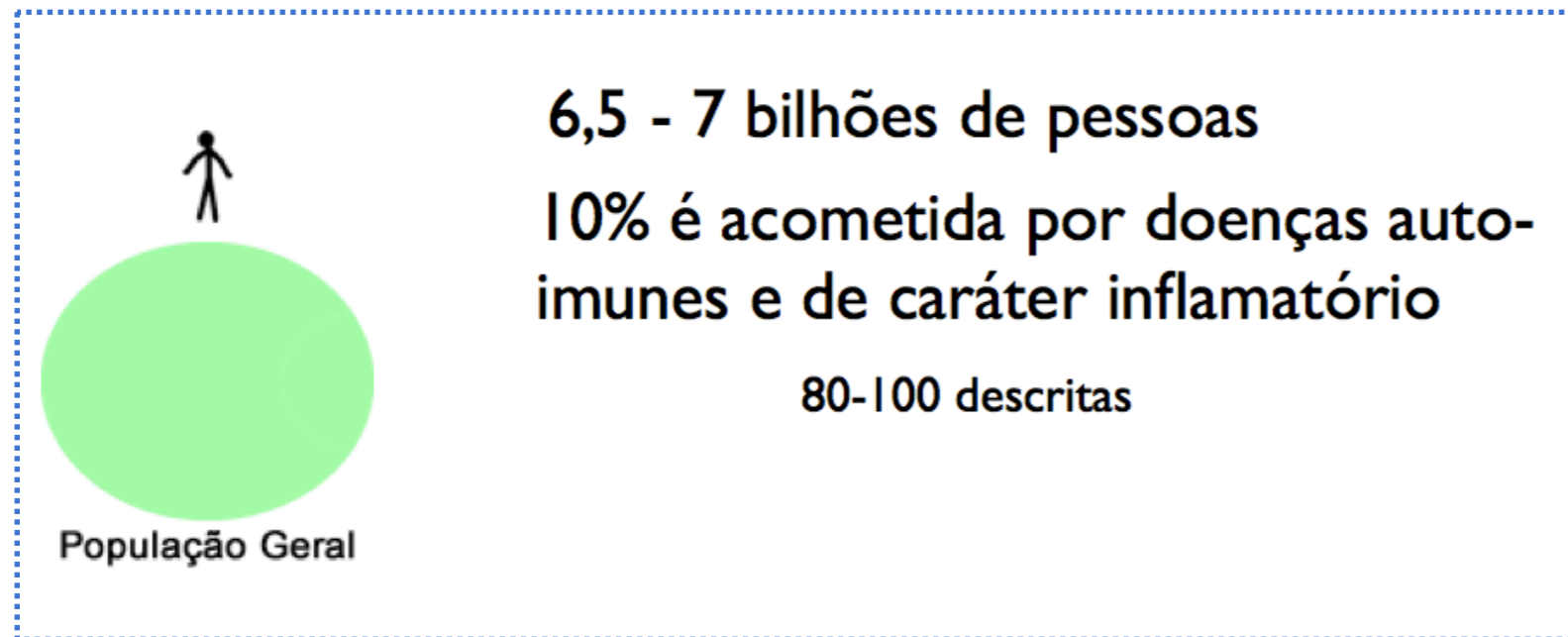
Activation of tissue APCs

Influx of self-reactive lymphocytes into tissues

Activation of self-reactive lymphocytes

Tissue injury: autoimmune disease

Doenças Autoimunes



horror autotoxicos

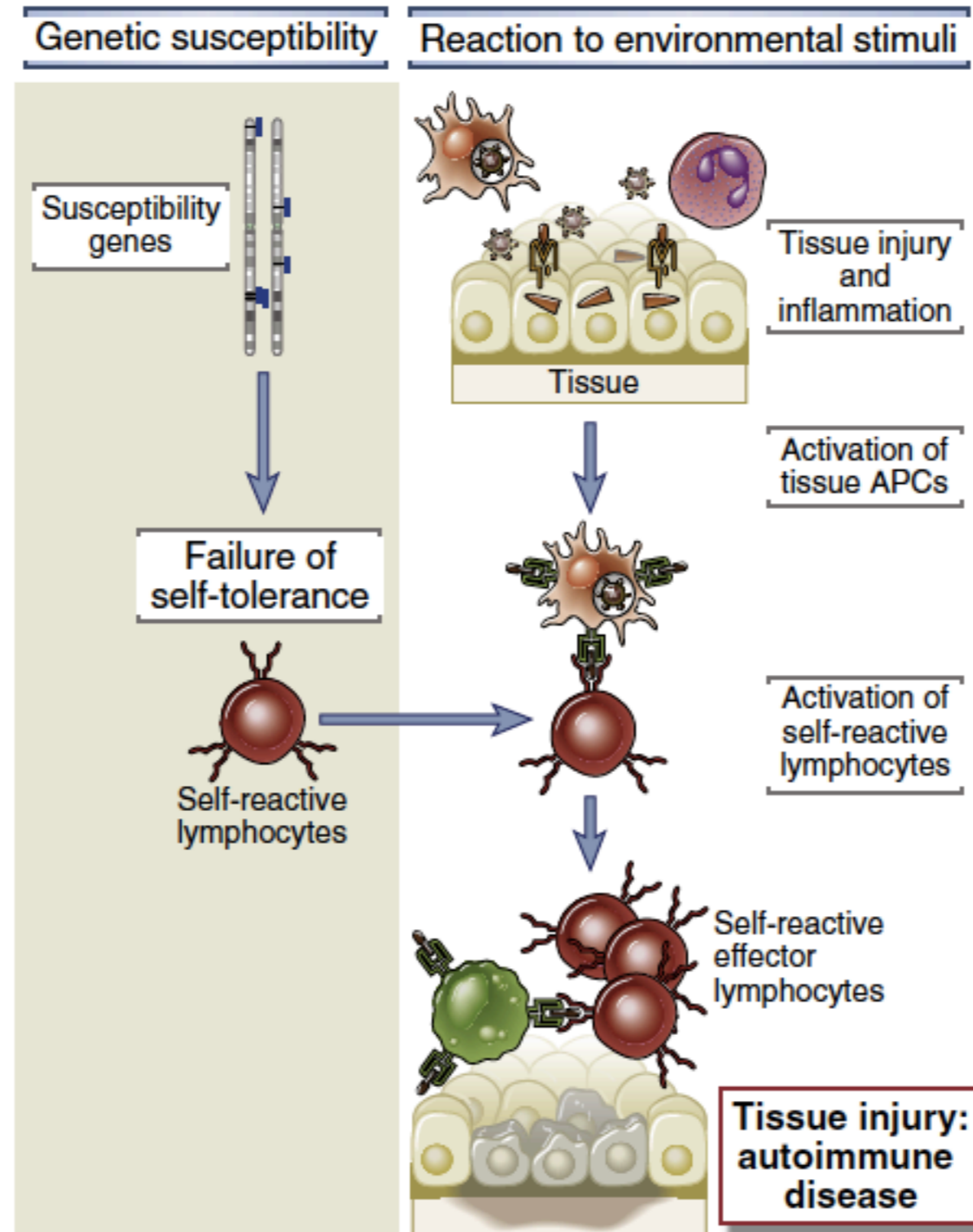
Falha do mecanismo de Auto-tolerância

Linfócitos auto-reativos
são ativados

As respostas imunológicas se voltam contra o próprio organismo



Doenças Autoimunes



- ✓ Perda de tolerância a Ag próprios
- ✓ Falha nos mecanismos de tolerancia

- ✓ trigger non genetico
- ✓ inflamação

Doenças autoimunes

TABLE 16-1 Some autoimmune diseases in humans

Disease	Self antigen/Target gene	Immune effector
ORGAN-SPECIFIC AUTOIMMUNE DISEASES		
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T _H 1 cells, auto-antibodies
Idiopathic thrombocytopenia purpura	Platelet membrane proteins	Auto-antibodies
Type 1 diabetes mellitus	Pancreatic beta cells	T _H 1 cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
SYSTEMIC AUTOIMMUNE DISEASES		
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T _H 1 cells and T _C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjögren's syndrome	Salivary gland, liver, kidney, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antibodies, immune complexes
Immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX)	Multiorgan, loss of <i>FoxP3</i> gene	Missing regulatory T cells
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)	Multiorgan, loss of <i>aire</i> gene	Defective central tolerance

Doenças autoimunes: fatores genéticos

TABLE 15-4 Examples of Single-Gene Mutations That Cause Autoimmune Diseases

Gene	Phenotype of Mutant or Knockout Mouse	Mechanism of Failure of Tolerance	Human Disease?
<i>AIRE</i>	Destruction of endocrine organs by antibodies, lymphocytes	Failure of central tolerance	Autoimmune polyendocrine syndrome (APS)
<i>C4</i>	SLE	Defective clearance of immune complexes; failure of B cell tolerance	SLE
<i>CTLA4</i>	Lymphoproliferation; T cell infiltrates in multiple organs, especially heart; lethal by 3-4 weeks	Failure of anergy in CD4 ⁺ T cells; defective function of regulatory T cells	CTLA-4 polymorphisms associated with several autoimmune diseases
<i>FAS/FASL</i>	Anti-DNA and other autoantibodies; immune complex nephritis; arthritis; lymphoproliferation	Defective deletion of anergic self-reactive B cells; reduced deletion of mature CD4 ⁺ T cells	Autoimmune lymphoproliferative syndrome (ALPS)
<i>FOXP3</i>	Multiorgan lymphocytic infiltrates, wasting	Deficiency of functional regulatory T cells	IPEX
<i>IL2, IL2Rα/β</i>	Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies	Defective development, survival, or function of regulatory T cells	None known
<i>SHP1</i>	Multiple autoantibodies	Failure of negative regulation of B cells	None known

Doenças autoimunes: fatores genéticos

TABLE 15-2 Association of HLA Alleles with Autoimmune Disease

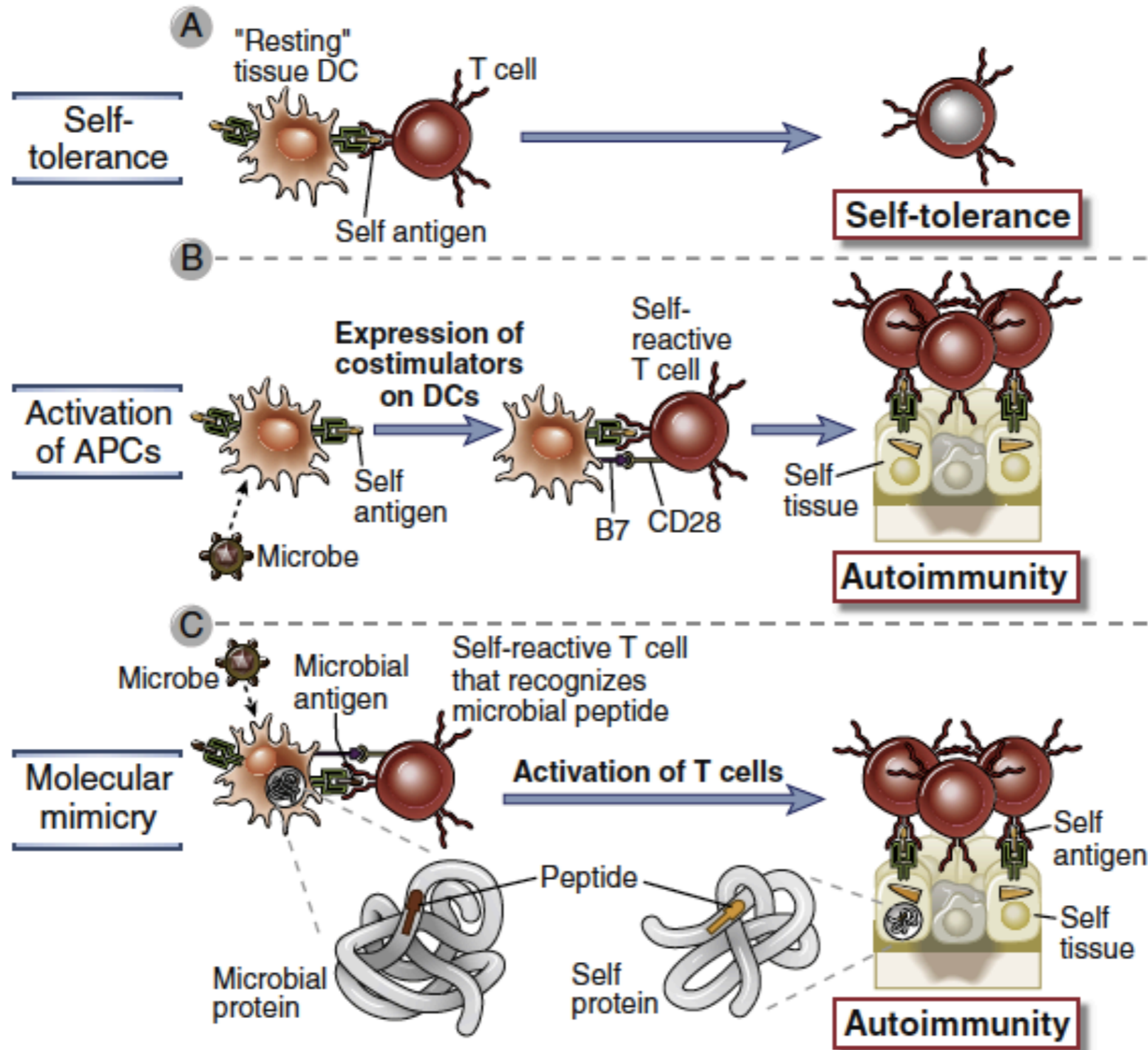
Disease	HLA Allele	Odds Ratio ¹
Rheumatoid arthritis (anti-CCP Ab positive) ²	<i>DRB1</i> , 1 SE allele ³	4
	<i>DRB1</i> , 2 SE alleles	12
Type 1 diabetes	<i>DRB1*0301-DQA1*0501-DQB1*0201</i> haplotype	4
	<i>DRB1*0401-DQA1*0301-DQB1*0302</i> haplotype	8
	<i>DRB1*0301/0401</i> heterozygotes	35
Multiple sclerosis	<i>DRB1*1501</i>	3
Systemic lupus erythematosus	<i>DRB1*0301</i>	2
	<i>DRB1*1501</i>	1.3
Ankylosing spondylitis	<i>B*27</i> (mainly <i>B*2705</i> and <i>B*2702</i>)	100-200
Celiac disease	<i>DQA1*0501-DQB1*0201</i> haplotype	7

TABLE 15-3 Selected Non-HLA Genetic Polymorphisms Associated with Autoimmune Diseases

Gene of Interest	Function	Diseases
Genes Involved in Immune Regulation		
<i>PTPN22</i>	Protein tyrosine phosphatase; role in T and B cell receptor signaling	RA, T1D, IBD
<i>CD2/CD58</i>	Costimulation of T cells	RA, MS
<i>IL23R</i>	Component of IL-23 receptor; role in generation and maintenance of T _H 17 cells	IBD, PS, AS
<i>IL10</i>	Downregulates expression of costimulators, MHC molecules, IL-12 in dendritic cells; inhibits T _H 1 responses	IBD, SLE, T1D
<i>CTLA4</i>	Inhibitory receptor of T cells, effector molecule of regulatory T cells	T1D, RA
<i>IL2/IL21</i>	Growth and differentiation factors for T cells; IL-2 is involved in maintenance of functional Tregs	IBD, CeD, RA, T1D, MS
<i>IL12B</i>	p40 subunit of IL-12 (T _H 1-inducing cytokine) and IL-23 (T _H 17-inducing cytokine)	IBD, PS
<i>BLK</i>	B lymphocyte tyrosine kinase, involved in B cell activation	SLE, RA
<i>IL2RA</i>	IL-2 receptor α chain (CD25); role in T cell activation and maintenance of regulatory T cells	MS, T1D
Genes Involved in Responses to Microbes		
<i>NOD2</i>	Cytoplasmic sensor of bacteria	IBD
<i>ATG16</i>	Autophagy (destruction of microbes, maintenance of epithelial cell integrity)	IBD
<i>IRF5, IFIH1</i>	Type I interferon responses to viruses	SLE

Doenças autoimunes: infecções

Infeções virais e bacteriana podem contribuir no desenvolvimento de doenças autoimunes



Doenças autoimunes: infecções

TABLE 20-3 MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS

Protein*	Residue†	Sequence‡
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	147	T K E S L V I I S
Insulin receptor	764	N K E S L V I S E
<i>Klebsiella pneumoniae</i> nitrogenase	186	S R Q T D R E D E
HLA-B27 molecule	70	K A Q T D R E D L
Adenovirus 12 E1B	384	L R R G M F R P S Q C N
α-Gliadin	206	L G Q G S F R P S Q Q N
Human immunodeficiency virus p24	160	G V E T T T P S
Human IgG constant region	466	G V E T T T P S
Measles virus P3	13	L E C I R A L K
Corticotropin	18	L E C I R A C K
Measles virus P3	31	E I S D N L G Q E
Myelin basic protein	61	E I S F K L G Q E

*In each pair, the human protein is listed second. The proteins in each pair have been shown to exhibit immunologic cross-reactivity.

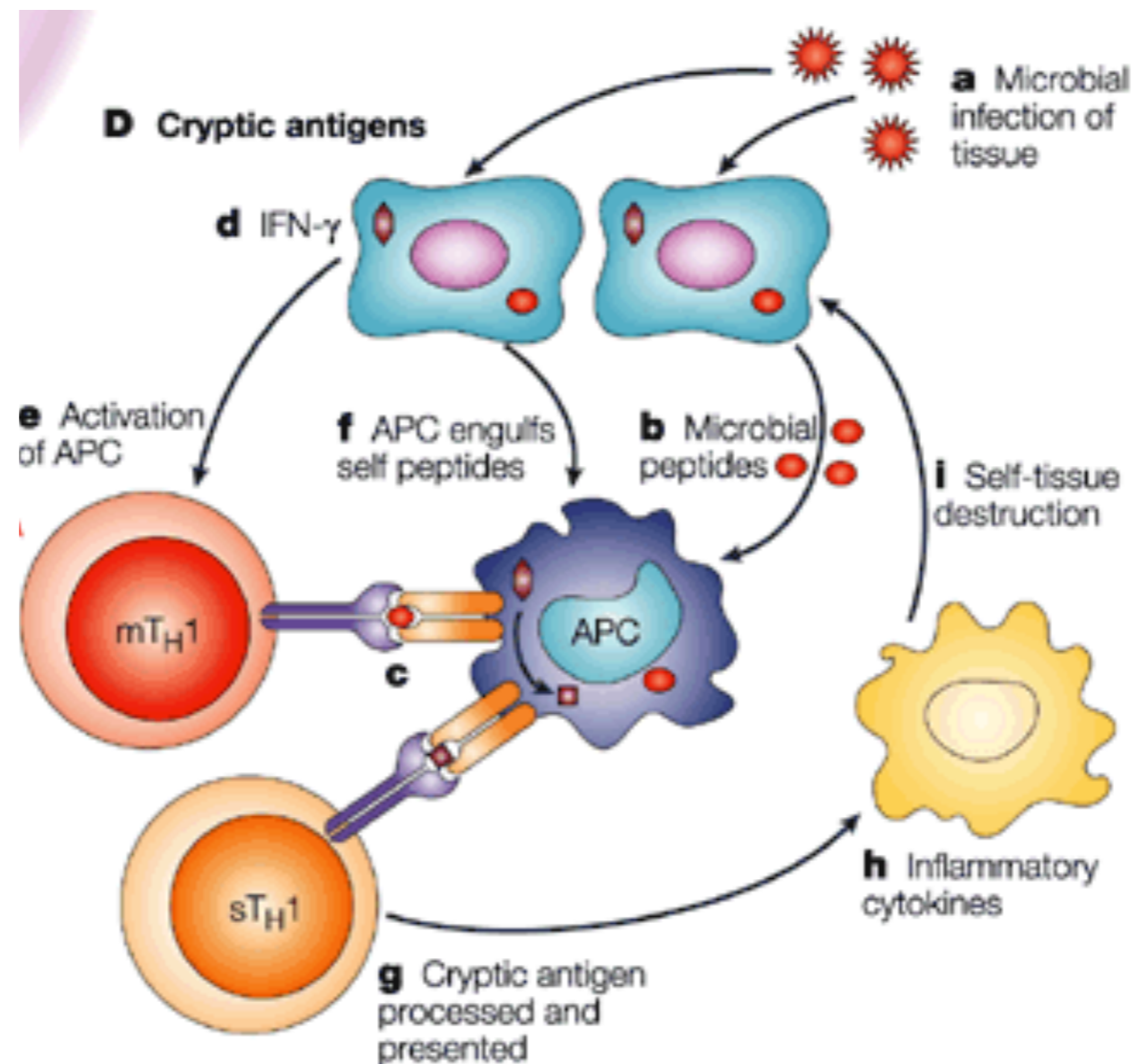
†Each number indicates the position in the intact protein of the amino-terminal amino acid in the listed sequence.

‡Amino acid residues are indicated by single-letter code. Identical residues are shown in blue.

SOURCE: Adapted from MBA Oldstone, 1987, *Cell* 50:819.

Doenças autoimunes: outros fatores

Alterações anatômicas nos tecidos causadas por dano mecânico (traumas), inflamação (secundaria a infecção ou isquemia) levam a exposição de Ag normalmente "sequestrados" (sítios imuno-privilegiados, ex: olhos, testis)



Doenças autoimunes: mecanismos de dano

Detalhes na próximas aulas (reações de hipersensibilidade II-IV)

Humoral mediated damage

- Ab block normal function

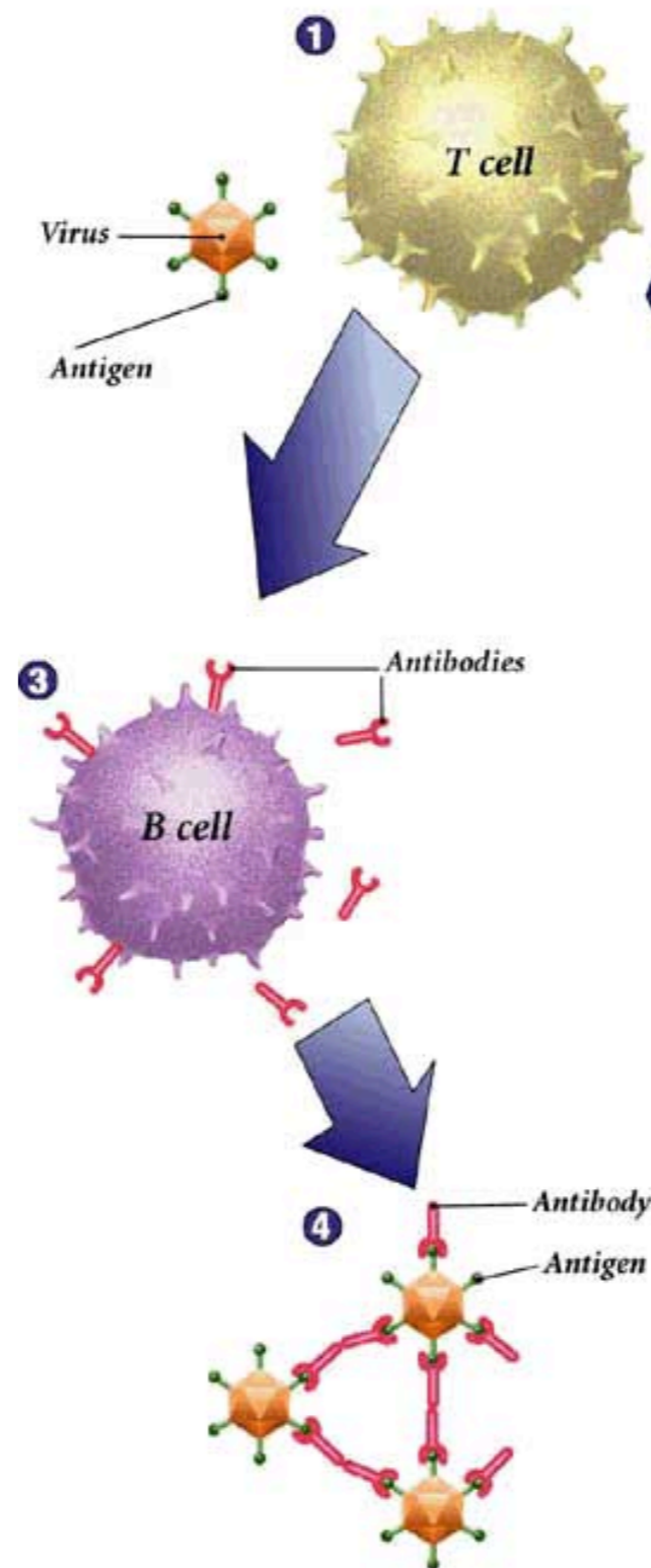
Myasthenia gravis: Ab bind acetylcholine receptors

- Ab stimulate inappropriate function

Graves' disease: Ab bind TSH-R activating unregulated thyroid hormone production

- Ag-Ab complexes affect function

Rheumatoid arthritis: IgM-IgG complexes deposited in joints inflammation



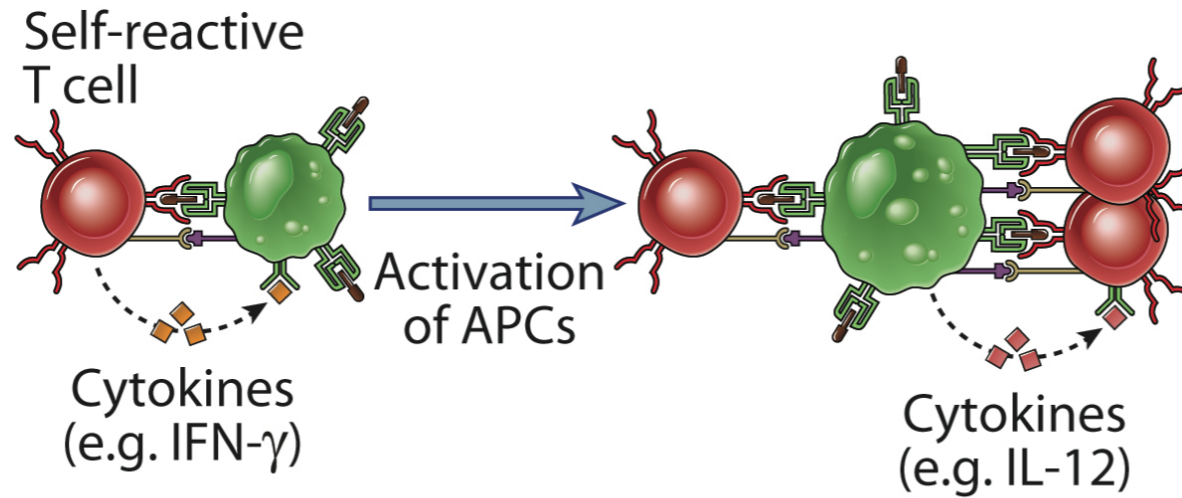
The diagram shows a T cell (yellow) interacting with a cluster of infected cells (pink). The T cell is positioned above the infected cells, and a line connects it to the label 'Infected cells'.

Cell mediated tissue destruction

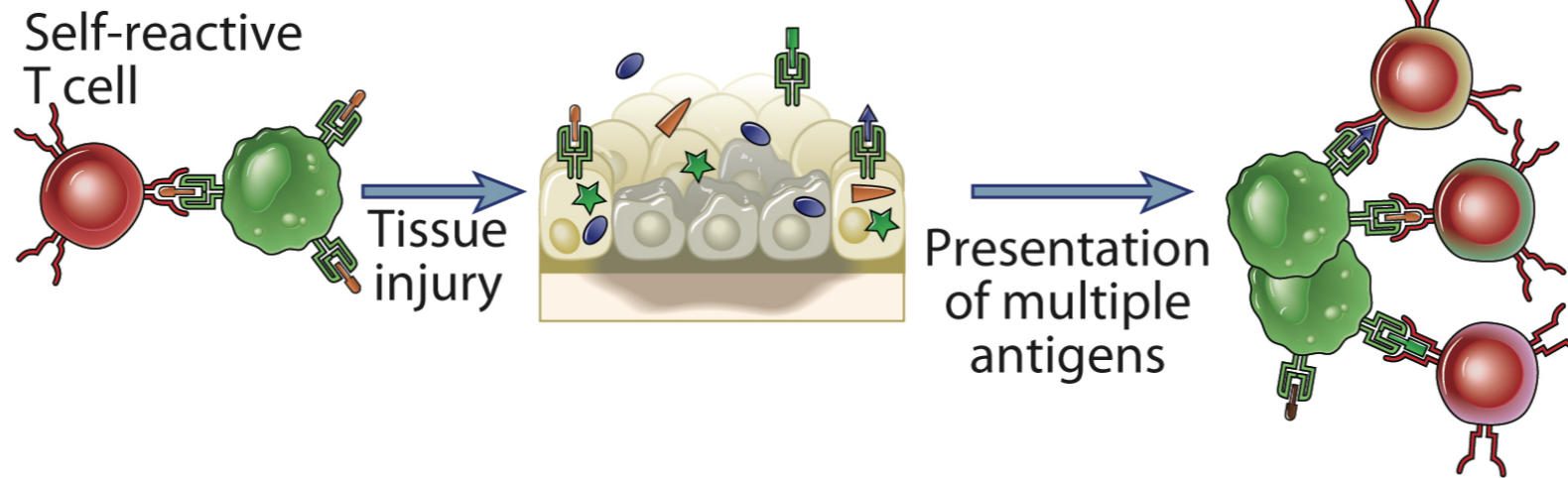
IDDM: CTLs destroy insulin-producing β -cells in pancreas

Doenças autoimunes

Amplification
of response



Epitope
spreading



**Increased
number of
self-reactive
clones**

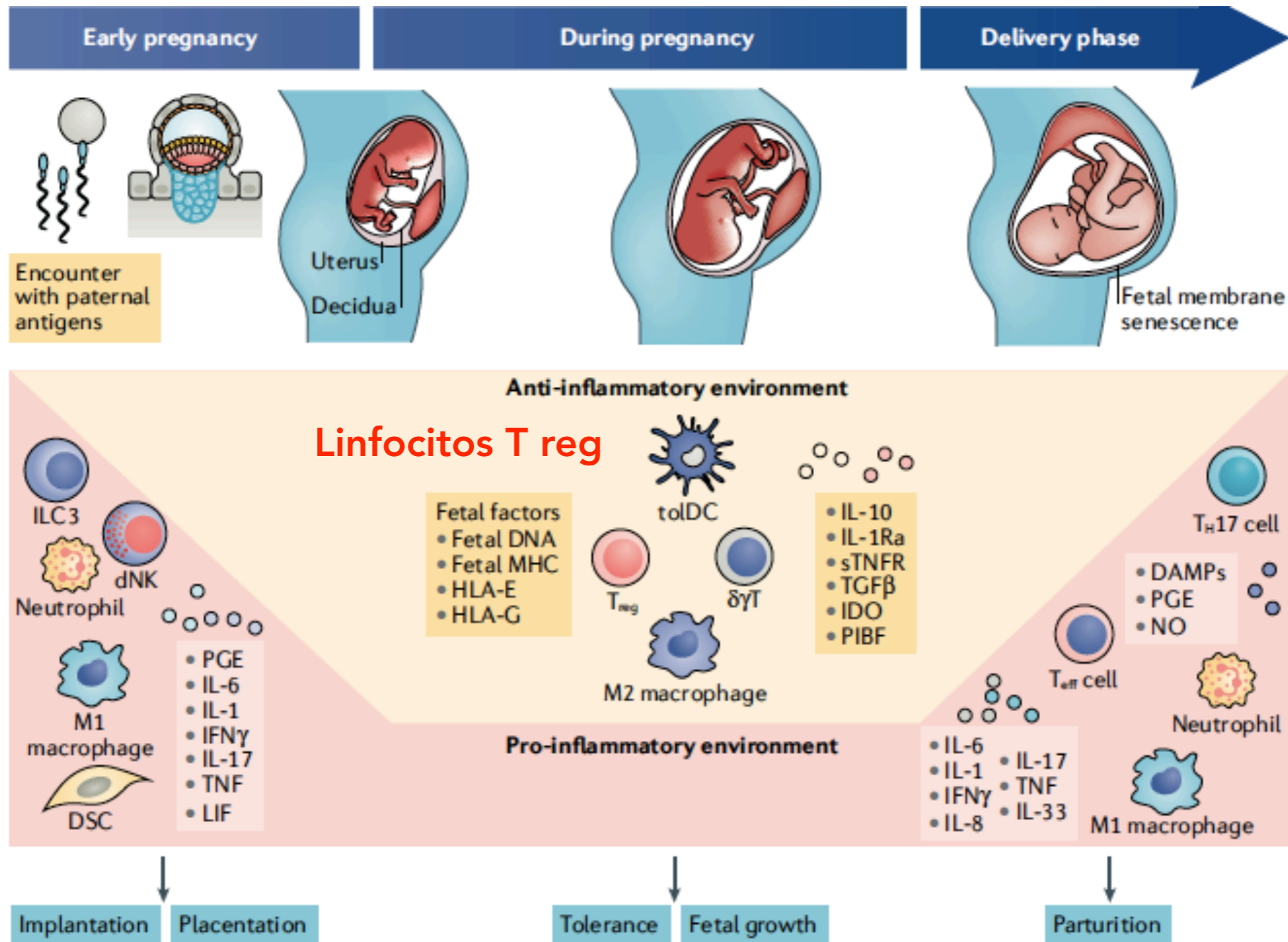
Outros problemas de Tolerância

- Gravidez
- Transfusão de sangue
- Transplante de órgão ou de MO

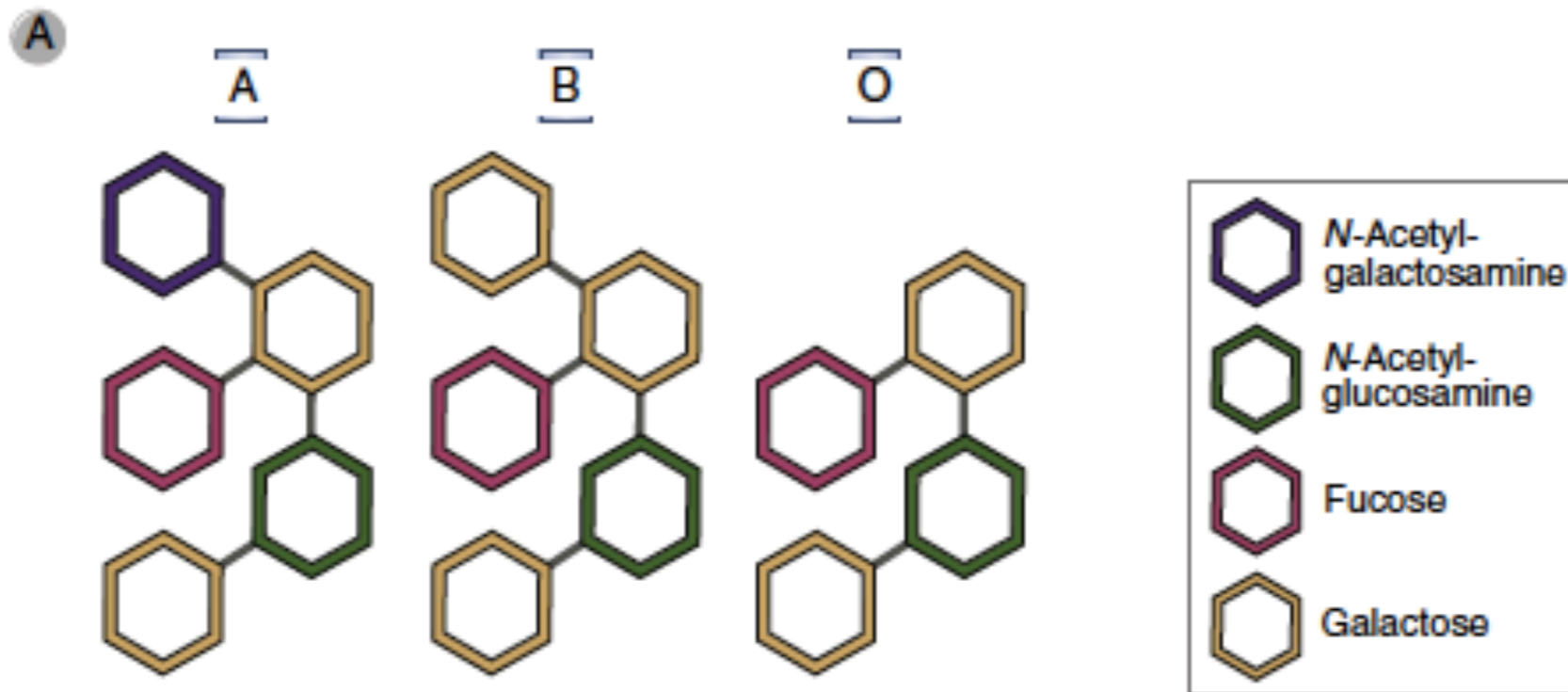
Gravidez

- Feto tem apenas 50% Ag próprios da mãe

TOLERANCIA



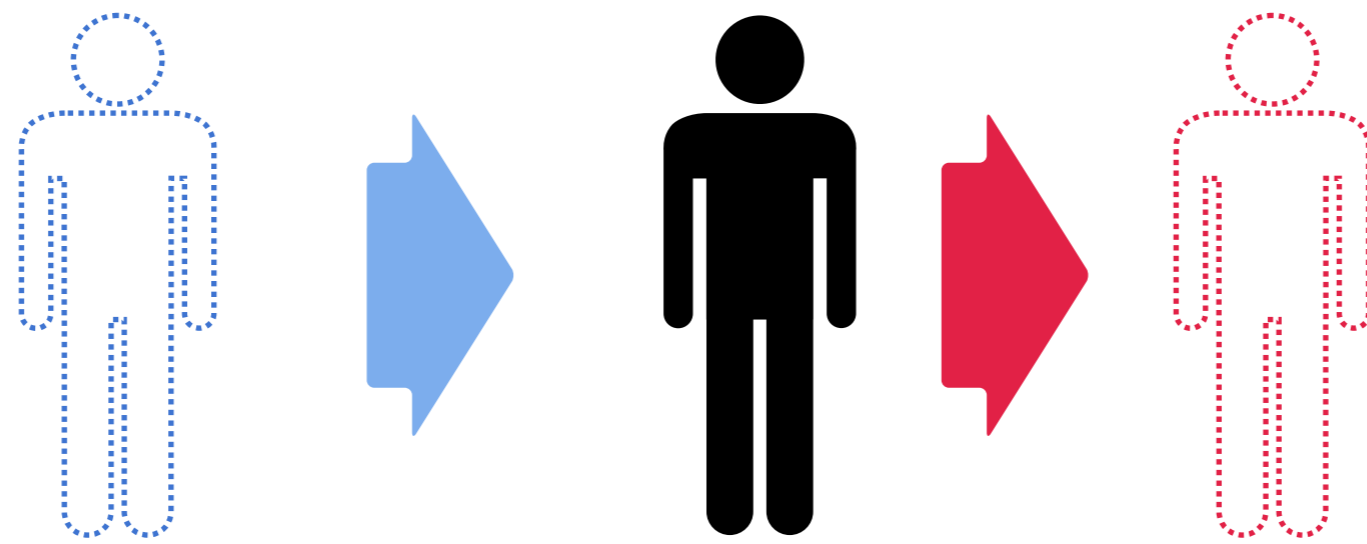
Grupo ABO e Transfusão de sangue



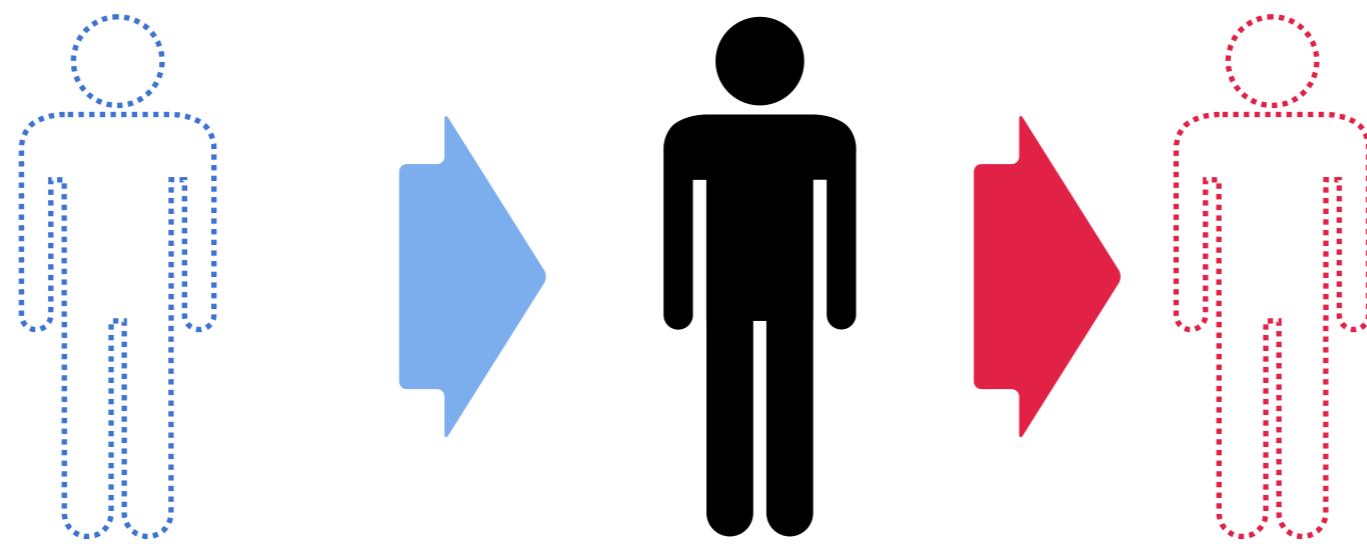
B

	Group A	Group B	Group AB	Group O
Red blood cell type	Type A 	Type B 	Type AB 	Type O
Antibodies present	Anti-B 	Anti-A 	None	Anti-A and Anti-B
Antigens present	A antigen 	B antigen 	A and B antigen 	None

Grupo ABO e Transfusão de sangue

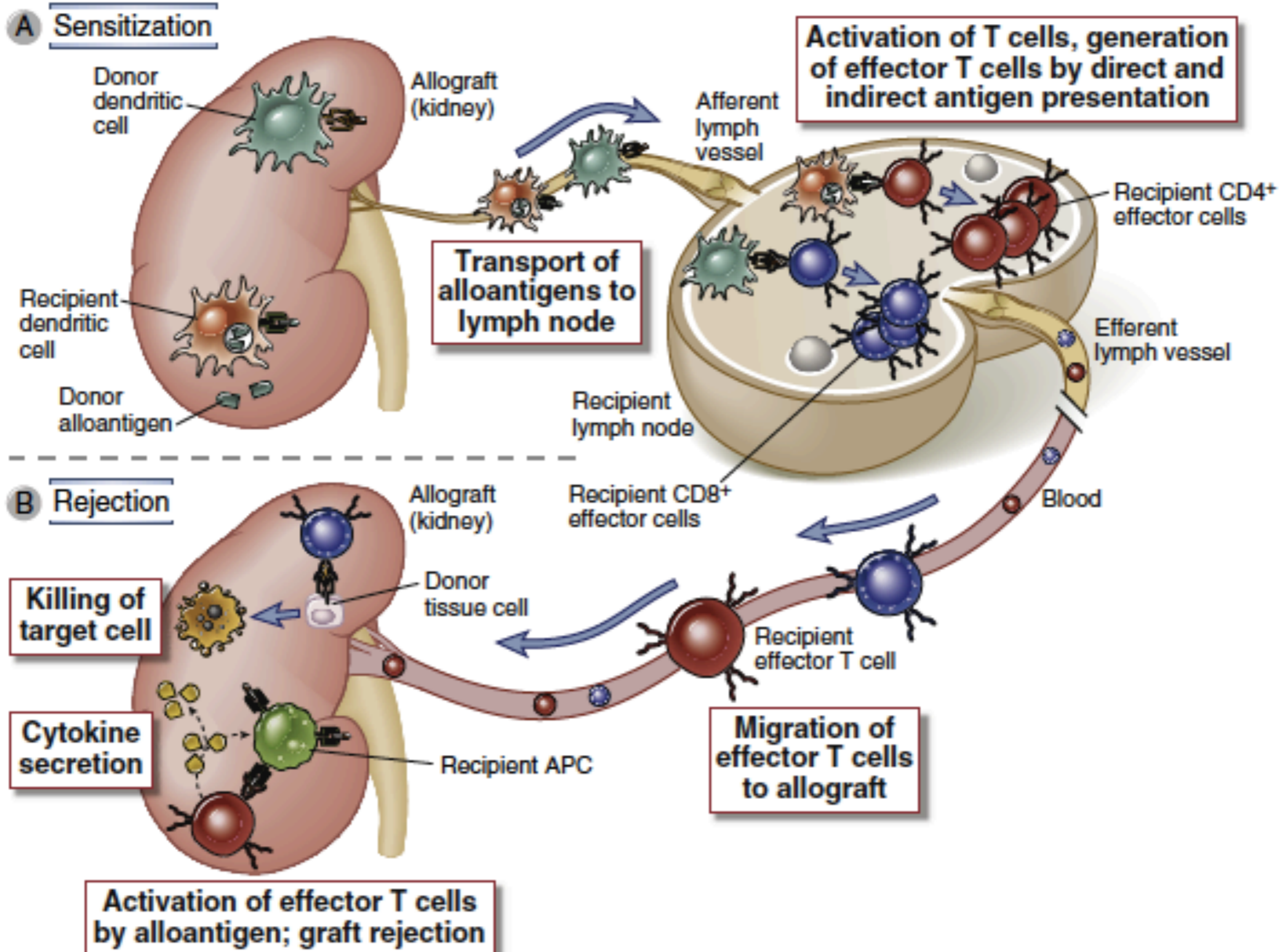


A

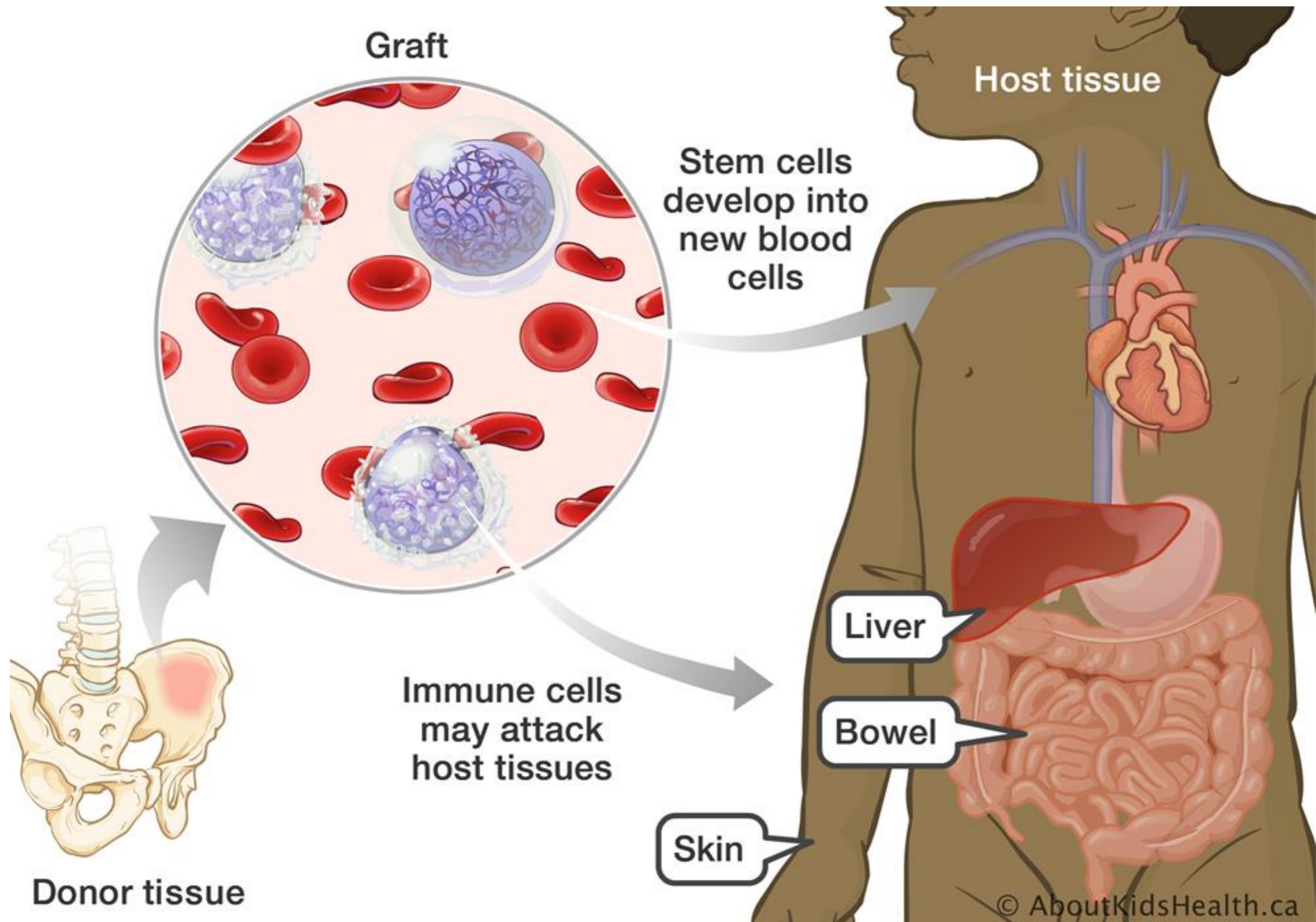


O

Transplante de órgãos e rejeição



Transplante de MO e reação do enxerto vs hospedeiro



Tolerancia imunologica & Homeostasia

A maior função das células do SI é

- o reconhecimento e eliminação de patógenos/dano
- distinguir o "próprio (self)" do "non-próprio (non-self)"
- distinguir o "non patogênico" do "patogênico"

A resposta imune prevê uma fase de ativação e uma de desativação para voltar a homeostasia (mecanismos efetores vs regulatórios)

E' NECESSÁRIA A TOLERÂNCIA PARA UMA CORETA ATUAÇÃO DO SI E PARA NAO ORIGINAR PATOLOGIAS RELACIONADAS A ATIVACAO DO SI CONTRA O PROPRIO ORGANISMO OU HIPER ATIVACÃO DO SI (REACOES ALERGICAS, proxima aula)

OS AVANÇOS DA MEDICINA LEVARAM A DESAFIOS PARA OS MECANISMOS DE TOLERÂNCIA