Imunologia para Graduação em Nutrição e Metabolismo

- Introdução ao Sistema Imune
- Aspectos evolutivos da nutrição humana e imunidade

Coordenadora: Isabel Kinney Ferreira
Vice Coordenadora: Daniela Carlos

Características da Resposta Imune

- **Diversidade**
  - Uma função crítica do sistema imune é ser capaz de reconhecer e interagir com o universo de moléculas existentes
- **Especificidade**
  - Uma função crítica do sistema imune é ser capaz focar sobre apenas um tipo de padrão molecular
- **Memória**
  - Uma função crítica do sistema imune é ser capaz de reconhecer e especificamente uma molécula com o qual já teve interação anterior de iniciar uma resposta imune rapidamente
- **Tolerância**
  - Uma função crítica do sistema imune é distinguir o próprio do não-próprio

O universo de moléculas - Antígenos

Por definição, na ciência de Imunologia um antígeno é uma molécula, estrutura molecular ou matéria particulada como grão de pólen capaz de interagir quimicamente com os receptores de reconhecimento da imunidade adquirida/adaptativa/configurável do Sistema Immune. Isto é: **anticorpos e receptores de linfócitos T**

Nem todo antígeno desencadeia resposta immune

aulas de: as reações antígenos-anticorpos; apresentação de antígenos, ativação da resposta immune e tolerância

Inicialmente antígeno se referia a substância que gerava anticorpos

'geno' - gerador de

'anti' - contra

"gerador de anti corpo" ou "gerador de anti entidade molecular"

Antigen comes from a French word, antigène, from Greek root anti-, "against, and the word-forming suffix -gen, "thing that produces or causes."

Antigens can be proteins, peptides (amino acid chains), polysaccharides (chains of monosaccharides/simple sugars), lipids, or nucleic acids.

Resposta **configurada antes de encontrar antígenos** (inata)

- baixa diversidade de moléculas para reconhecimento de antígenos

VERSUS:

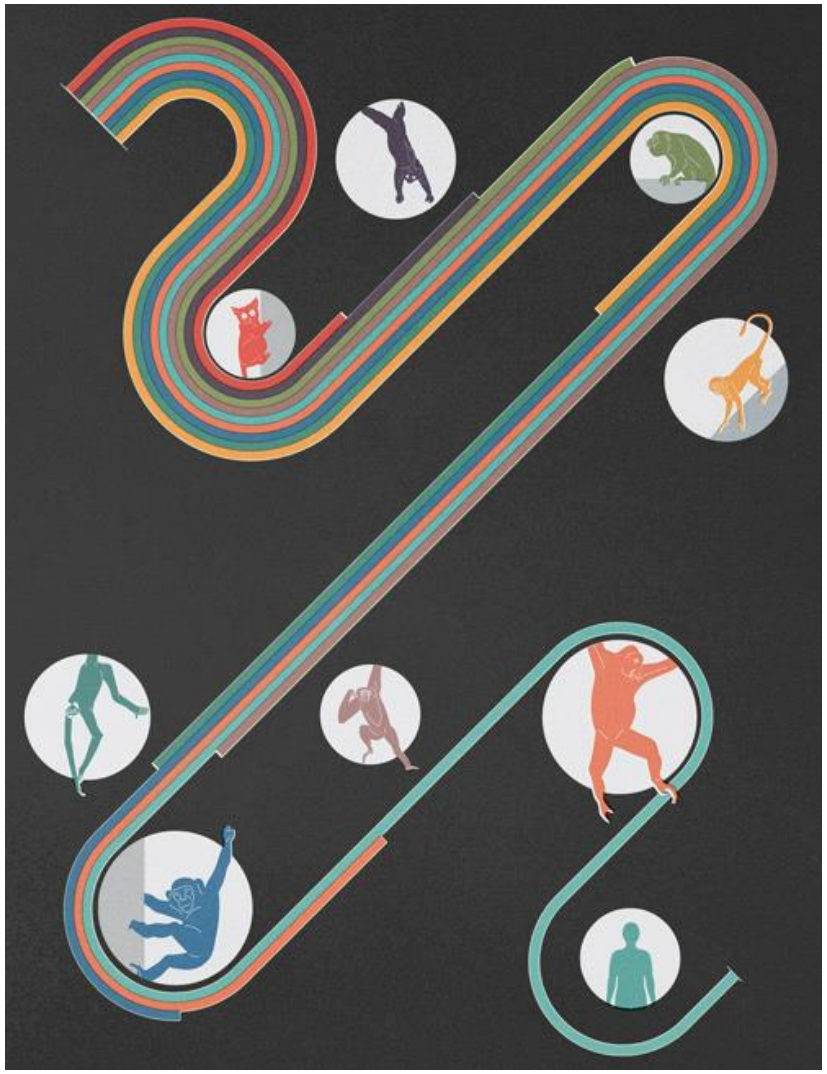
Resposta **configurável depois de encontrar antígenos** (adaptativa ou adquirida)

- alta diversidade de moléculas de reconhecimento de antígenos

Defesa x Aquisição de Nutrientes
Não-próprio x Próprio
Danos - Perigo x Apoptose – Homeostasia
Reparo de Tecidos x Renovação de Tecidos

As Cinco Causas de Doenças

- Neoplasia
- Degeneração
- Isquemia
- Infecção
- **Inflamação**
  - Entre os primatas, o *Homo sapiens* deve sua grande longevidade à capacidade de inflamar mais que outros primatas não-humanos
  - Inflamação tem um preço...



Life spans of primates

HOMININ EVOLUTION

Expanded geographic distribution and dietary strategies of the earliest Oldowan hominins and *Paranthropus*

Thomas W. Plummer[1,2,3,4]*, James S. Oliver[5], Emma M. Finestone[6,7], Peter W. Ditchfield[8], Laura C. Bishop[9,10], Scott A. Blumenthal[4,11,12], Cristina Lemorini[13], Isabella Caricola[13,14], Shara E. Bailey[3,15], Andy I. R. Herries[16,17], Jennifer A. Parkinson[4,18], Elizabeth Whitfield[9], Fritz Hertel[19], Rahab N. Kinyanjui[4,20,21], Thomas H. Vincent[9], Youjuan Li[22,23], Julien Louys[24], Stephen R. Frost[11], David R. Braun[25,26], Jonathan S. Reeves[26], Emily D. G. Early[4,27], Blasto Onyango[20], Raquel Lamela-Lopez[2,3], Frances L. Forrest[28,29], Huaiyu He[30], Timothy P. Lane[9], Marine Frouin[31], Sébastien Nomade[32,33], Evan P. Wilson[2,3], Simion K. Bartilol[34], Nelson Kiprono Rotich[35], Richard Potts[4,20]

The oldest Oldowan tool sites, from around 2.6 million years ago, have previously been confined to Ethiopia's Afar Triangle. We describe sites at Nyayanga, Kenya, dated to 3.032 to 2.581 million years ago and expand this distribution by over 1300 kilometers. Furthermore, we found two hippopotamid butchery sites associated with mosaic vegetation and a C_4 grazer–dominated fauna. Tool flaking proficiency was comparable with that of younger Oldowan assemblages, but pounding activities were more common. Tool use-wear and bone damage indicate plant and animal tissue processing. *Paranthropus* sp. teeth, the first from southwestern Kenya, possessed carbon isotopic values indicative of a diet rich in C_4 foods. We argue that the earliest Oldowan was more widespread than previously known, used to process diverse foods including megafauna, and associated with *Paranthropus* from its onset.

Fig. 3. Stone tool–damaged fossilized bones from Bed NY-1. (**A**) Hippopotamid tibia (Exc5-170, proximal end oriented to left) displaying a series of identically oriented cut marks with striae on anterior tibial crest. (**B**) Cut mark on a middle of the mark. (**C**) Parallel cut marks extending along the spine of size three bovid scapula NY17-1. (**D**) A series of parallel cut marks (top) as well as percussion load points and flake scars created during marrow processing

Hominídeos comem carne há pelo menos 2,6 milhões de anos

Pergunta:

Como a aquisição de mutações na **Apolipoproteína E** contribuiu para permitir mudanças na dieta do ser humano de vegetariano para omnívoro, maior capacidade para inflamar e, consquentemente maior longevidade por combater melhor as infecções?

Proc Natl Acad Sci U S A. 2010 Jan 26;107 Suppl 1:1718-24.
doi: 10.1073/pnas.0909606106.

Evolution of the human lifespan and diseases of aging: Roles of infection, inflammation, and nutrition

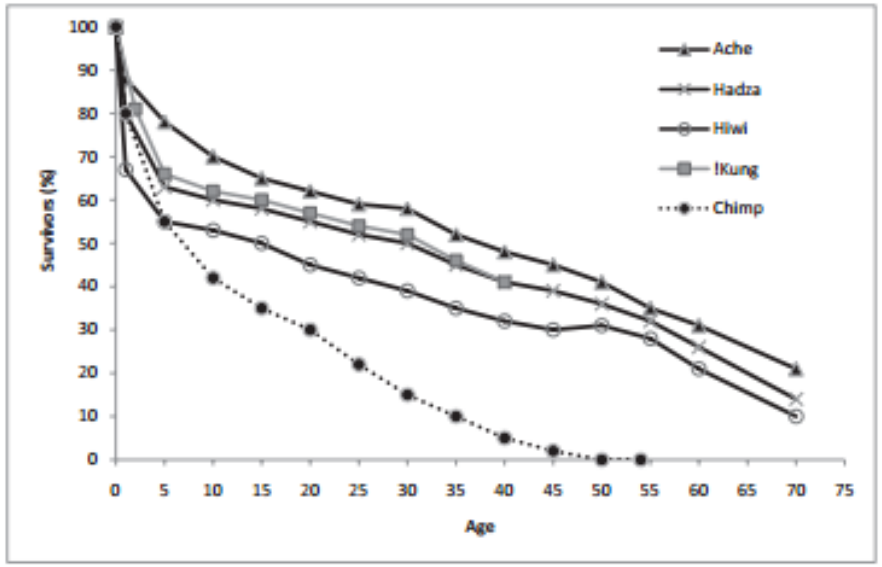
Caleb E. Finch[1]

Davis School of Gerontology and the University of Southern California, Los Angeles, CA 90089

Edited by Stephen Curtis Stearns, Yale University, New Haven, CT, and accepted by the Editorial Board October 12, 2009 (received for review August 25, 2009)

Humans have evolved much longer lifespans than the great apes, which rarely exceed 50 years. Since 1800, lifespans have doubled again, largely due to improvements in environment, food, and medicine that minimized mortality at earlier ages. Infections cause most mortality in wild chimpanzees and in traditional forager-farmers with limited access to modern medicine. Although we know little of the diseases of aging under premodern conditions, in captivity, chimpanzees present a lower incidence of cancer, ischemic heart disease, and neurodegeneration than current human populations. These major differences in pathology of aging are discussed in terms of genes that mediate infection, inflammation, and nutrition. Apolipoprotein E alleles are proposed as a prototype of pleiotropic genes, which influence immune responses, arterial and Alzheimer's disease, and brain development.

11) (Fig. 1). In healthy populations of humans and lab animals, the acceleration of mortality is preceded by increasing morbidity from chronic degenerative disease (2, 10). For wild chimpanzees, typical early mortality rates are 20% per year in infancy, within the range of hunter-gatherers, then decreasing to a q_{min} of about 3.5% per year in preadult ages. The chimpanzee life expectancy at birth (LE_0) is about 13 years, whereas those reaching adulthood (age 15) have about 15 years of further life expectancy (6, 11) (Table 1). Very few have survived beyond age 50, even in captivity with modern veterinary care (13). In contrast, human mortality after the early years is much greater, with >2-fold longer LE_0 and >3-fold lower q_{min}, even with limited access to medicine (Table 1). Since 1800, the LE_0 in developed nations rose progressively to >70 years. Only recently has sur-



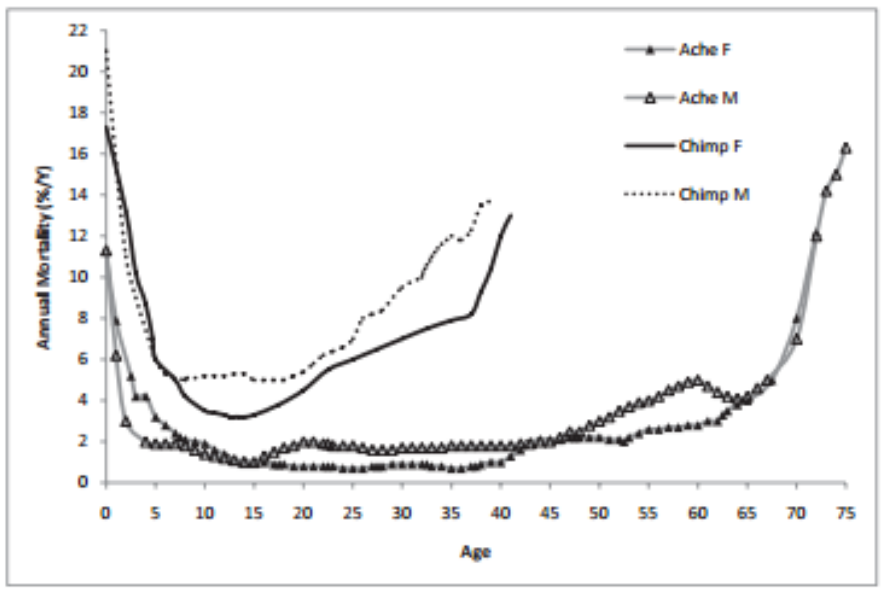


Fig. 1. Demographic comparisons of wild chimpanzees with human populations living under poor hygiene and with little access to medicine. [Reproduced with permission from ref. 6 (Copyright 2000, John Wiley & Sons).] (*A*) Survival curves. (*B*) Age-specific mortality. At all ages after infancy, chimpanzees have higher mortality than the Ache and show acceleration of mortality at least 20 years earlier.

Table 2. Cause of death in feral chimpanzees and hunter-gatherers

	Chimpanzees, %[a]	Traditional humans, %[b]
Infections	67 (TB, polio, mange)	73
Violence/accidents	32	17
Senescence	1	10

"DNA differences between humans and chimpanzees shows **evidence of positive selection**.

Fixed divergence at the species level for proteins is about 1%.

Genes undergoing positive selection based on the ratio of nonsynonymous:synonymous mutations are overrepresented for immunity and host defense, diet, and brain.

Moreover, genes associated with immunity and brain have variation clusters of highly localized groups of changes in coding regions"

Apolipoprotein E: a meat-adaptive candidate gene in the increases of the human lifespan

(*apud* Sapolsky & Stanford)

Table 3. Apolipoprotein E polymorphisms in humans and species differences

ApoE residue (mature peptide)	61[a]	112	158
Human apoE3	R	C	R
ApoE4	R	R	R
Chimpanzee	T	R	R
Gorilla	T	R	R
Orangutan	T	R	R
Mouse	T	R	R

[a]Residue 61 determines apoE protein structure by domain interactions that influence lipid binding by the C terminus (1, 100, 108). Though chimpanzees, other primates, and many mammals have the R112 and R158 that define apoE4, these species differ from human apoE at residue 61. Genetically engineering the mouse apoE with R61T changed lipid-binding affinity to resemble human apoE4 (108). Thus, chimpanzee apoE is predicted to have lipid binding like apoE3 (1). Nonetheless, other amino acid differences from the chimpanzee may be important, because 4 of the 8 residues that showed evidence of positive selection in the human lineage are seated in the lipid-binding C terminus (109).

"Apolipoprotein E (*ApoE*) alleles modulate chronic inflammation and many aspects of aging in brain and arteries.

Blood apoE mediates the clearance of triglyceride-rich lipoprotein components, and brain apoE transports cholesterol to neurons *ApoE4*, the minor allele in all human populations (<1%–45%), is considered ancestral in the genus *Homo*. The uniquely human *apoE3* allele **spread** about 0.226 million years ago and precedes the emigration of modern *H. sapiens* from Africa and overlap with the increased organized hunting of large animals and the use of fire.
The *apoE4* allele shortens lifespan by several years and accelerates degenerative changes in arteries and brain; carriers have higher total blood cholesterol, more oxidized blood lipids, and greater risk of coronary heart disease (*ca.* 40%) and Alzheimer's disease; *E4/E4* homozygotes have >10-fold excess risk). *ApoE4* carriers also have worse outcomes in traumatic brain injury and some neurological conditions. One mechanism may involve heightened inflammatory responses."

Estimated worldwide human allele frequencies of ApoE* in Caucasian population				
Allele	ε2	ε3	ε4	
General Frequency	8.4%	77.9%	13.7%	
AD Frequency	3.9%	59.4%	36.7%	

A Tolerância à Doença como Estratégia de Defesa

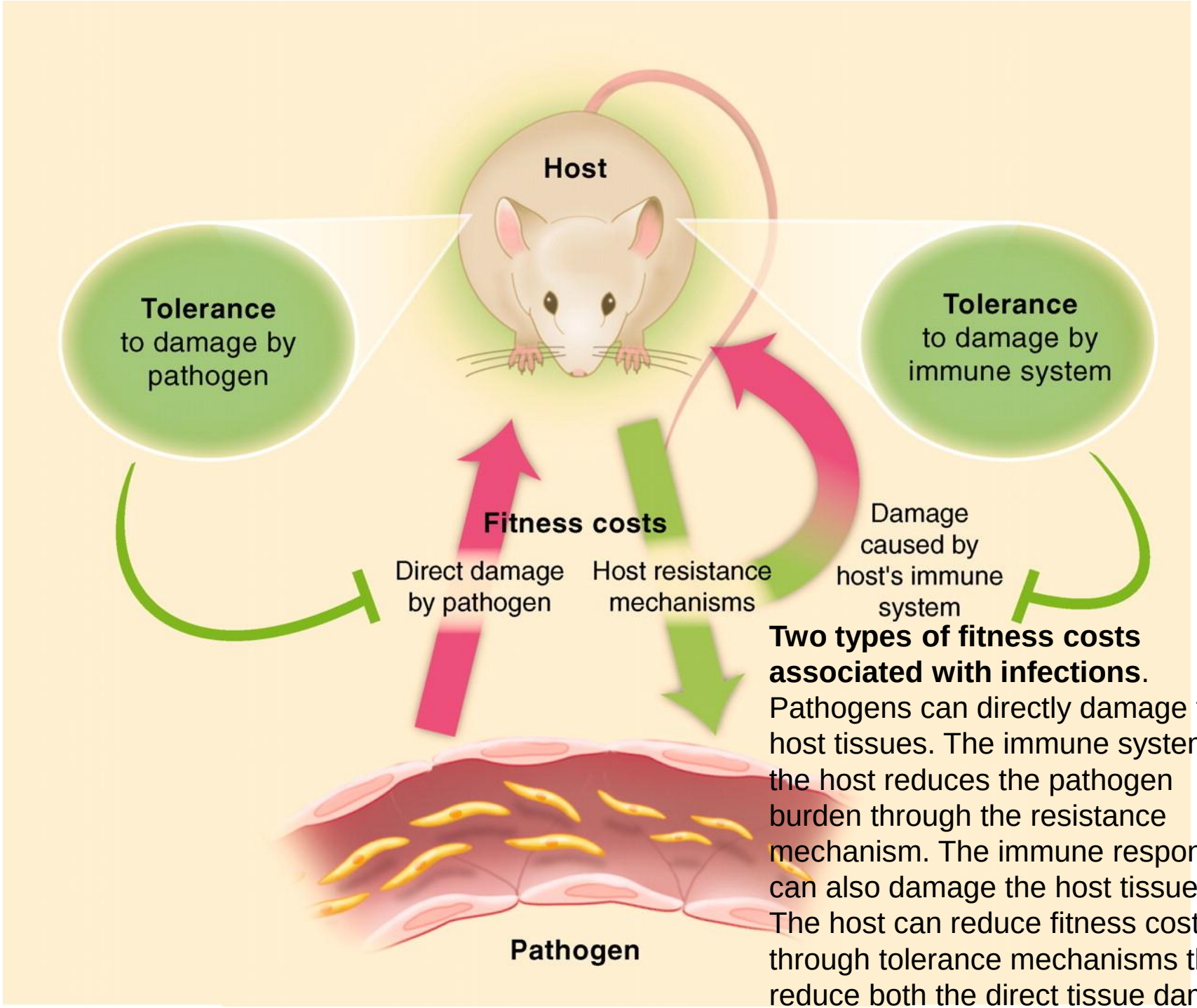
Ruslan Medzhitov, David S. Schneider, Miguel P. Soares

Science 24 February 2012: Vol. 335 no. 6071 pp. 936-941 DOI: 10.1126/science.1214935

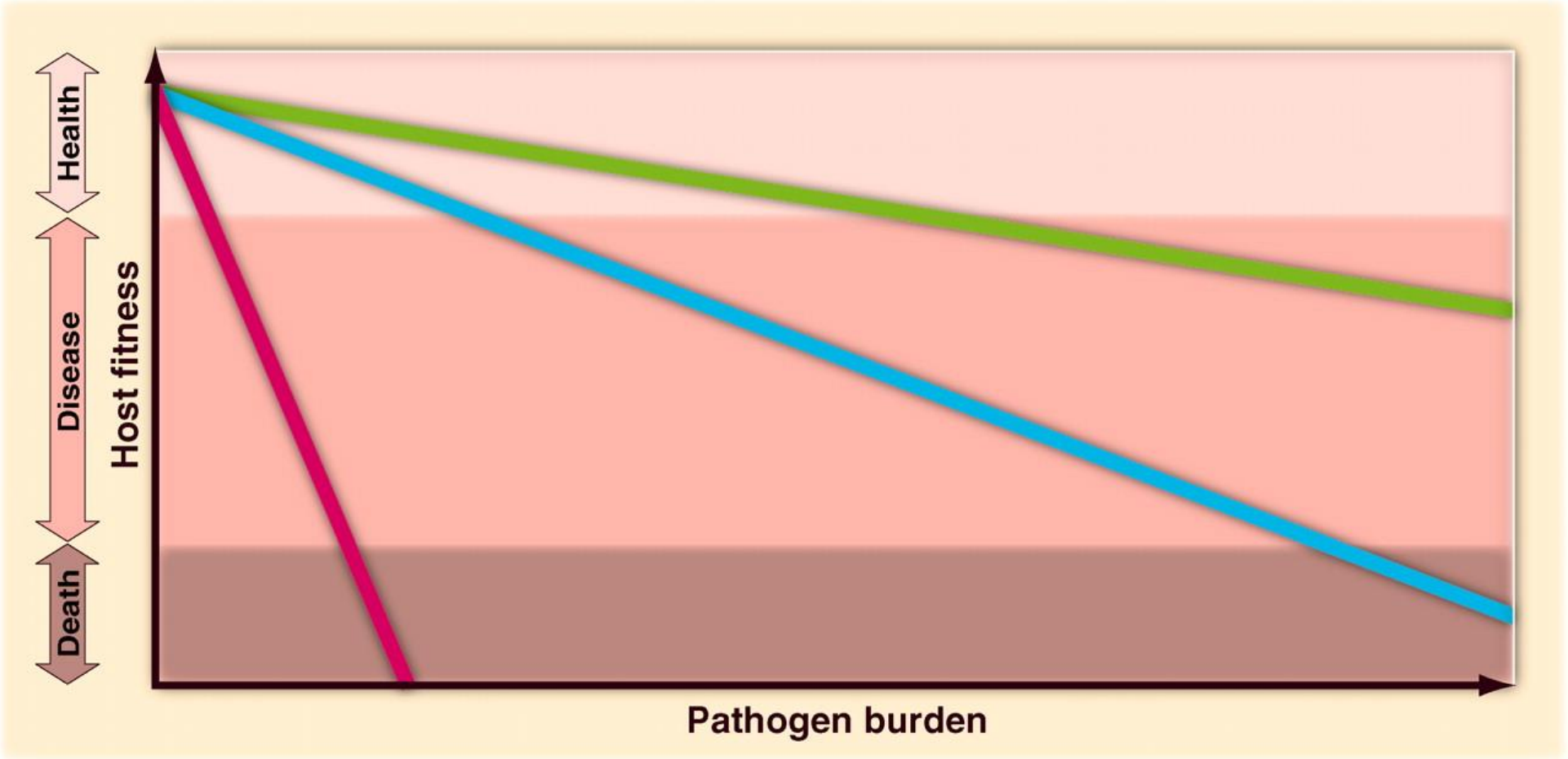
- **"Avoidance" = Evitar o parasita**
- **Resistência = Diminuir a carga do parasita (versus matar o parasita)**
- **Tolerância – Tolerar as injúrias**
  - **mediadas pelo parasita (toxinas, hemólise, etc)**
  - **mediadas pela Resposta Imune (imunopatologia)**
- **Repelência = repelir o parasita**

***El Garrotillo* por Francisco de Goya y Lucientes (1808-1812)**

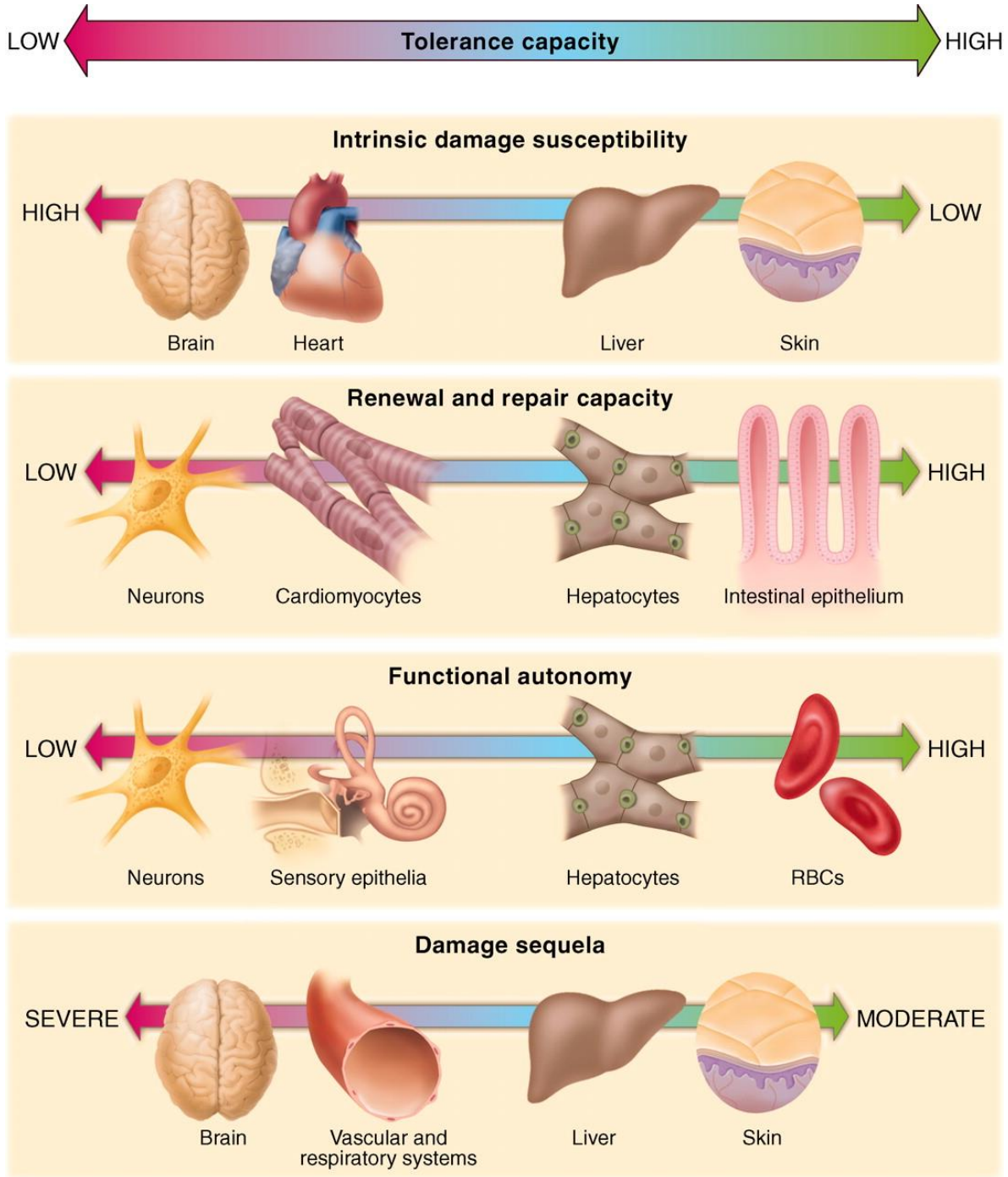
Diphthera: "leather"; couro. Mediada por toxina da bactéria Corynebacterium diphteriae que inibe síntese protéica de c'lulas do hospedeiro



Two types of fitness costs associated with infections. Pathogens can directly damage the host tissues. The immune system of the host reduces the pathogen burden through the resistance mechanism. The immune response can also damage the host tissues. The host can reduce fitness costs through tolerance mechanisms that reduce both the direct tissue damage



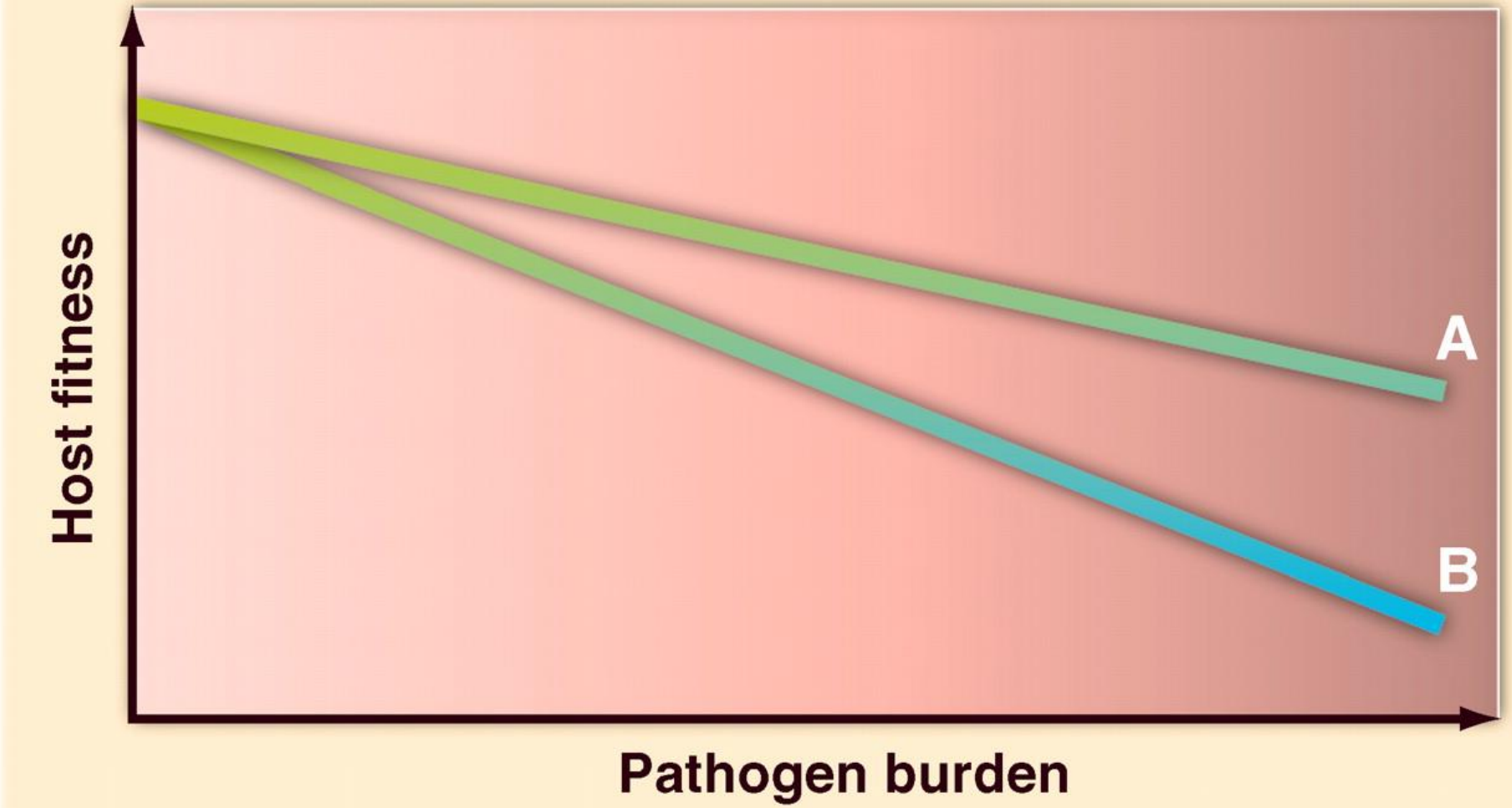
Different tissues and physiological processes vary in tolerance capacity. Tissues depicted in red have the lowest tolerance to damage, the blue has an intermediate tolerance, and the green has the highest tolerance capacity.



Tolerance capacity is a function of :

- **intrinsic damage susceptibility,**
- **repair capacity,**
- **functional autonomy**
- **damage sequelae of different tissues and organs.**

Although tissues generally tend to fall at the same ends of the four spectra, the four characteristics do not necessarily correlate with each other



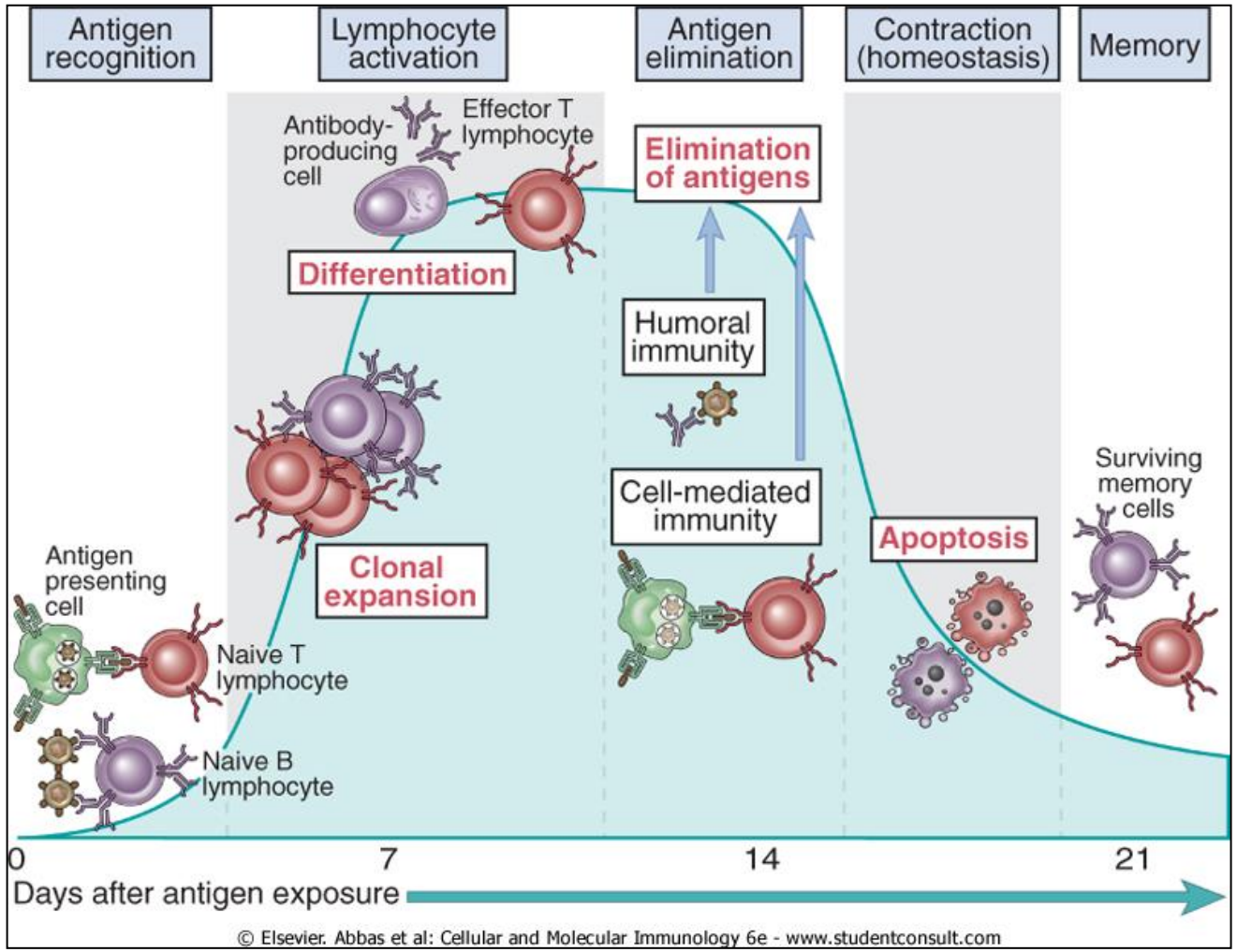
A is more tolerant to a given level of pathogen burden than B. An equivalent increase in pathogen burden will have greater negative impact on B than on A. A and B are typically **different genotypes** studied in the same environment. Alternatively, A and B can be two **different environments** where an organism with the same phenotype has different tolerance to infection.

"Given these adverse effects of *apoE4*, at least in modern environments, the persistence of the allele has been proposed as the result of balancing selection, as in:

- malarial protection by heterozygotes of hemoglobinopathies
- hepatitis C infections, *apoE4* carriers incurred less fibrotic damage by allele dose
- Brazilian slum children carrying *apoE4* showed less diarrhea and associated impairments of cognitive development

The hyperreactivity of human T cells noted previously, and the inflammatory responses in apoE4 carriers, may be part of an evolved group of heightened immune defenses relative to great apes that decreased baseline mortality represented in the q_{min}, as discussed earlier. However, the heightened immune responses could then have delayed adverse effects in cardiovascular disease and other chronic conditions of aging that involve inflammation and that became more prevalent in the 20th century. This suggestion extends the antagonistic pleiotropy theory of aging in which genes selected for early advantages can have delayed adverse effects that are under weaker selection.

The unique human social system of **multigenerational support in child nurture** has been argued as a key factor in the selection for delayed disability and increased life expectancy at later ages"


Antigen recognition
Lymphocyte activation
Antigen elimination
Contraction (homeostasis)
Memory
Antibody-producing cell
Effector T lymphocyte
Differentiation
Elimination of antigens
Humoral immunity
Cell-mediated immunity
Clonal expansion
Apoptosis
Surviving memory cells
Antigen presenting cell
Naive T lymphocyte
Naive B lymphocyte
0
7
14
21
Days after antigen exposure
© Elsevier. Abbas et al: Cellular and Molecular Immunology 6e - www.studentconsult.com

Conceitos Fundamentais em Imunologia:

- A Resposta Imune apresenta grande **DIVERSIDADE**

Resposta **configurada antes de encontrar antígenos** (inata)

- baixa diversidade de moléculas para reconhecimento de antígenos

VERSUS:

Resposta **configurável depois de encontrar antígenos** ("adaptativa" ou adquirida)

- alta diversidade de moléculas de reconhecimento de antígenos

- A Resposta Imune apresenta **ESPECIFICIDADE**
- A Resposta Imune é **TOLERANTE**
- A Resposta Imune possui **MEMÓRIA**

Defesa x Aquisição de Nutrientes

Não-próprio x Próprio

Danos -Perigo x Apoptose – Homeostasia

Reparo de Tecidos x Renovação de Tecidos