Mechanisms of Autontibodies Production in Rheumatic Diseases

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Introduction

- Rheumatic diseases:
- Cause inflammation, swelling, and pain in the joints and muscles.

- There are dozens of kinds of rheumatic diseases, including osteoarthritis and rheumatioid arthritis.

- There are roughly 46 million people in the United States living with rheumatic diseases

Introduction

- The systemic autoimmune rheumatic diseases (SARD):
  - Rheumatoid Arthritis (RA),
  - Systemic Lupus Erythematosus (SLE)
  - Sjögren's syndrome (SjS),
  - Systemic Sclerosis (SSc),
  - Polymyositis (PM),
  - Dermatomyositis (DM).

- Rheumatoid arthritis is the most prevalent disease in this group

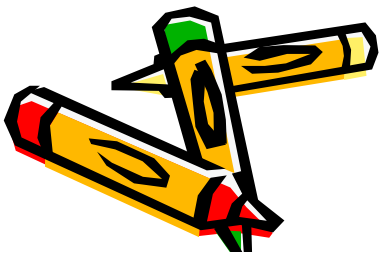
- **Why does autoimmunity develop in about 5% of people?**

Why Autoimmunity doesn't happen?

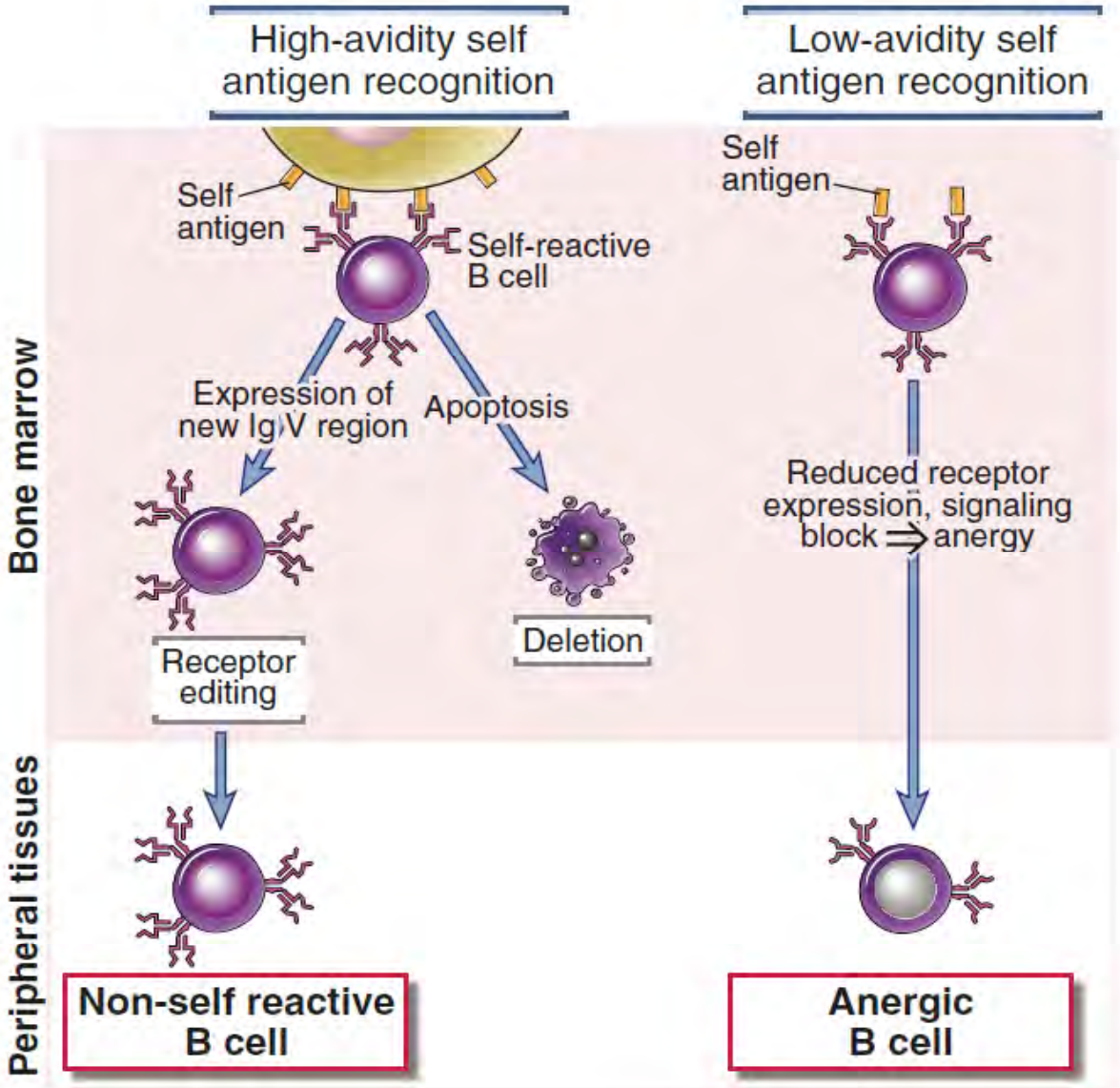
- Lack of immune responsiveness to an individual's own tissue antigens

Central Tolerance

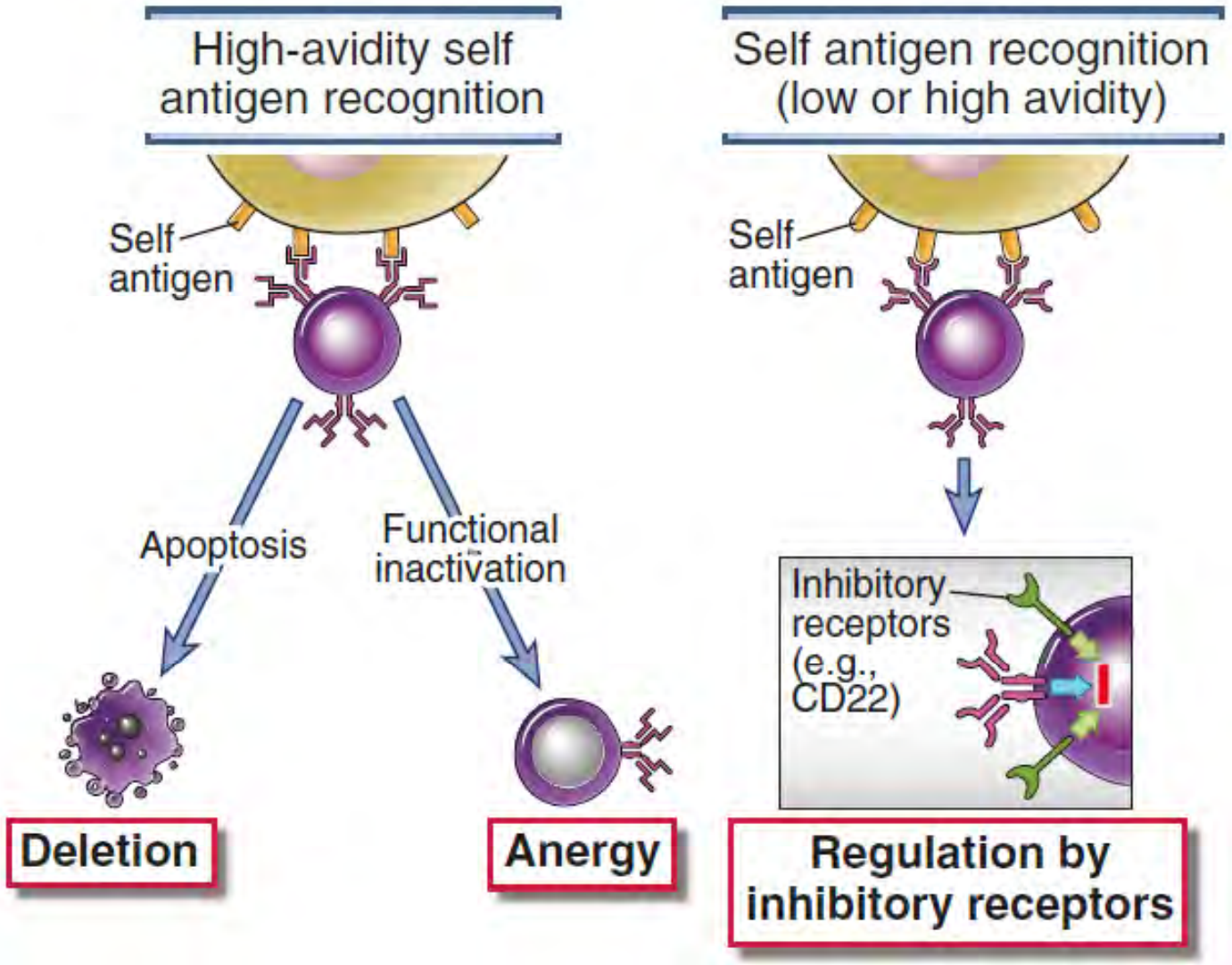
Peripheral tolerance



Central tolerance in B cells



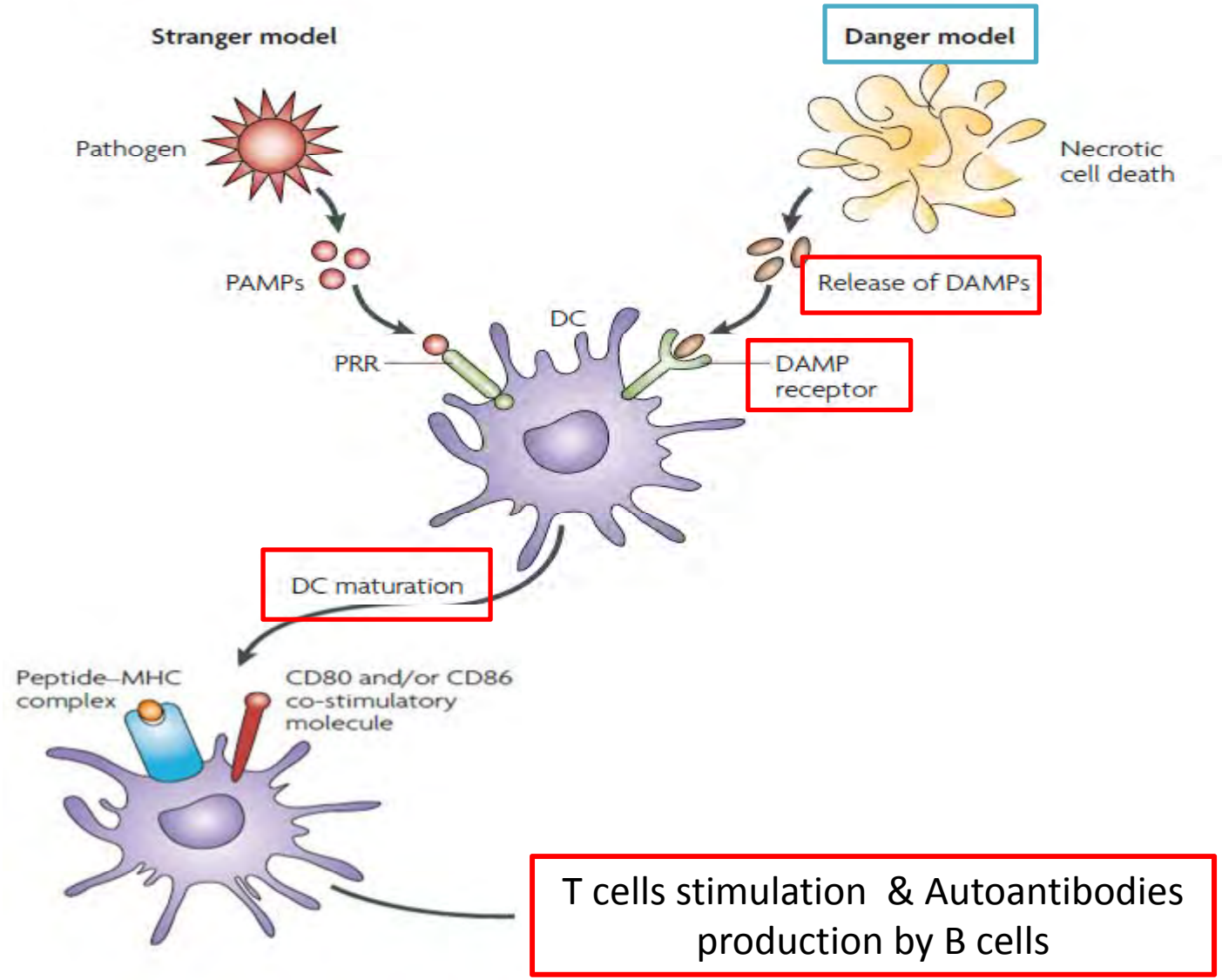
Peripheral tolerance in B cells



Why Autoimmunity doesn't happen?

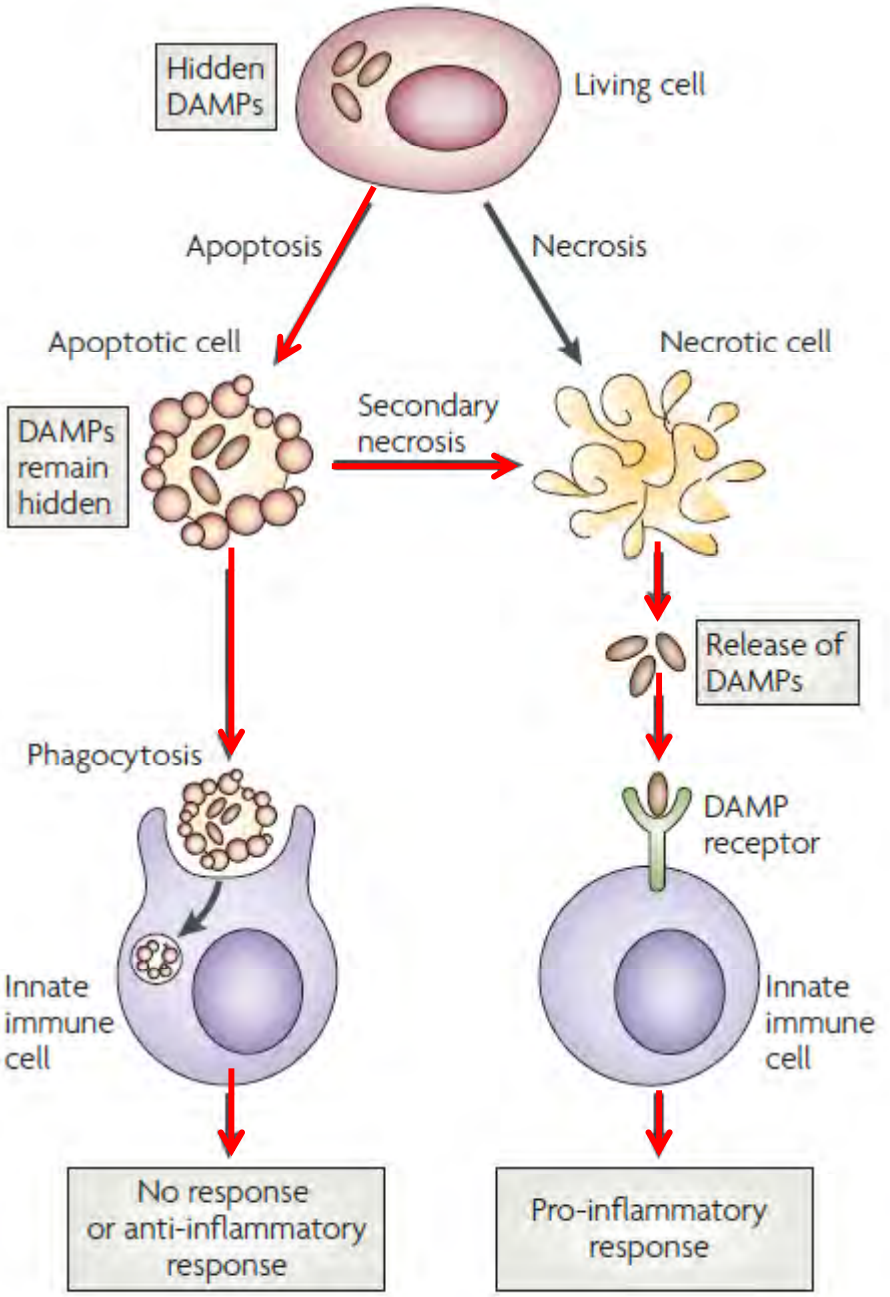
- Antigens are sequestered
- Immunoregulation works
- T-cells don't help autoreactvie B-Cells
- Especial malfunctioning:
  - Polyclonal lymphocyte activation
  - Somatic hypermutation

Danger Theory



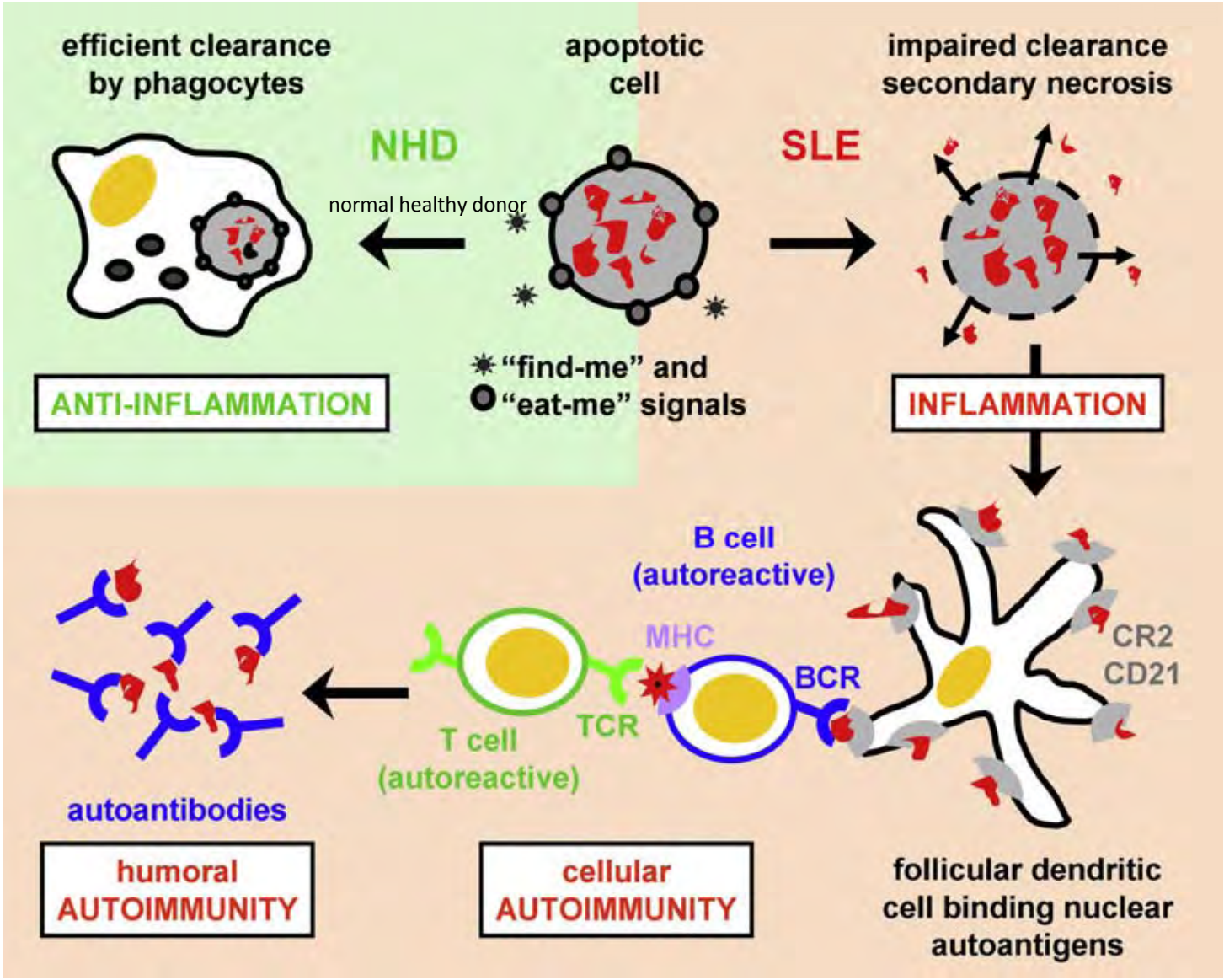
Nature Reviews Immunology (April 2008)

Clearance of apoptotic bodies



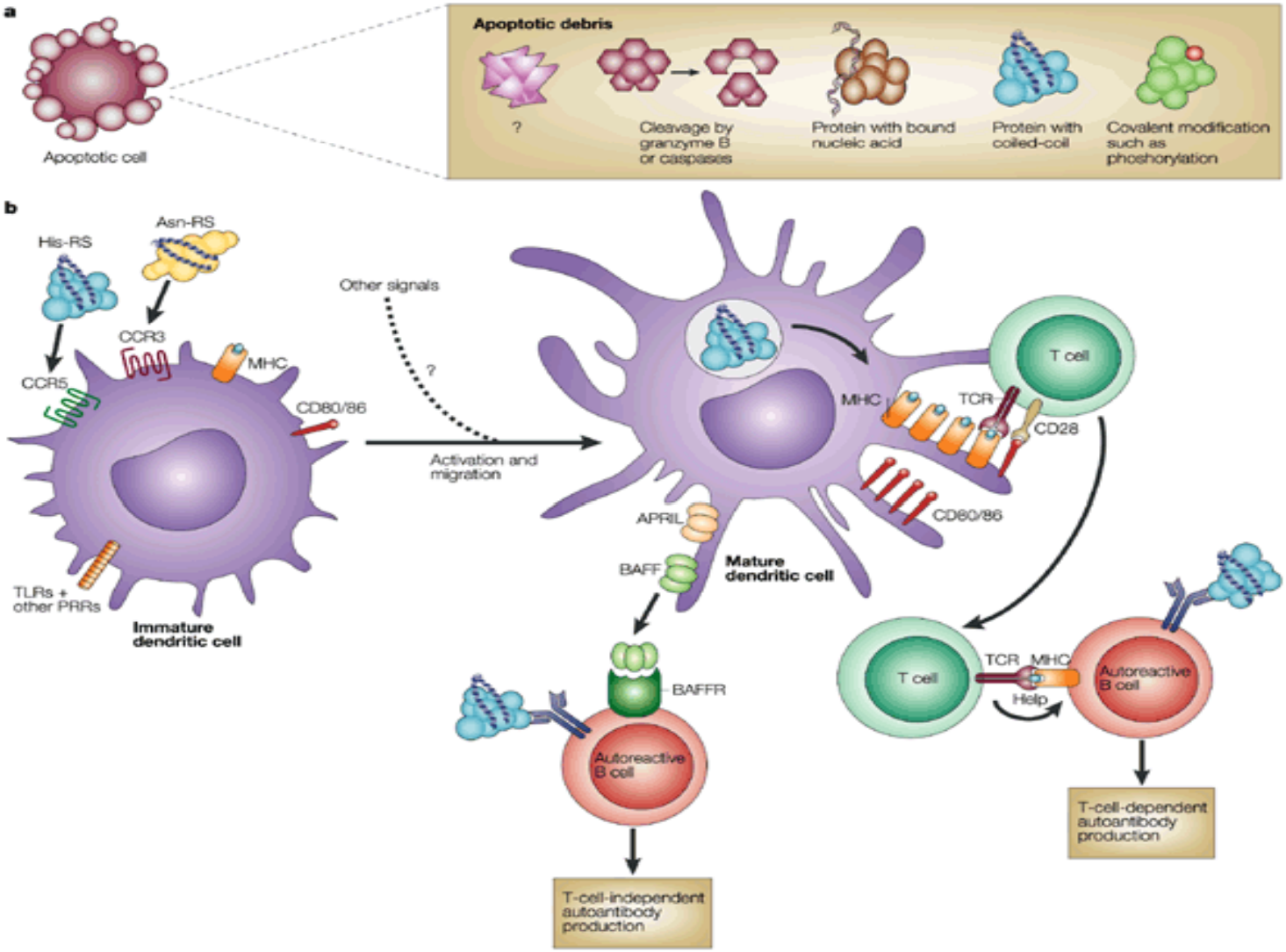
Nature Reviews Immunology (April 2008)

Clearance deficiencies



Autoimmunity Reviews 8 (2008)

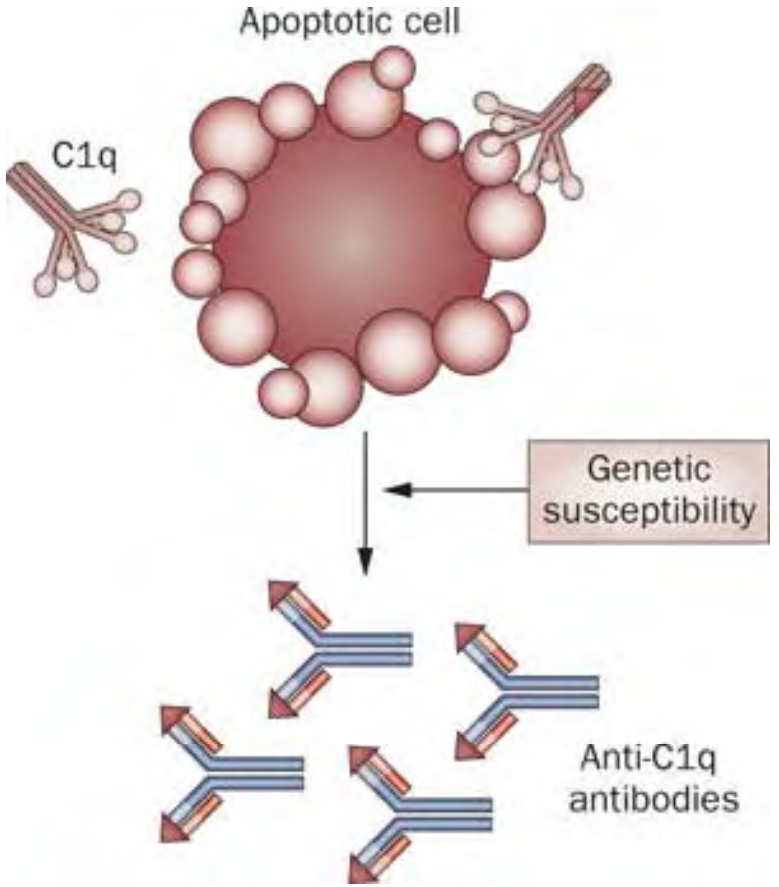
Proposed path from a dying cell to the production of autoantibodies.



Nature Reviews Immunology (January 2003)

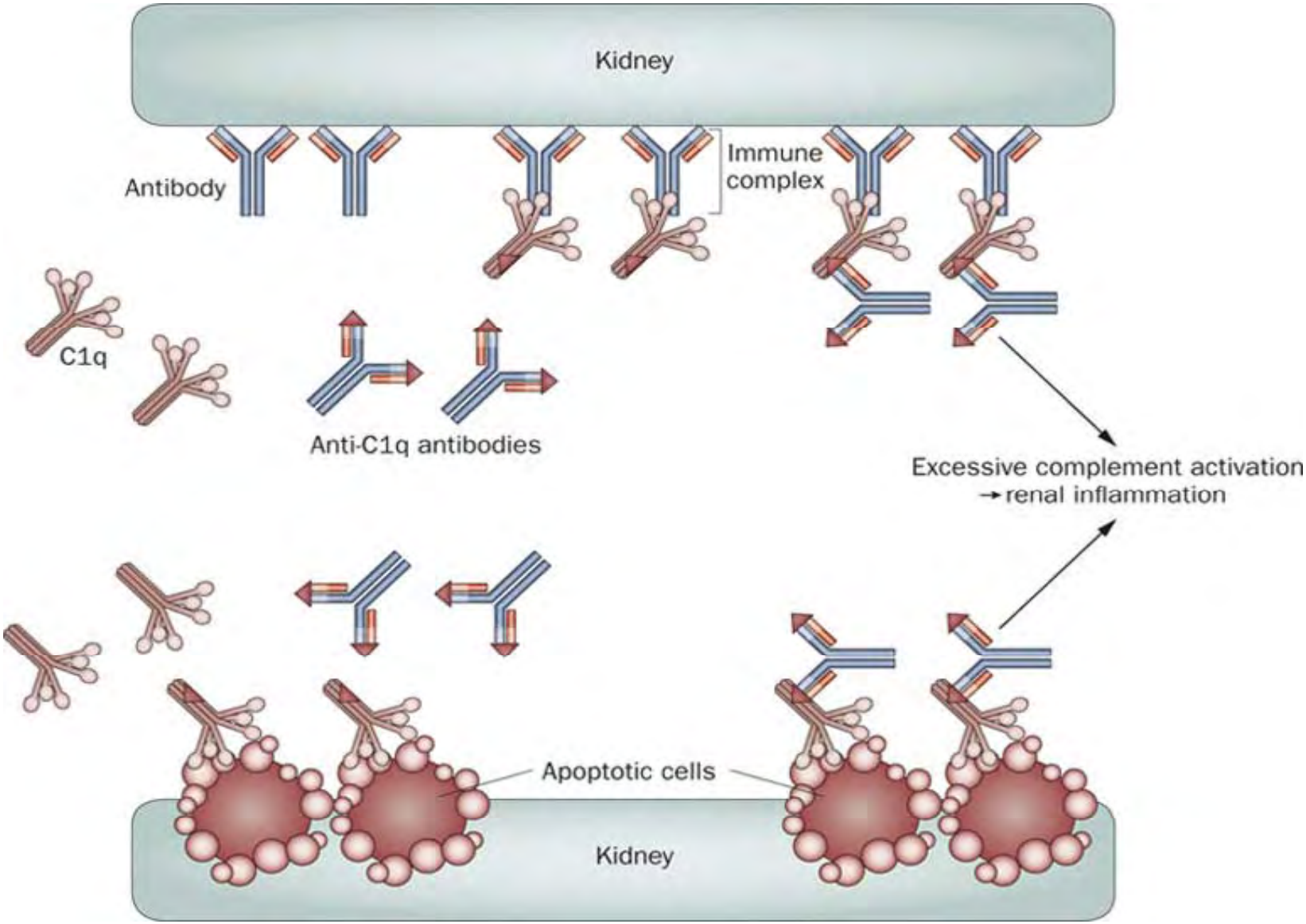
How Anti-C1q is produced?

- Anti-C1q antibodies are strongly associated with the development of proliferative lupus nephritis



Nature Reviews Rheumatology (August 2010)

Renal inflammation and anti-C1q antibodies



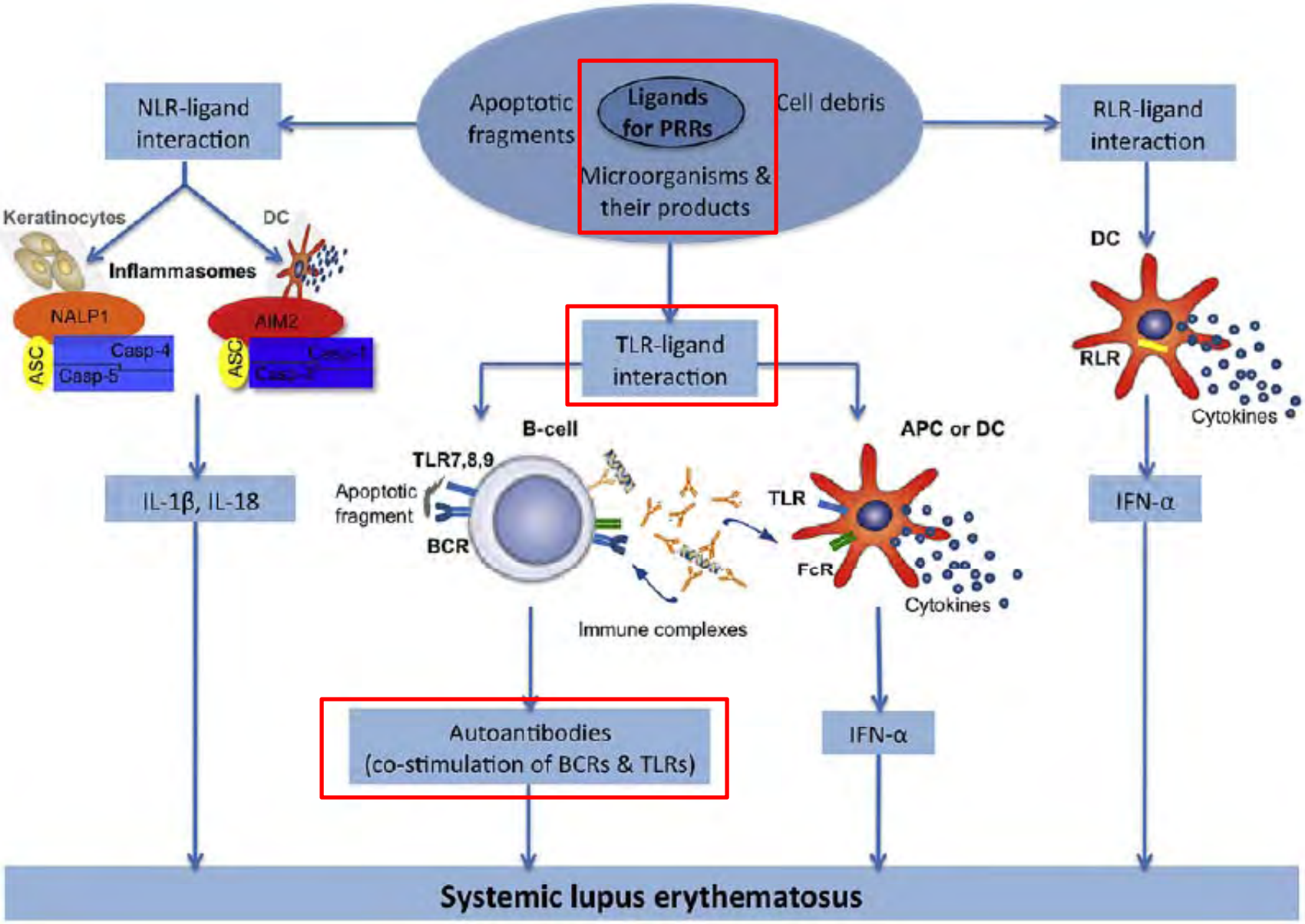
Nature Reviews Rheumatology (August 2010)

Role of TLRs

- TLRs are key components of the innate immune system, activating multiple inflammatory pathways

- Inappropriate activation of TLR pathways by endogenous or exogenous ligands may lead to the initiation and/or perpetuation of autoimmune responses

- B cell activation was dependent on:
  - TLR9, the endosomal sensor for dsDNA,
  - TLR7, an endosomal sensor for ssRNA



Journal of Autoimmunity (2010)

Dysregulation of germinal centers

- In germinal centers, somatic hypermutation and B cell selection increase antibody affinity and specificity for the immunizing antigen
- but the generation of autoreactive B cells is an inevitable by-product of this process.
- abnormalities in each of the germinal center cellular constituents
  - B cells, T follicular helper cells, follicular dendritic cells and macrophages
- lead to production of autoantibodies
- selection of autoreactive B cells can propagate long-lived autoantibody responses and cause autoimmune diseases.

Dysregulation of germinal centers

- ***Tolerance in germinal centers is important***

- More than half of all early B cells in humans are specific for self-antigens

- A large proportion of these are removed during B-cell development in the bone marrow before entry to the mature B-cell compartment.

- Yet autoreactive B cells still constitute up to 5–20% of circulating, mature B cells in healthy individuals

- Indeed, antibody forming cells that emerge from germinal centers are a greater risk for the development of autoimmunity than are their extra follicular counterparts,

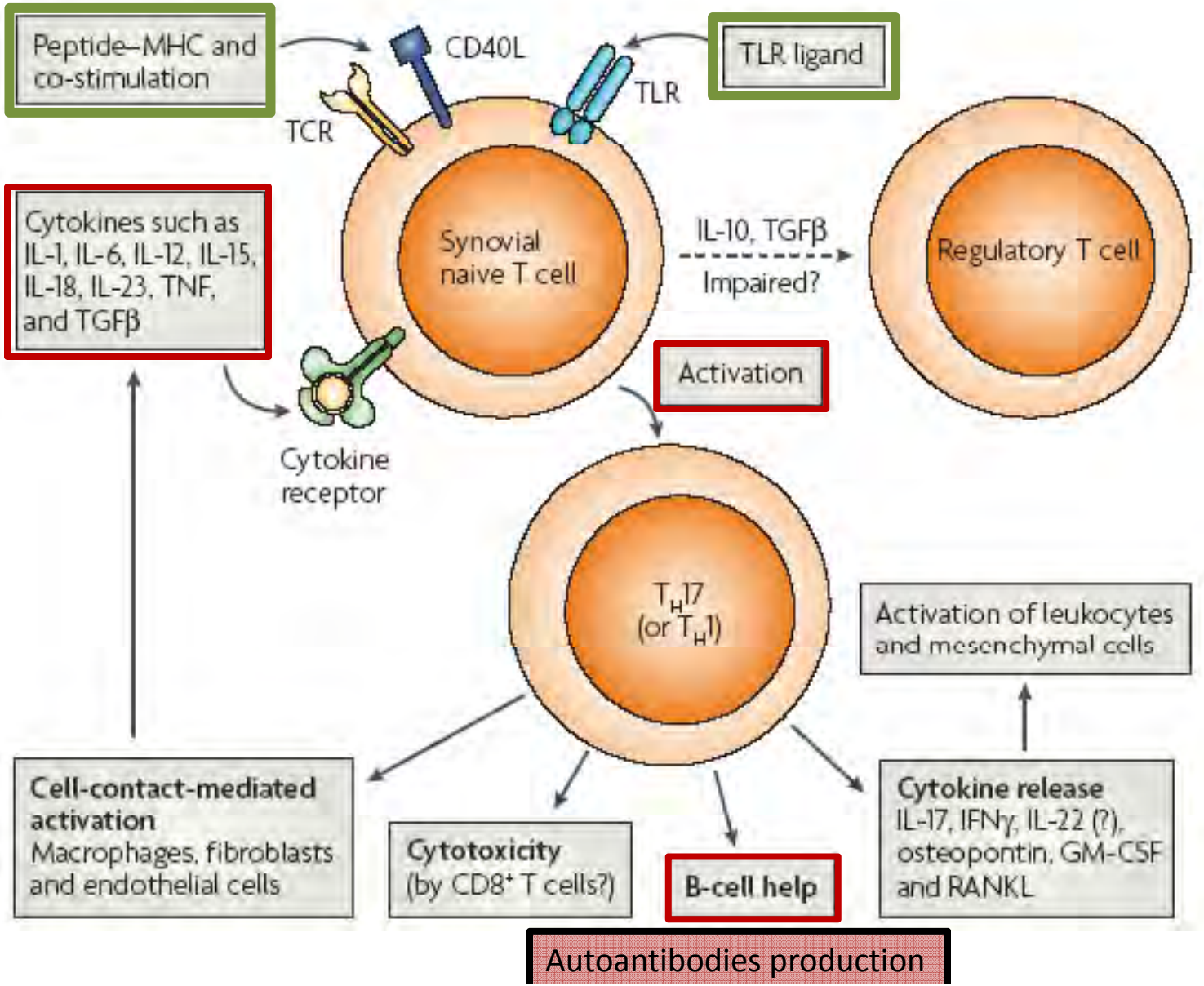
Dysregulation of germinal centers

- However, in patients with SLE, self-reactive B cells are present in germinal centers and differentiate to become plasma cells and memory cells

- In these autoimmune situations, immunological tolerance among T cells has been compromised, especially within the TFH-cell subset.

- strongest evidence support the involvement of TFH cells in autoantibody production

Cytokine


Peptide–MHC and co-stimulation
CD40L
TLR ligand
TCR
TLR
Cytokines such as IL-1, IL-6, IL-12, IL-15, IL-18, IL-23, TNF, and TGFβ
Synovial naive T cell
IL-10, TGFβ
Impaired?
Regulatory T cell
Activation
Cytokine receptor
T_H17 (or T_H1)
Activation of leukocytes and mesenchymal cells
Cell-contact-mediated activation
Macrophages, fibroblasts and endothelial cells
Cytotoxicity
(by CD8+ T cells?)
B-cell help
Cytokine release
IL-17, IFNγ, IL-22 (?), osteopontin, GM-CSF and RANKL
Autoantibodies production

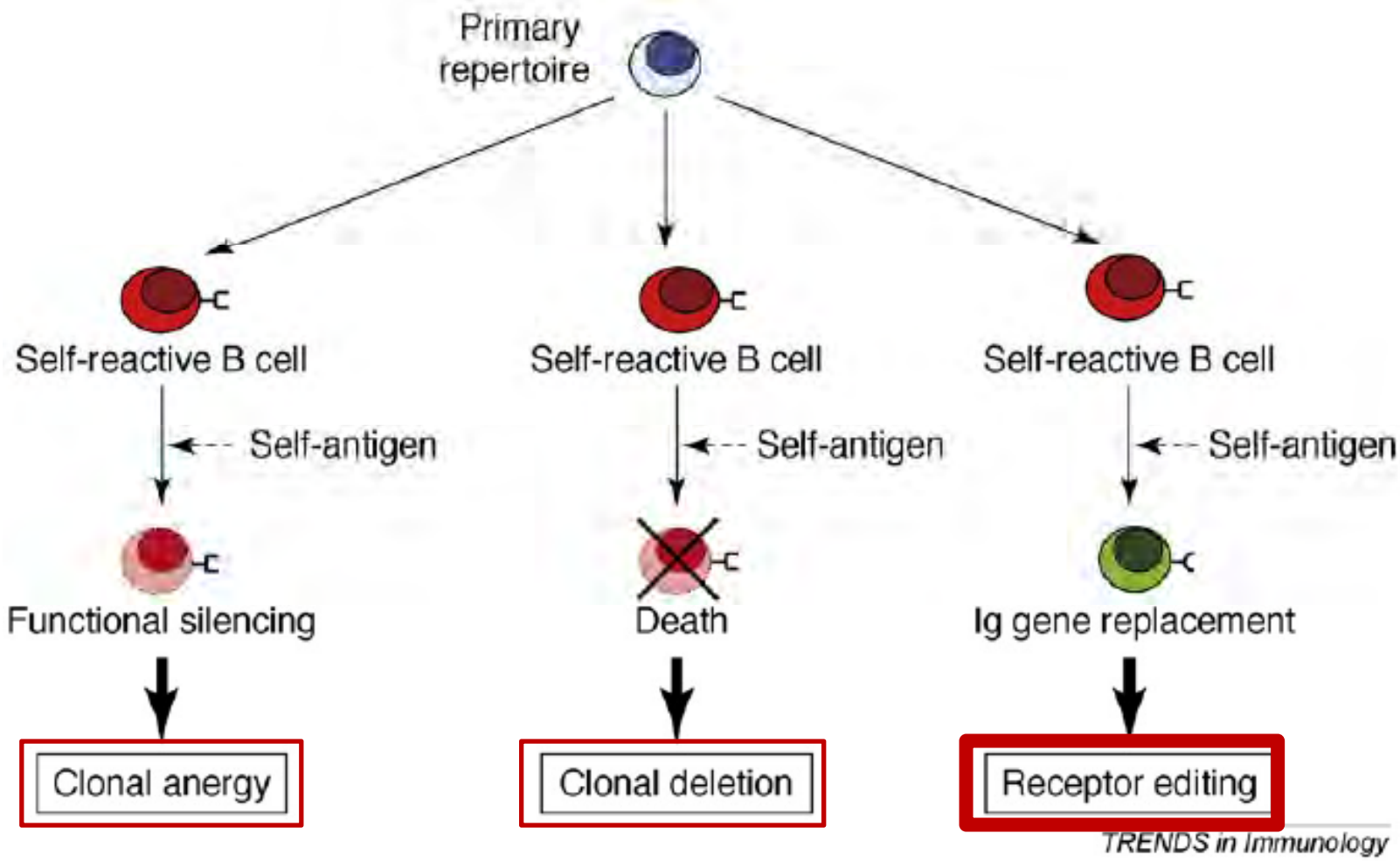
B cell receptor editing in tolerance and autoimmunity

- Receptor editing is a key mechanism of B cell tolerance that modifies the BCR specificity of self-reactive lymphocytes.

- evidence indicates that receptor editing in patients suffering from rheumatic autoimmune diseases:
  - is either impaired
  - or accelerated.

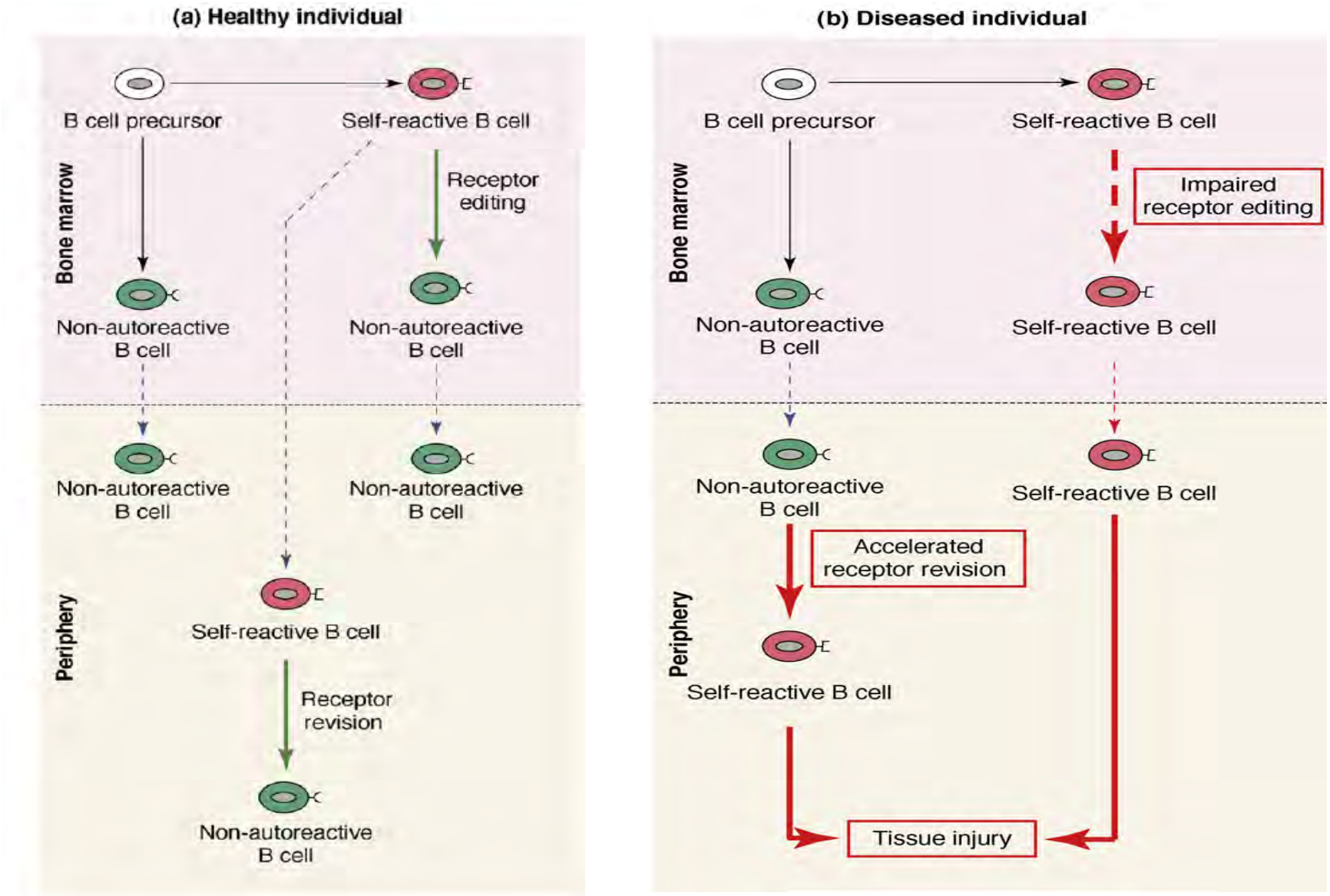
- Remarkably, both alterations promote the pathogenesis of autoimmune disorders by favoring the uncontrolled emergence and/or persistence of autoreactivity

Negative selection of self-reactive B cells

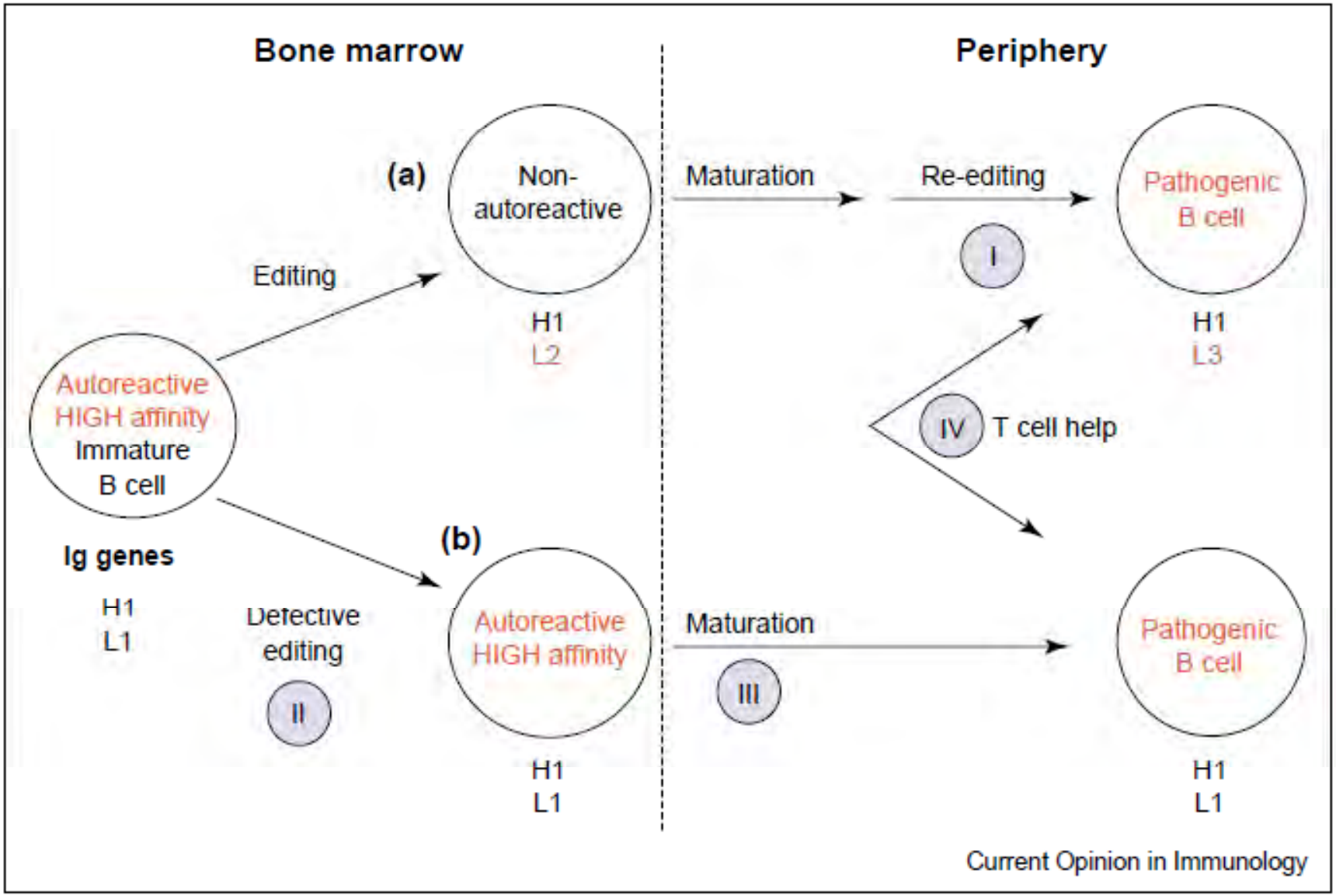


Trends in Immunology, 2008

Dysfunctional receptor editing



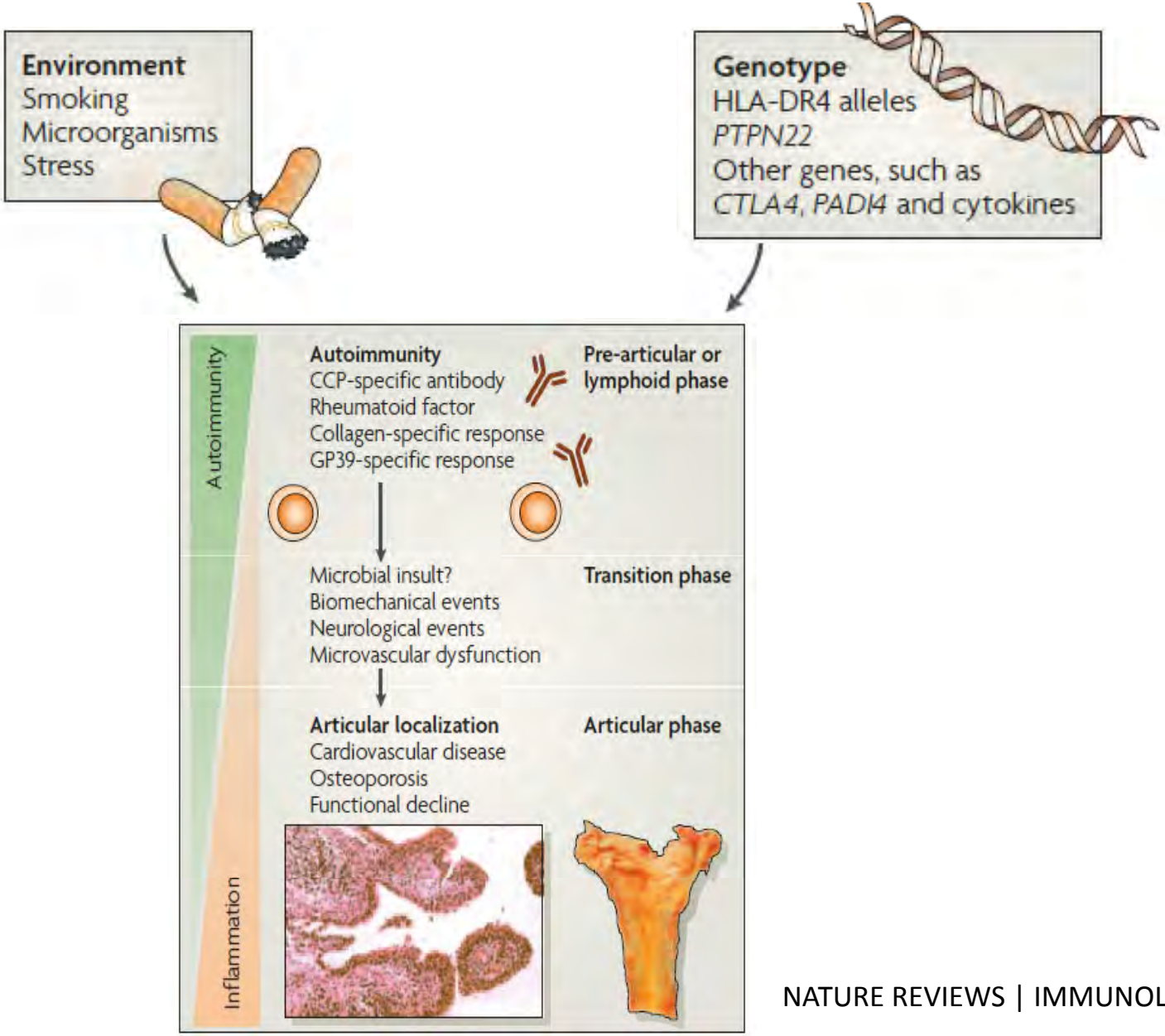
Alternative models for the appearance of high-affinity autoreactive B cells



Viral Infection Can Induce the Production of Autoantibodies

- viral agents (Epstein-Barr virus), which has been associated with many autoimmune diseases
- EBV is classically considered to induce SLE
- This occurs through molecular mimicry between EBV nuclear antigen 1 and lupus-specific antigens dsDNA
- Also, Cytomegalovirus has often been controversially associated with several autoimmune diseases

Nurture & Nature



NATURE REVIEWS | IMMUNOLOGY, 2007

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