Immune Tolerance

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Immune system - encounters antigen?

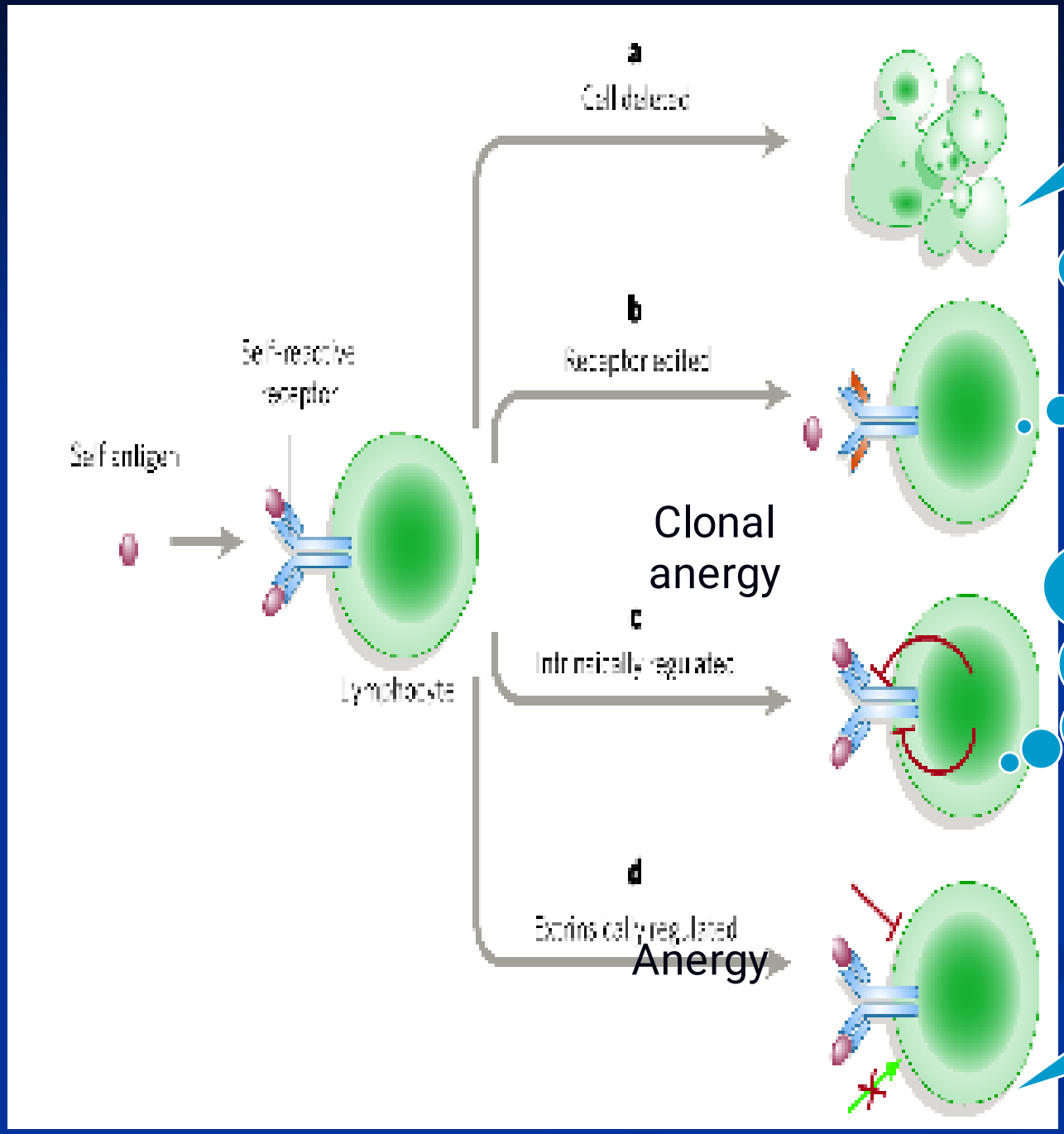
- Immune response – non-self antigens
  - pathogenic
- State of unresponsiveness – self antigens
  - embryonic life /body's own- self antigens

Features Immune Tolerance

- Specific -exposure to antigenic epitopes
  - (non-specific immunosuppression/ immunodeficiency)
- Active - antigen dependent process
- Cells of adaptive immune system
- Tolerance
  - T cell level longer lasting than B cell level

Immune Tolerance – induced ?

Cellular Strategies



Expressing factors mediating cell death

Expressing enzymes mediating receptor edition

Intrinsic factors - reduce the ability of the cells to be triggered by self-reactive receptors

Limiting / providing - external factor

- Tolerance is generated at 2 levels
  - Central tolerance – primary lymphoid organs
  - Peripheral tolerance - as a back-up process

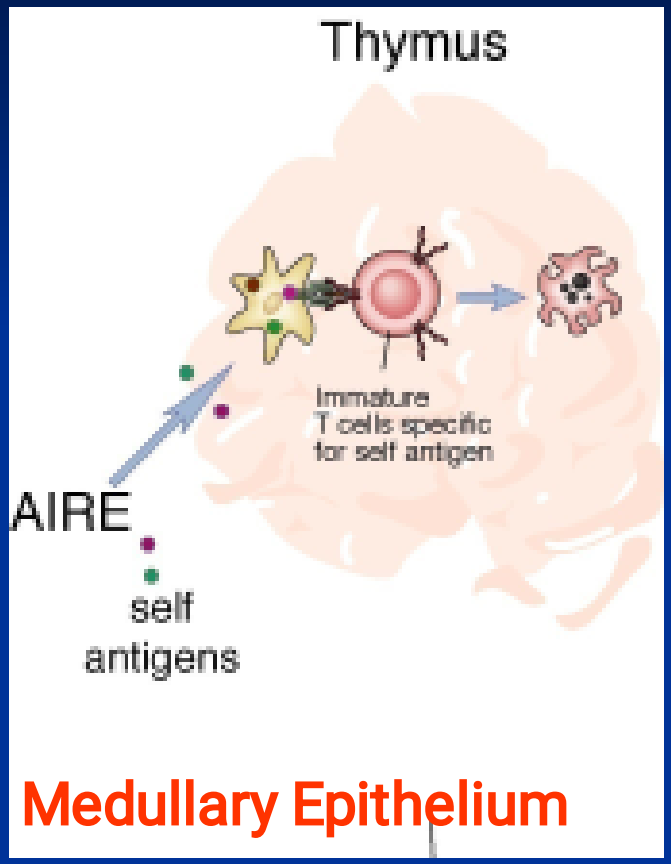
Central Tolerance-Bone Marrow

- What determines the discrimination of self from non-self?
  - Strength of the receptor cross linking
  - Intracellular signaling
- Mechanisms
  - Clonal deletion
  - Receptor edition

Central Tolerance-Thymus

- What determines the discrimination of self from non-self?
  - Binding affinity of TCR for self-peptide + MHC
- Mechanisms :
  - Clonal deletion
    - ↑FAS/FASL
  - Receptor edition
    - TCR -VDJ recombination

Deletion of self-reactive T cells in the thymus: AIRE drives self antigen expression in thymus



Medullary epithelium

Expresses B71

AIRE mediate organ specific protein expression

Highly self reactive TCR

↑BIM –pro-apoptotic

↑FAS/FASL

(Negative selection)

AIRE is a putative transcription factor that stimulates expression of many self antigens in the medullary epithelial cells of the thymus, required for deletion of self-reactive thymocytes;

Figure from Abbas, Lichtman and Pillai. Cellular and Molecular Immunology 6th ed, 2007

Peripheral Tolerance

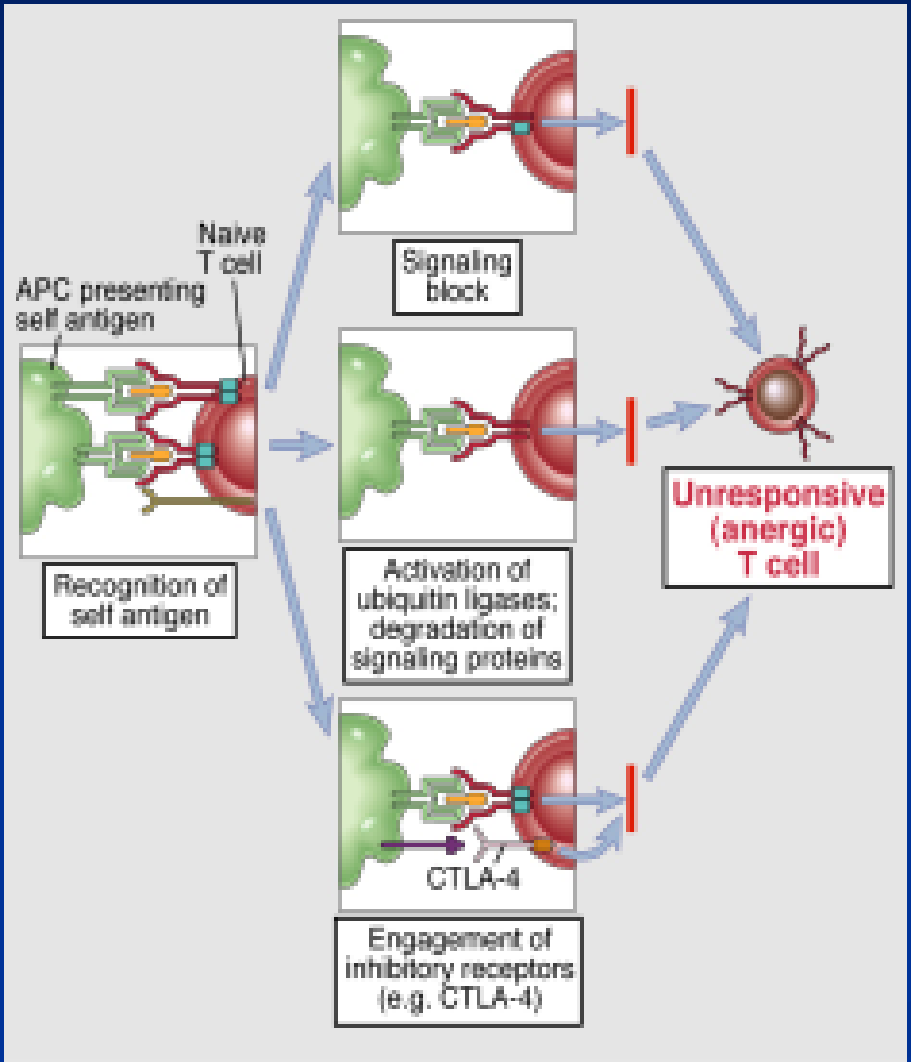
- Central tolerance does not delete autoreactive T cells
  - Organ-sequestered antigens
  - Cryptic epitopes
- T cells must be kept tolerant by
  - Elimination/ Clonal deletion
  - Receptor edition
  - Functional inactivation (anergy)
  - Suppression

Peripheral Tolerance

- Clonal deletion
  - Induction pro apoptotic factor
    - BAM/BAX/BAK
    - FAS
  - Limiting survival factors
    - BAFF
    - IL-7
  - Receptor edition
    - BCR hypermutation (Germinal centers of lymph nodes)

T cell Anergy / Functional inactivation

Regulated by Intrinsic factors



1. Induction of inhibitory receptors CTLA4

2. Induction of ubiquitin ligases

Tags TCR–CD28 or cytokine receptor signalling molecules

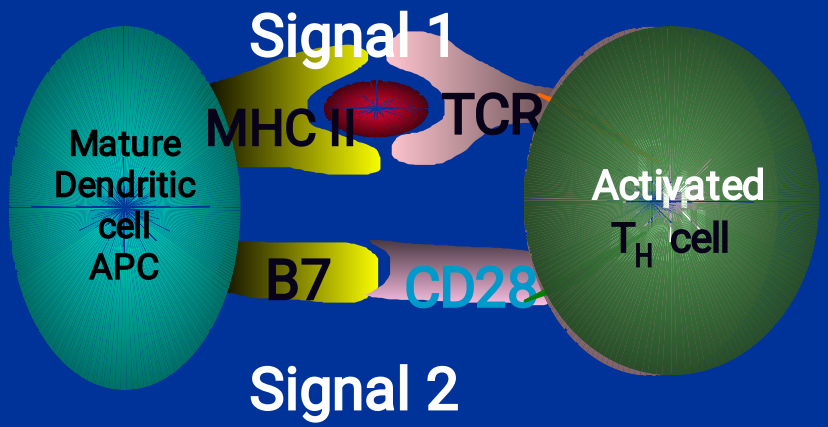
Endocytosis & promote proteolytic degradation

Figure from Abbas, Lichtman and Pillai. Cellular and Molecular Immunology 6th ed, 2007

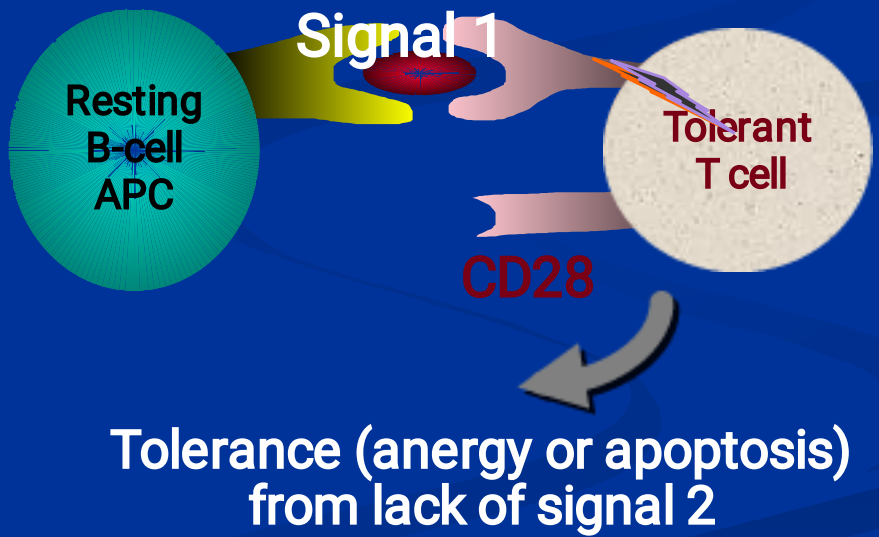
T cell Anergy/ Functional inactivation

Regulated by Extrinsic factors

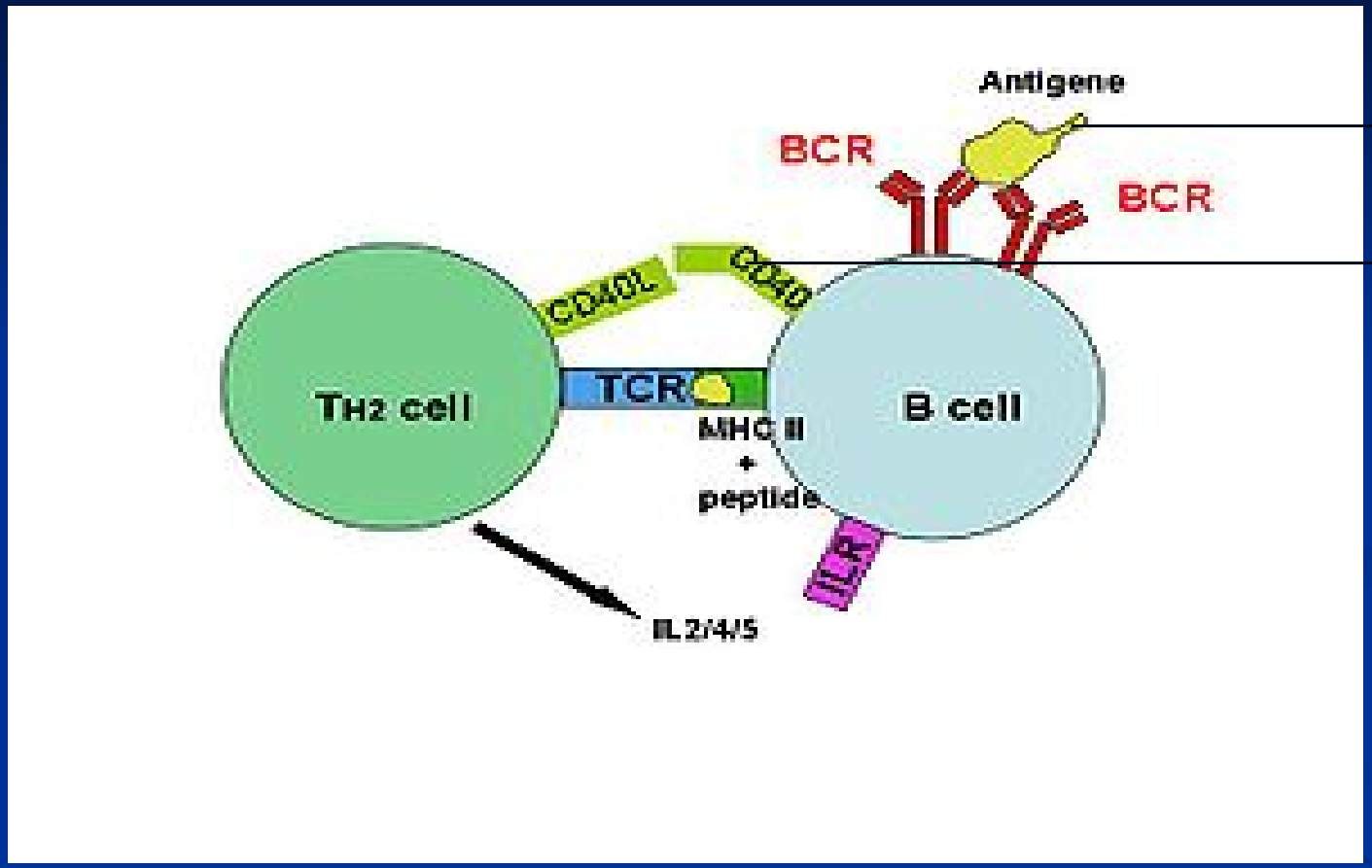
T-cell Activation



Tolerance in mature T cells



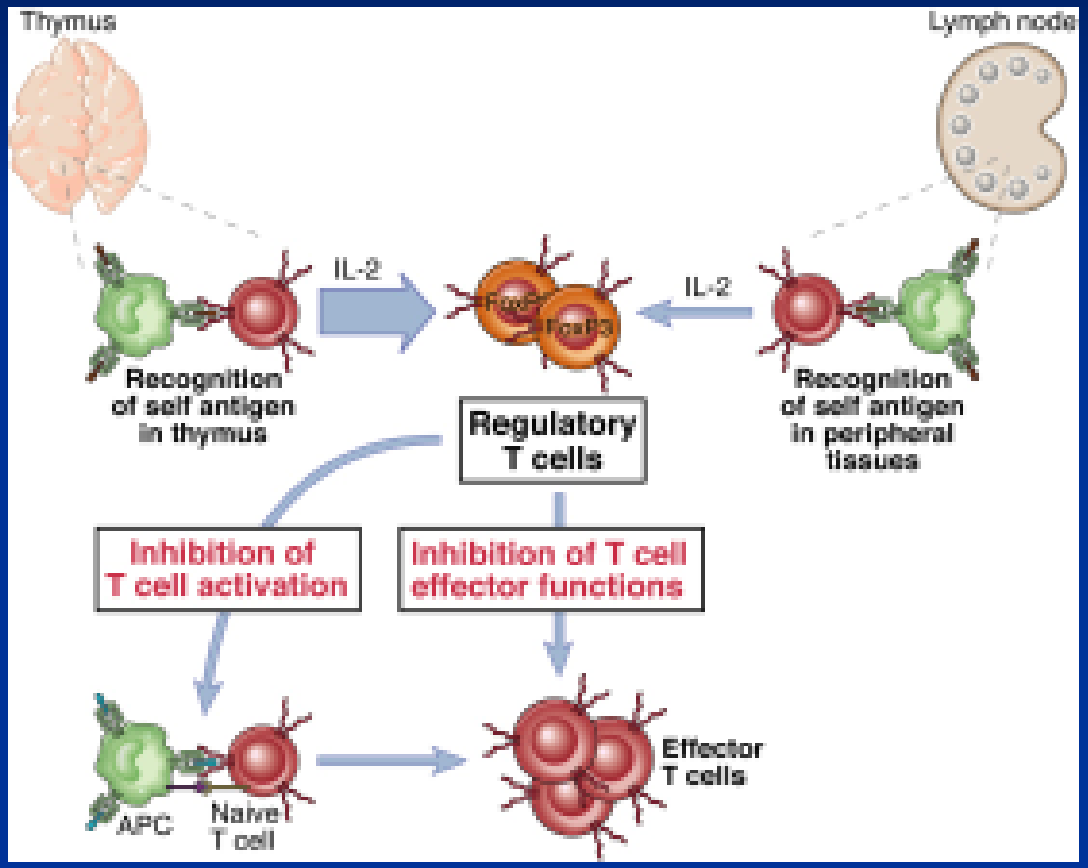
B cell Anergy/ Functional inactivation



2nd signal -B-cell proliferation and differentiation into antibody-secreting plasma cells

Active suppression

Regulated by Extrinsic factors



Providing factors like cytokine – TGF-β

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Induce transcription factor Foxp3

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Supressive cells – Tregs

From Abbas, Lichtman and Pillai. Cellular and Molecular Immunology 6th ed, 2007