Immune regulation and tolerance

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Lecture outline

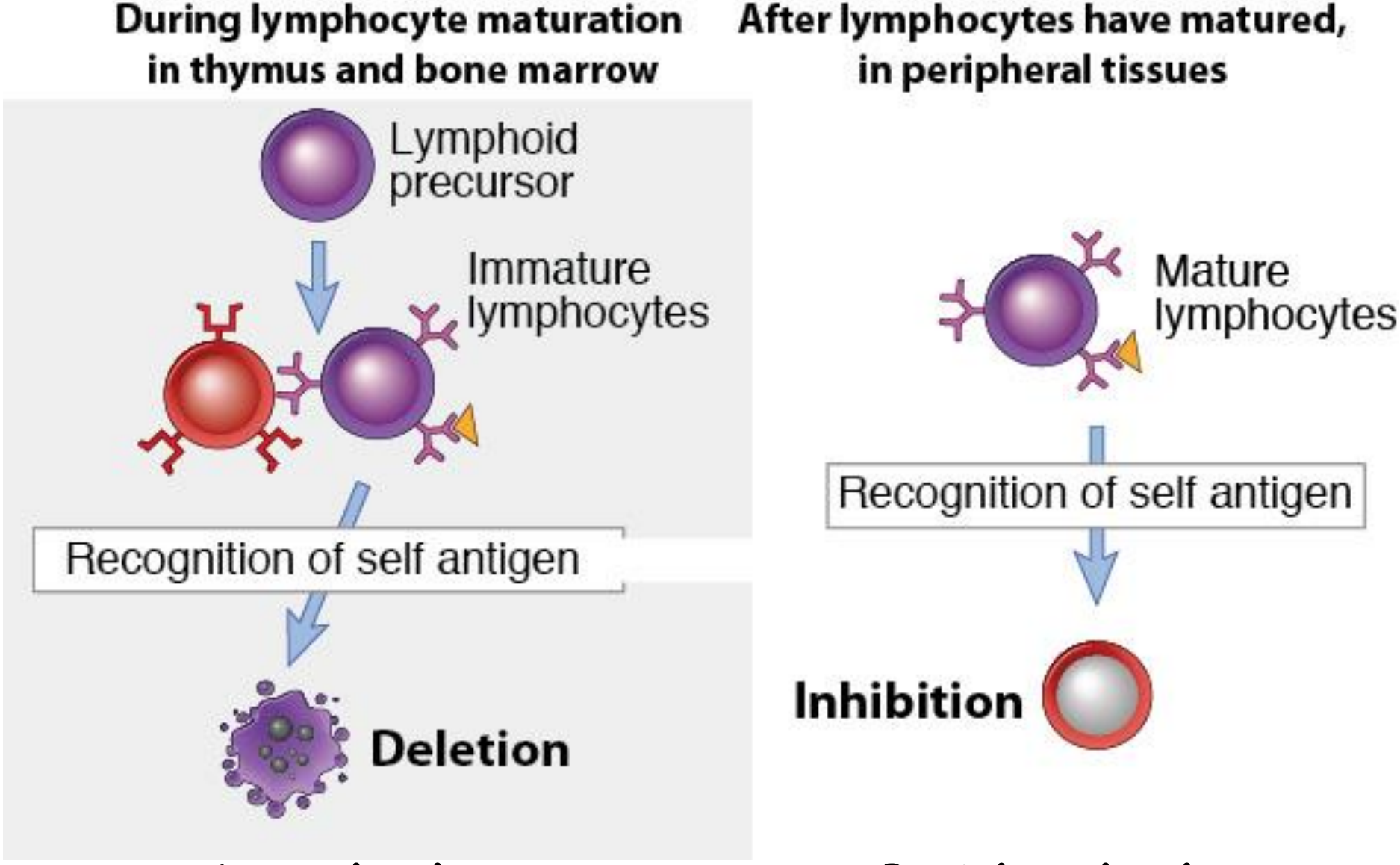
- Self-tolerance; central and peripheral tolerance
- Inhibitory receptors of T cells
- Regulatory T cells

Immunological tolerance

- **Definition:**
  - unresponsiveness to an antigen induced by exposure of lymphocytes to that antigen; antigen-specific (unlike "immunosuppression")

- **Significance:**
  - All individuals are tolerant of their own antigens (self-tolerance); breakdown of self-tolerance results in autoimmunity
  - **Therapeutic potential:** Inducing tolerance may be exploited to treat autoimmune and allergic diseases

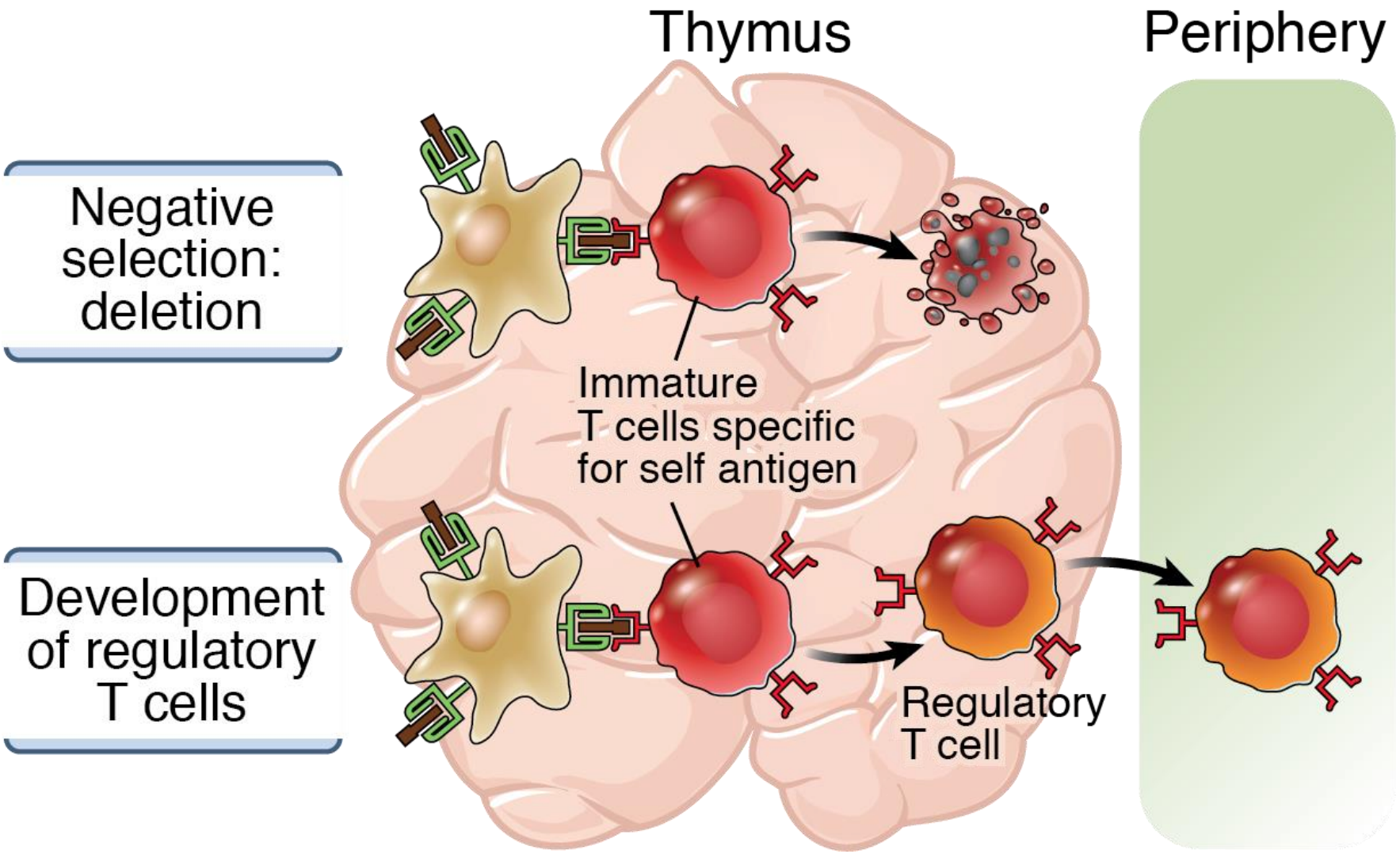
Where and when is self-tolerance induced?



Central tolerance

Peripheral tolerance

Consequences of self antigen recognition in thymus



What self antigens are seen in the thymus?

- Ubiquitous cell-associated and circulating proteins

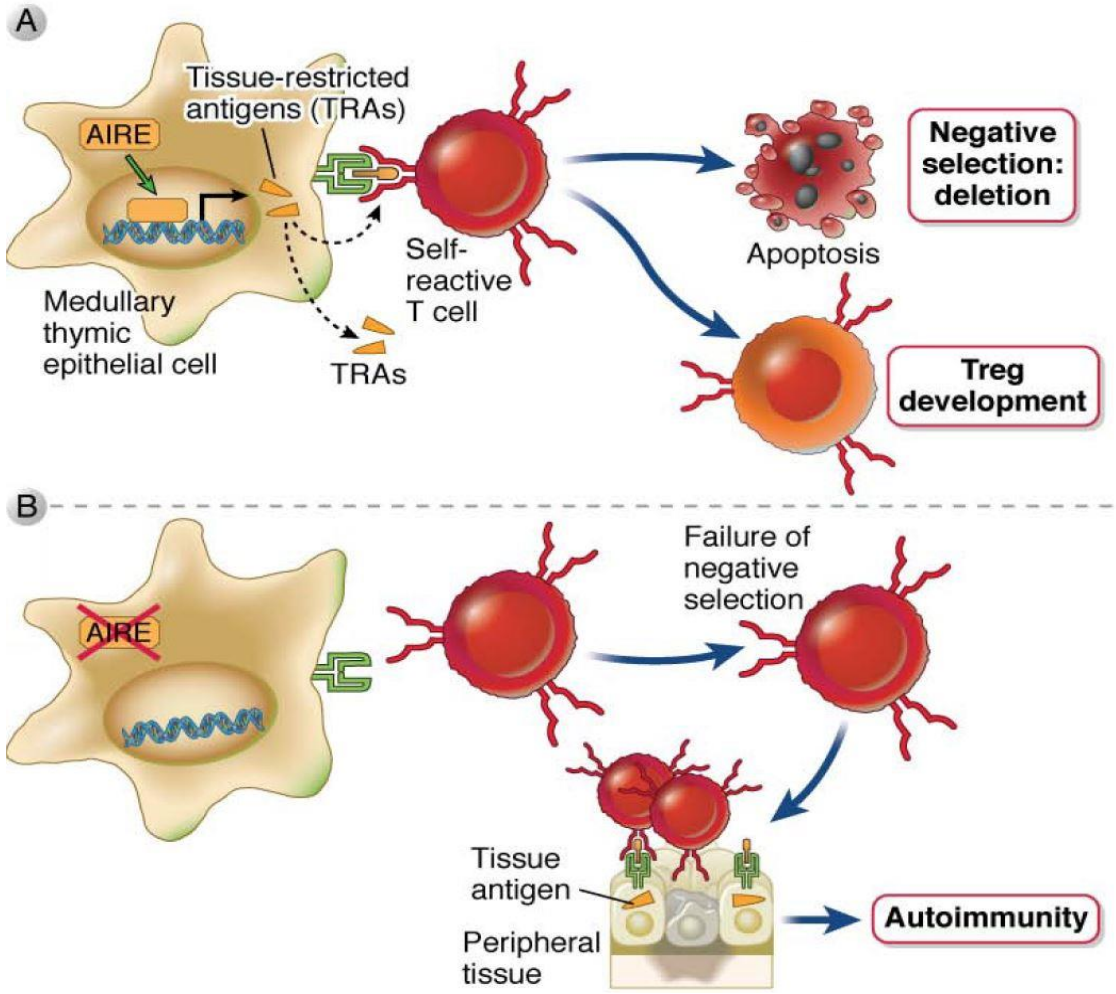
- The thymus has a special mechanism for displaying peripheral tissue antigens in thymic medullary epithelial cells, where they signal self-reactive thymocytes for death

Consequences of AIRE mutation

- Human disease: autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia (APECED), also called autoimmune polyendocrine syndrome (APS-1)
  - Associated gene identified by positional cloning, named *AIRE* ("autoimmune regulator")

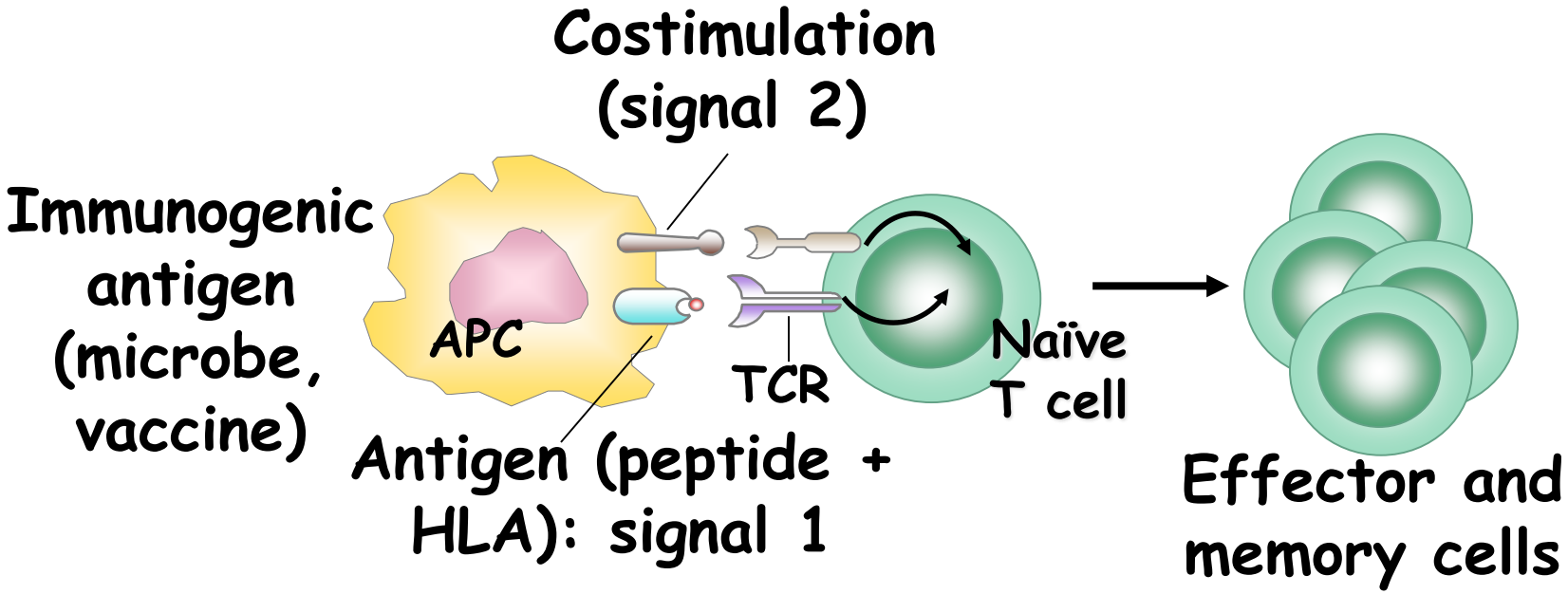
- Mouse knockout: autoantibodies against multiple endocrine organs, retina
  - Failure to express many self antigens in the thymus (revealed by transcriptome analysis of normal vs AIRE-/- thymic epithelial cells)

Deletion of self-reactive T cells in the thymus: how are self antigens expressed in the thymus?

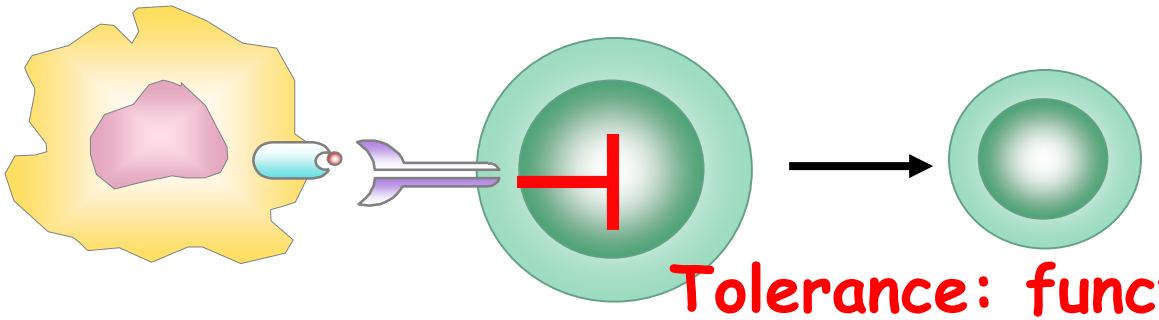


AIRE (autoimmune regulator) is a transcription factor that stimulates thymic expression of many self antigens which are largely restricted to peripheral tissues

Peripheral tolerance



Tolerogenic antigen (e.g. self)



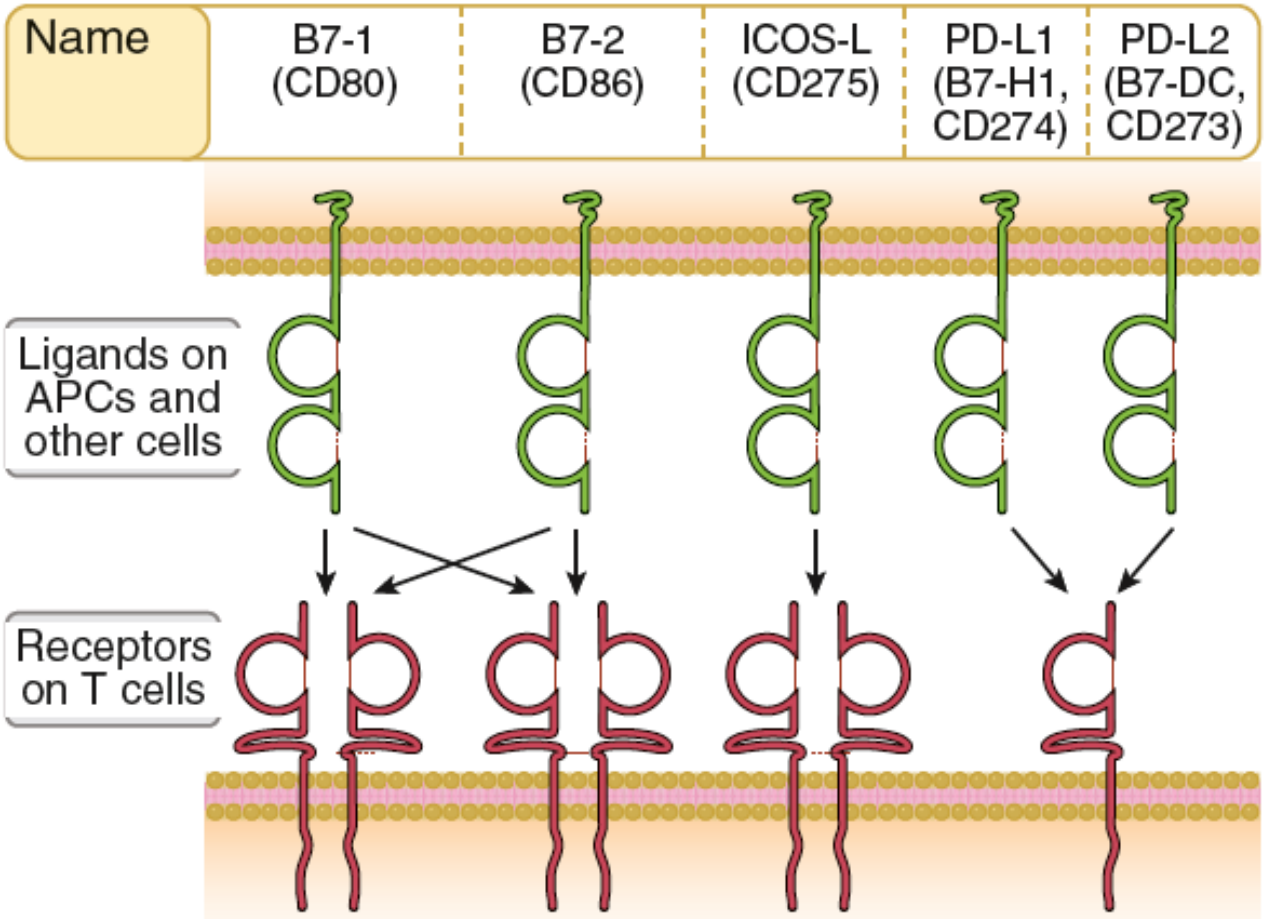
Tolerance: functional inactivation or cell death, or sensitive to suppression

Inhibitory receptors of T cells

- Prevent reactions against self antigens (their physiologic function)

- Suppress immune responses to some tumors, chronic infections (HCV, HIV)
  - Therapeutic application: checkpoint blockade for cancer immunotherapy

The B7:CD28 families



Major functions of selected B7-CD28 family members

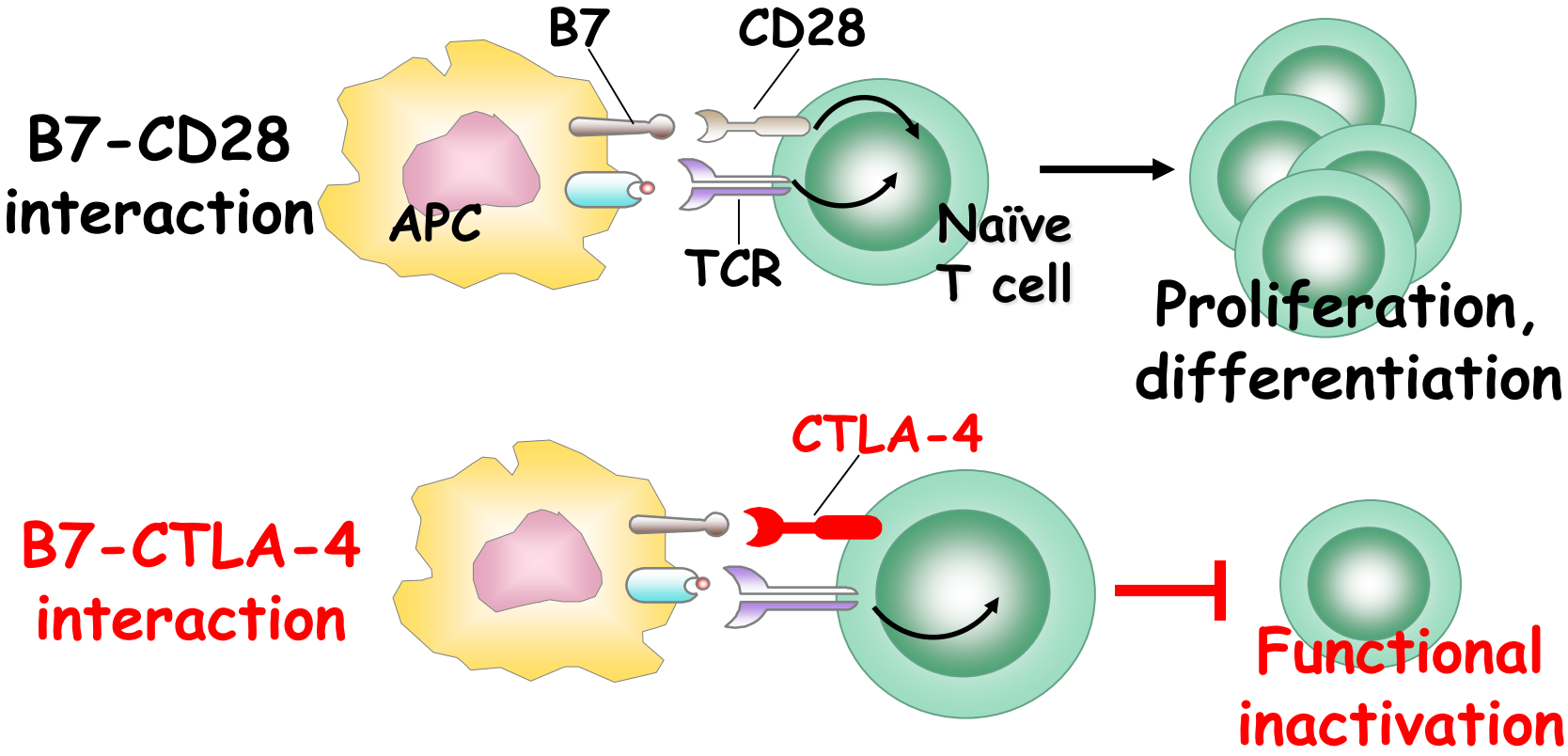
Activation

- CD28-B7: initiation of immune responses
- ICOS-ICOS-L: T cell help in germinal center reactions (antibody responses)

Inhibition

- CTLA-4-B7: inhibits early T cell responses in lymphoid organs
- PD-1:PD-L1,2: inhibits effector T cell responses in peripheral tissues

The opposing functions of CD28 and CTLA-4



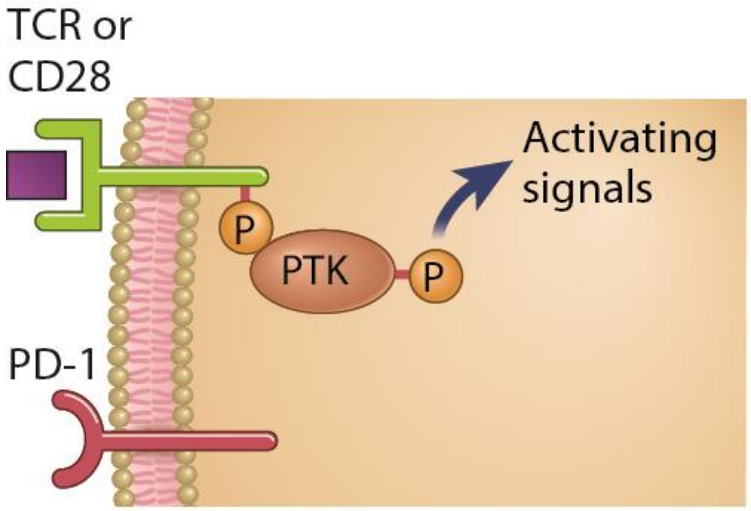
Knockout of CTLA-4 in mice and mutation in humans results in immune dysregulation (lymphoproliferation, multi-organ inflammation)

The PD-1 inhibitory pathway

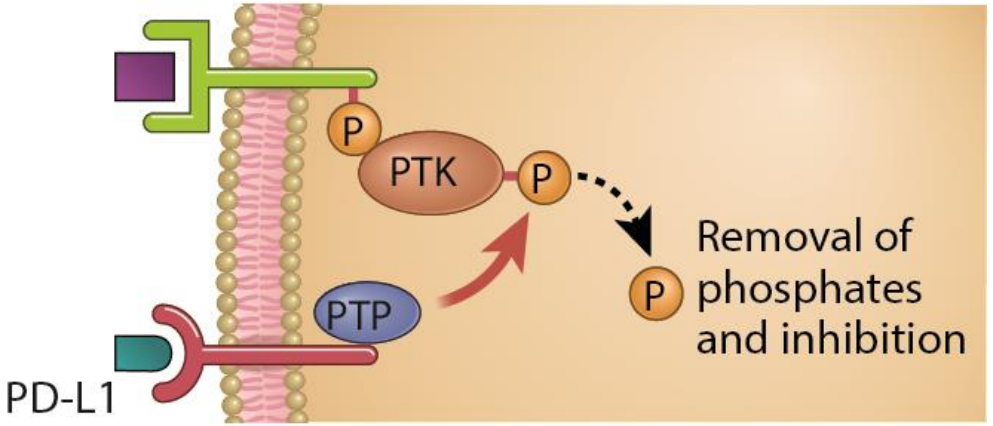
- PD-1 recognizes two widely expressed ligands (PD-L1, PD-L2)
- Knockout of PD-1 leads to autoimmune disease (less severe than CTLA-4-KO)
- Role of PD-1 in T cell suppression in chronic infections, tumors?

Action of PD-1

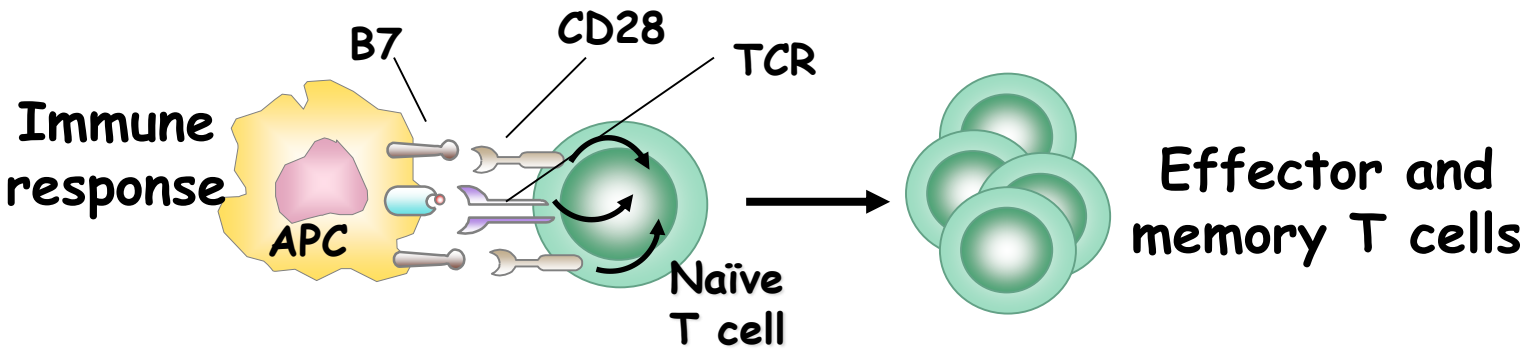
Normal response

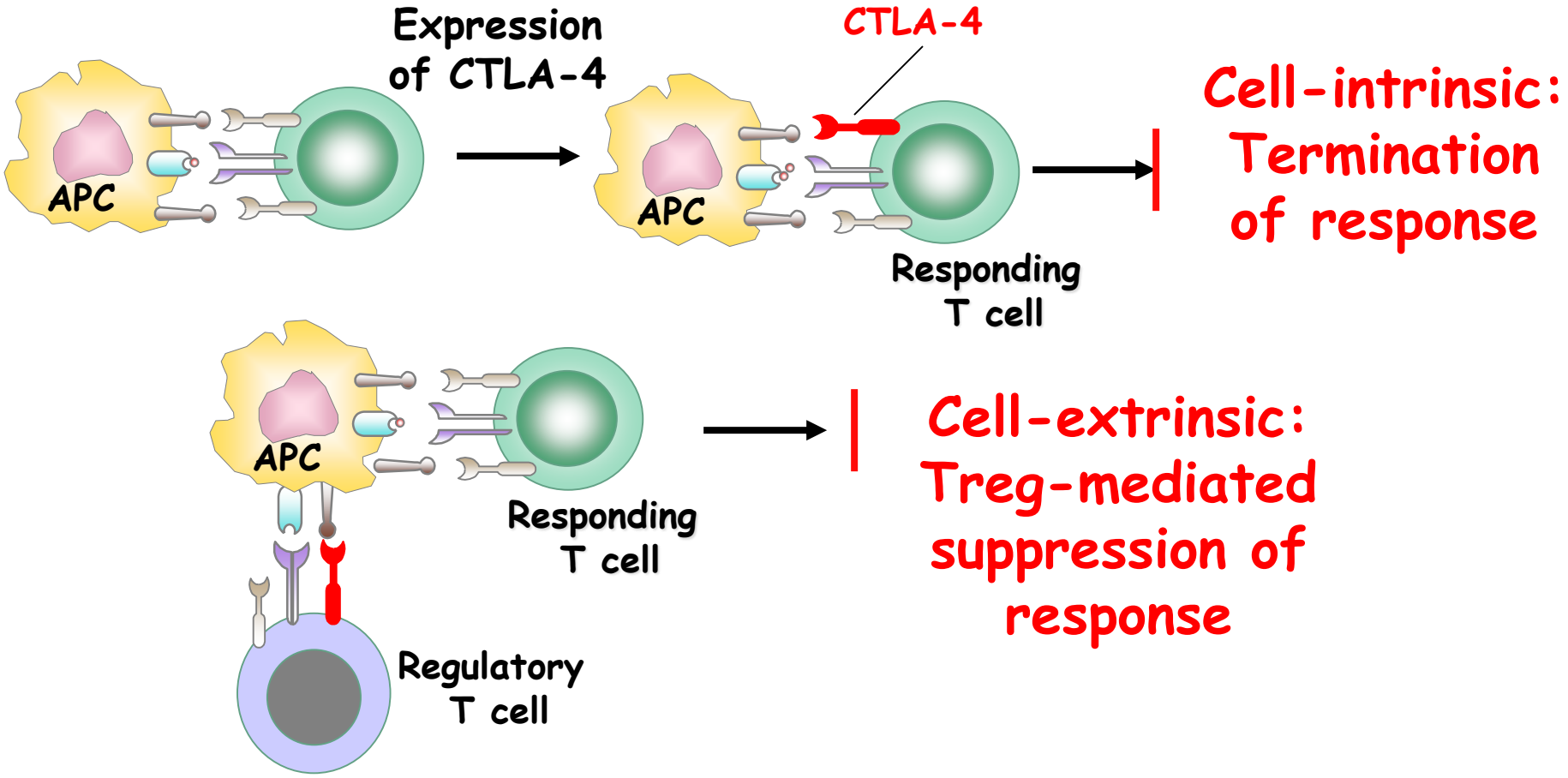


PD-1 engagement

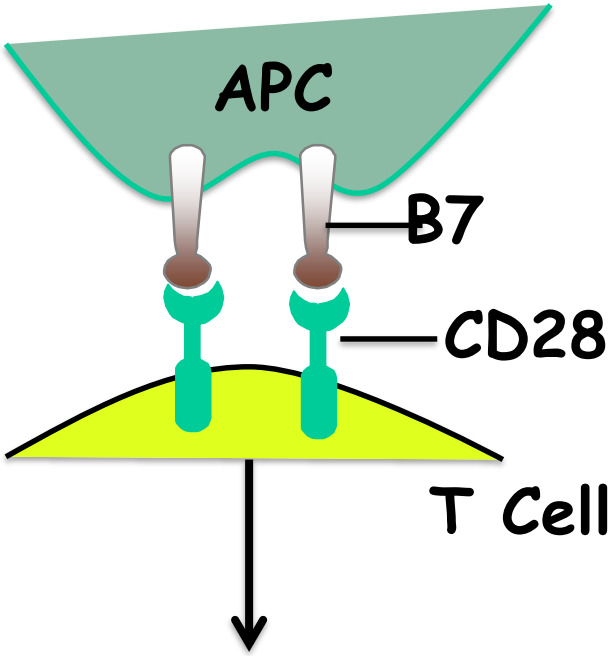


Actions of CTLA-4



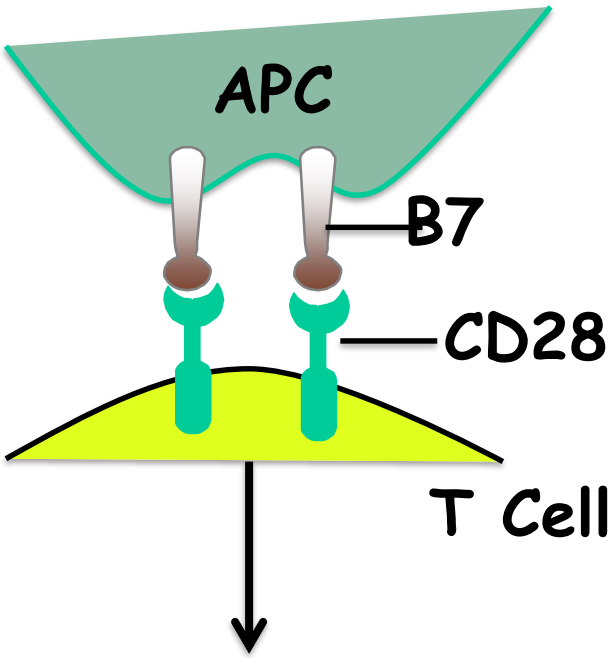


CTLA-4 competitively inhibits B7-CD28 engagement

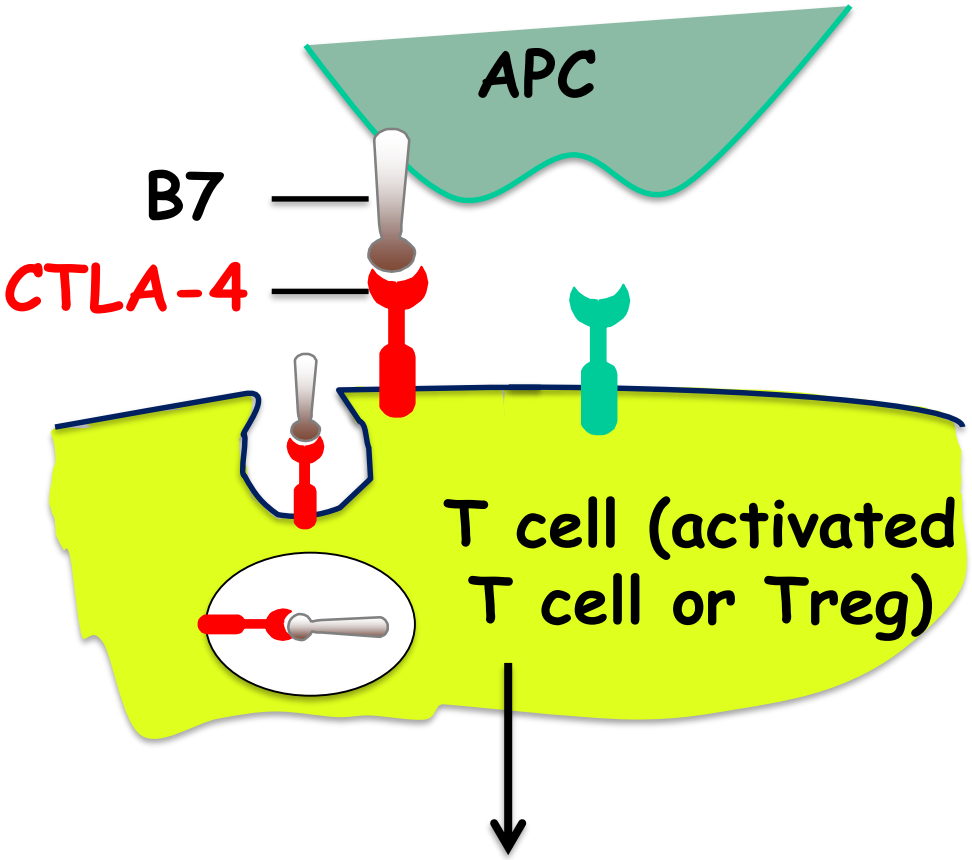


Costimulation →
T cell activation

CTLA-4 competitively inhibits B7-CD28 engagement



Costimulation →
T cell activation

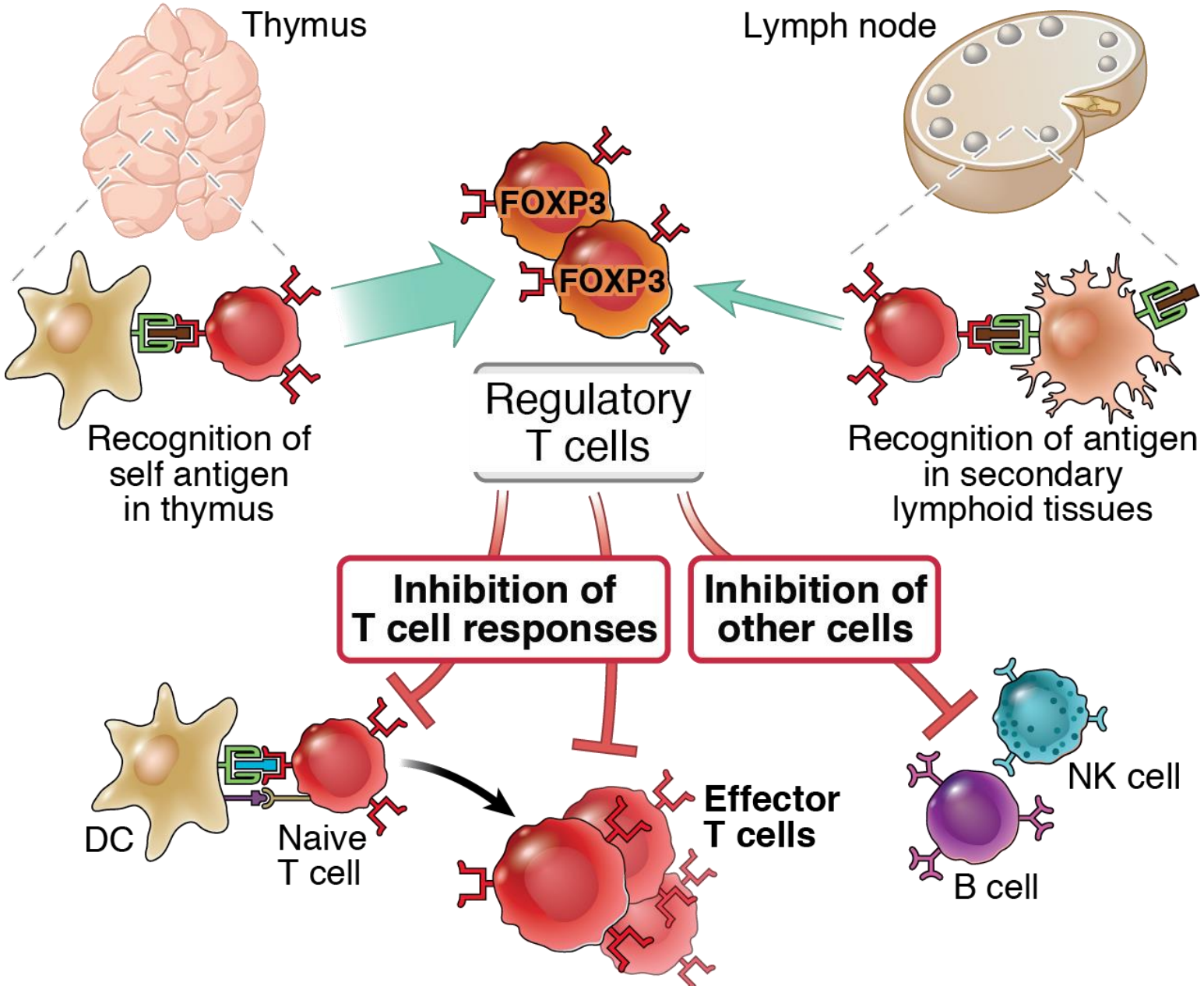


CTLA-4 blocks and removes
B7 → lack of costimulation
→ T cell inhibition

Functions of CTLA-4

- Limits activation of responding T cells
- Mediates suppressive function of regulatory T cells (Tregs)
- How does the T cell choose to use CD28 to be activated (e.g. with microbes) or CTLA-4 to shut down (e.g. with self Ag)?
  - Level of B7 expression and affinity of receptors: Low B7 (e.g. when DC is displaying self or tumor antigen) --> engagement of high-affinity CTLA-4
  - High B7 (e.g. after microbe encounter) --> engagement of lower affinity CD28

Regulatory T cells



Properties of regulatory T cells

- **Phenotype:** CD4+, high IL-2 receptor (CD25), Foxp3 transcription factor; other markers

- **Essential features** of stable Tregs:
  - Foxp3 expression: requires demethylated non-coding CNS2 sequence in promoter
  - CD25 (IL-2Rα) expression: IL-2 is a necessary survival factor
  - CTLA-4 expression: required for suppressive function of most Tregs
  - (Inability to produce IL-2)

The significance of Foxp3+ Tregs

- Genetic evidence: Foxp3 mutations --> autoimmune disease (IPEX); in mice, disease can be corrected by providing normal Foxp3+ cells

- Do defects in Foxp3+ Tregs or resistance to Treg-mediated suppression contribute to common autoimmune diseases?
  - Inconsistent and variable data

Mechanisms of action of Foxp3+ Tregs

- CTLA-4 on Tregs removes B7 on APCs, reduces CD28 engagement and T cell activation
  - Genetic deletion of CTLA-4 in Foxp3+ cells results in severe systemic autoimmunity and lymphoproliferation
  - Commonly used assay for Treg function in humans bypasses the need for B7 and cannot measure this activity

Mechanisms of action of Foxp3+ Tregs

- CTLA-4 on Tregs removes B7 on APCs, reduces CD28 engagement and T cell activation

- **Inhibitory cytokines produced by Tregs (IL-10, others?) suppress immune responses (DCs, Macs, T cells)**
  - **IL-10 is especially important for regulating mucosal immune responses (deletion of IL10 in Foxp3+ cells results in colitis)**

- **Consumption of IL-2**
- **Many others reported**

Role of Tregs in fetal tolerance

- In evolution, placentation developed at the same time as the ability to generate FoxP3+ peripheral Tregs
- Paternal antigens expressed in the fetus induce long-lived antigen-specific Tregs
- Elimination of fetal antigen-specific Tregs in mice results in fetal resorption

- Anatomic restriction of immune regulation?
- Role in humans? Are defects in regulatory memory the basis of recurrent fetal loss?

Regulatory T cells

- Explosion of information about the generation, properties, functions and significance of these cells
- Will cellular therapy with ex vivo expanded Treg become a reality?
- Therapeutic goal: induction or activation of Treg in immune diseases

The therapeutic potential of regulatory T lymphocytes

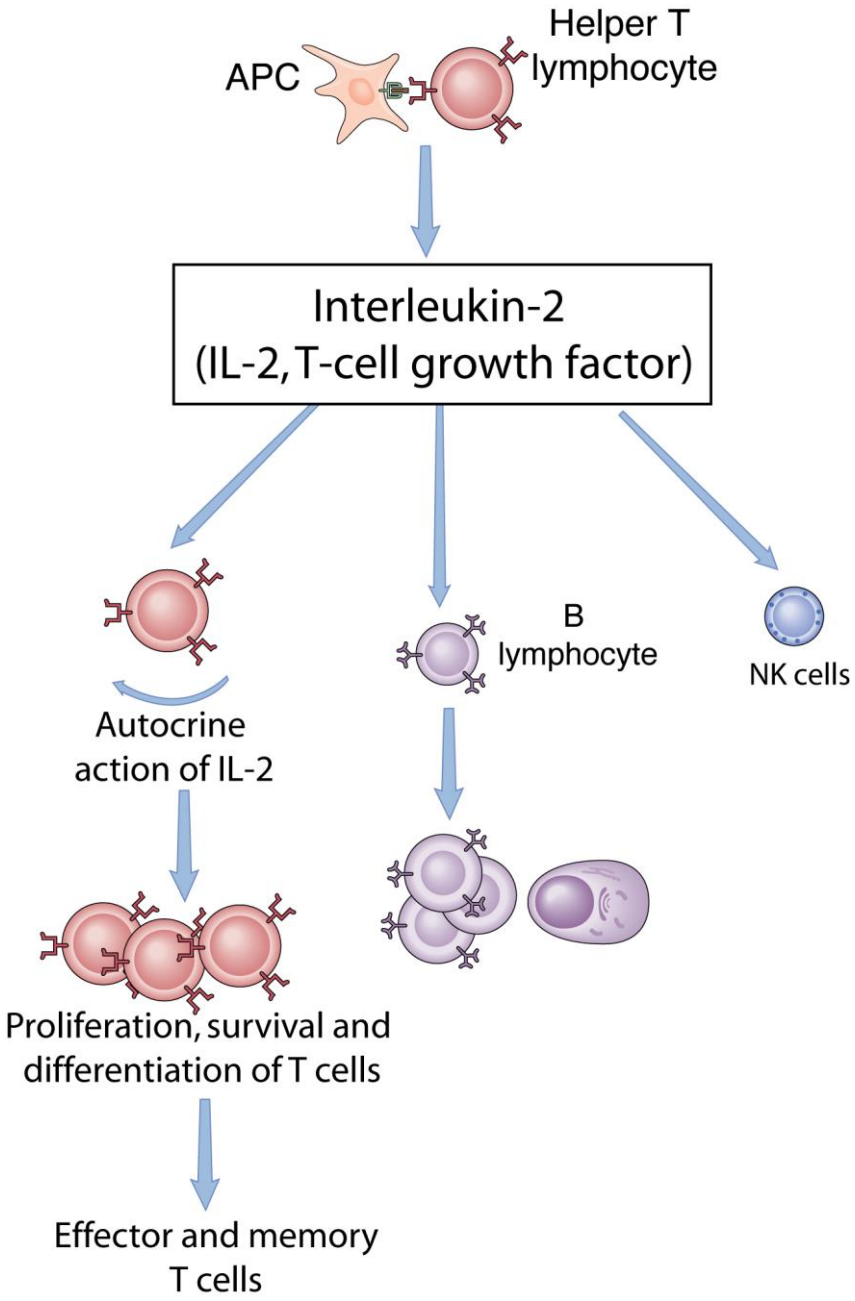
- Cell transfer of autologous Tregs to suppress immune responses
  - Grow up patient's Tregs ex vivo
  - Ongoing clinical trials in graft rejection, T1D show it is safe
  - Very little efficacy data
  - Technically difficult, individualized

The therapeutic potential of regulatory T lymphocytes

- Cell transfer of autologous Tregs to suppress immune responses

- **Administer antigen or cytokine in ways that preferentially induce Tregs?**
  - **Antigen without adjuvant?**
  - **IL-2**

Functions of Interleukin-2: the dogma



The unexpected biology of IL-2

- Interleukin-2 is the prototypic T cell growth factor (TCGF), required for initiating clonal expansion of T cells in response to antigen

- **Prediction**: what will be the consequence of eliminating IL-2 or the IL-2 receptor?

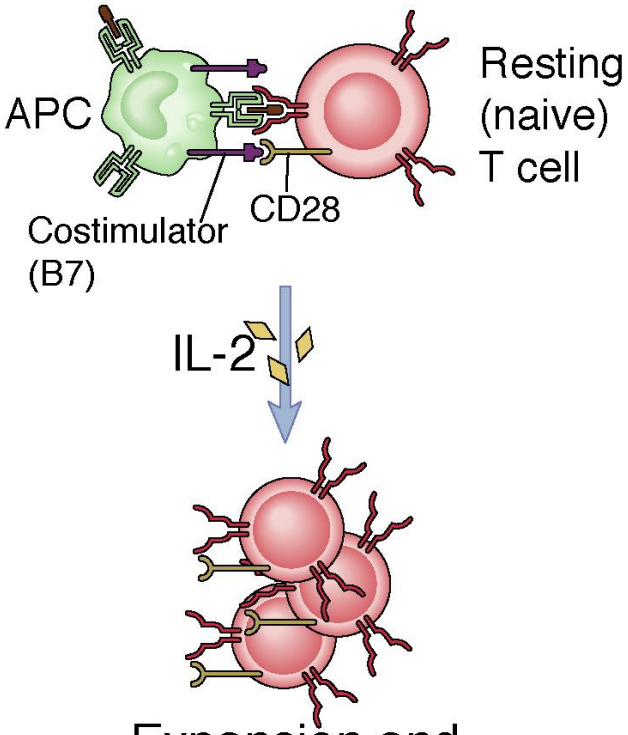
The unexpected biology of IL-2

- Interleukin-2 is the prototypic T cell growth factor (TCGF), required for initiating clonal expansion of T cells in response to antigen

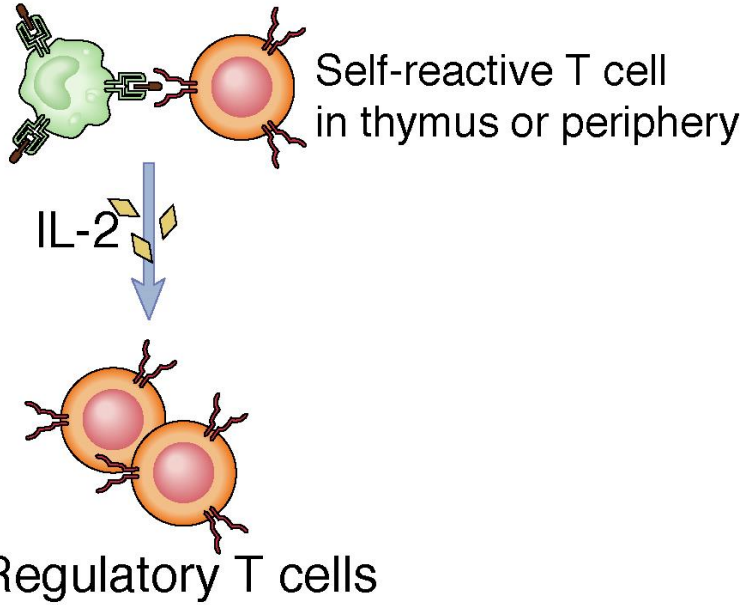
- BUT: knockout of IL-2 or the α or β chain of the IL-2R results not in immune deficiency but in systemic autoimmunity and lymphoproliferation

Dual roles of IL-2 in T cell responses

Induction of immune response



Control of immune response



Surprising conclusion from knockout mice: the non-redundant function of IL-2 is in controlling immune responses

Therapeutic potential of IL-2: a revision

- IL-2 was originally used to boost immune responses in cancer, HIV infection (enhancing effector and memory T cells)
  - IL-2 treatment can increase number and functional activity if Tregs
- Use of IL-2 to boost Tregs: design IL-2 to bind to high-affinity CD25
  - Low-dose IL-2
  - Mutant IL-2 that binds preferentially to CD25

Regulating immune responses: where are we?

- Elucidating the mechanisms of immune regulation is one of the dominant themes of modern Immunology; obvious relevance to immune-mediated inflammatory diseases, therapeutics, vaccines

- Already leading to new therapeutic strategies

- Continuing challenge is to establish the importance of control mechanisms in the development of inflammatory diseases