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Immunological tolerance and immune regulation -- 1

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Lecture outline

- Principles of immune regulation
- Self-tolerance; mechanisms of central and peripheral tolerance
- Inhibitory receptors of T cells

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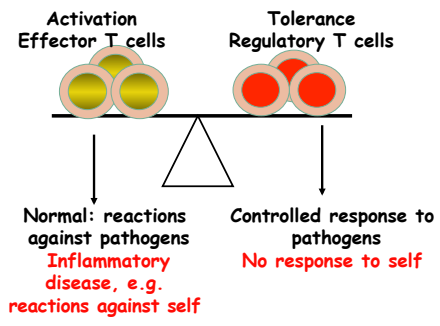
The immunological equilibrium: balancing lymphocyte activation and control



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The importance of immune regulation

- To avoid excessive lymphocyte activation and tissue damage during normal protective responses against infections
- To prevent inappropriate reactions against self antigens ("self-tolerance")
- Failure of control mechanisms is the underlying cause of immune-mediated inflammatory diseases

Take home messages

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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 prevent graft rejection, treat autoimmune and allergic diseases, and prevent immune responses in gene therapy and stem cell transplantation**

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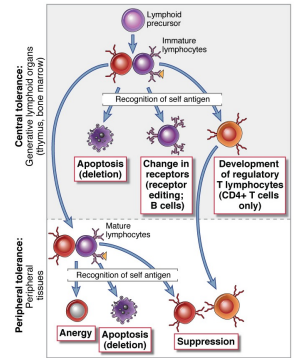
Central and peripheral tolerance to self



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The principal fate of lymphocytes that recognize self antigens in the generative organs is death (deletion), BUT:

Some B cells may change their specificity (called "receptor editing")

Some T cells may differentiate into regulatory (suppressor) T lymphocytes

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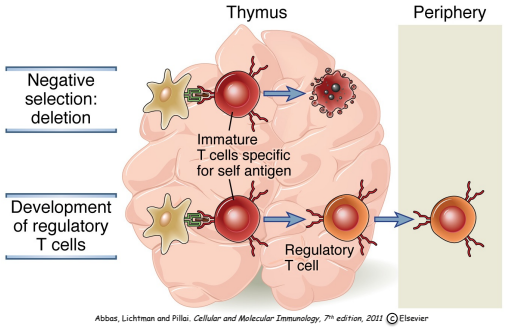
Consequences of self antigen recognition in thymus



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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

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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 --> failure of negative selection

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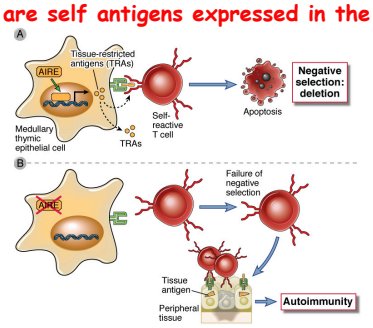
Deletion of self-reactive T cells in the thymus: how are self antigens expressed in the thymus?



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

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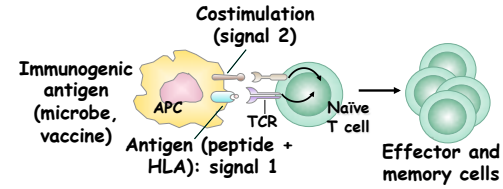
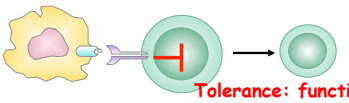
Peripheral tolerance



Tolerogenic antigen (e.g. self)



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

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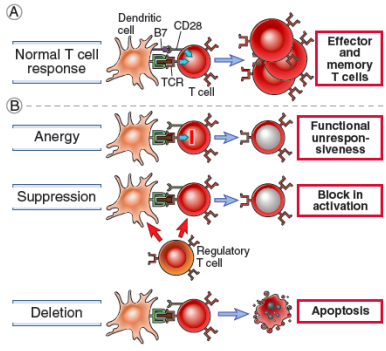
Peripheral T cell tolerance



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T cell anergy

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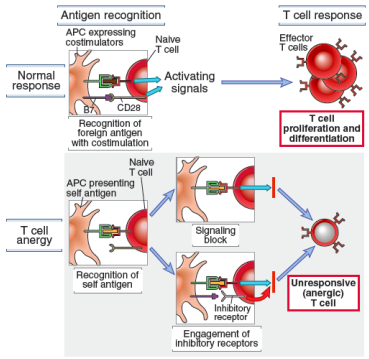

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Inhibitory receptors of the immune system

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- One mechanism by which the system maintains a balance between activation and inhibition is to use different receptors for different outcomes
- Inhibitory receptors are present in NK cells, T cells and B cells; perhaps other immune cells?
- In many instances, activating receptors work by recruiting kinases and inhibitory receptors activate phosphatases

The B7:CD28 families

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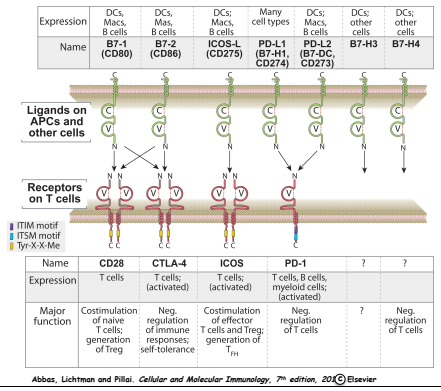

Expression	DCs, Macs, B cells	DCs, Mas, B cells	DCs; Macs, B cells	Many cell types	DCs; Macs, B cells	DCs; other cells	DCs; other cells
Name	**B7-1 (CD80)**	**B7-2 (CD86)**	**ICOS-L (CD275)**	**PD-L1 (B7-H1, CD274)**	**PD-L2 (B7-DC, CD273)**	**B7-H3**	**B7-H4**

Name	**CD28**	**CTLA-4**	**ICOS**	**PD-1**	?	?
Expression	T cells	T cells; (activated)	T cells; (activated)	T cells, B cells, myeloid cells; (activated)		
Major function	Costimulation of naive T cells; generation of Treg	Neg. regulation of immune responses; self-tolerance	Costimulation of effector T cells and Treg; generation of T_{FH}	Neg. regulation of T cells	?	Neg. regulation of T cells

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Major functions of selected B7-CD28 family members

- **B7-CD28:** initiation of immune responses
- **ICOS-ICOS-L:** role in B cell activation in germinal centers
- **B7-CTLA-4:** inhibits early T cell responses in lymphoid organs
- **PD-1:PD-L1,2:** inhibits effector T cell responses in peripheral tissues

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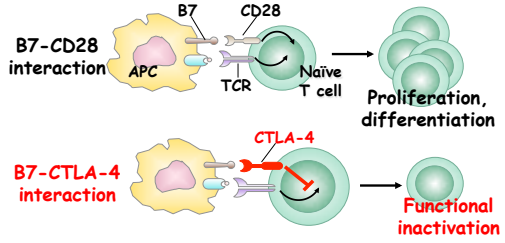
The opposing functions of CD28 and CTLA-4



Knockout of CTLA-4 results in autoimmune disease:
- *multi-organ lymphocytic infiltrate, lethal by 3-4 weeks*
- *lymphadenopathy, splenomegaly*

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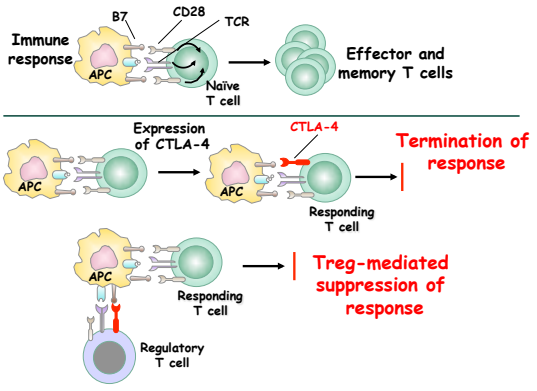
Actions of CTLA-4



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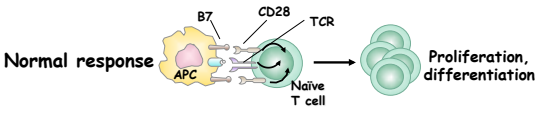
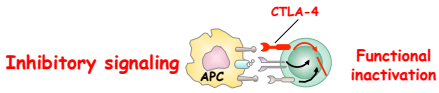
Mechanisms of action of CTLA-4: the original hypothesis





Cytoplasmic tail of CTLA-4 contains ITIM (inhibitory motif), may bind and activate phosphatase

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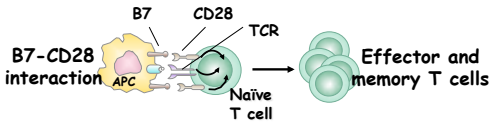
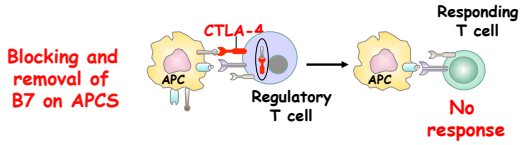
How CTLA-4 on Tregs inhibits responding T cells





Removal of costimulators from APCs ("transendocytosis"): novel mechanism of action of inhibitory receptors

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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)?

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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 antigen) --> engagement of high-affinity CTLA-4; High B7 (e.g. after microbe encounter) --> engagement of lower affinity CD28
  - Kinetics: CD28 early, CTLA-4 later

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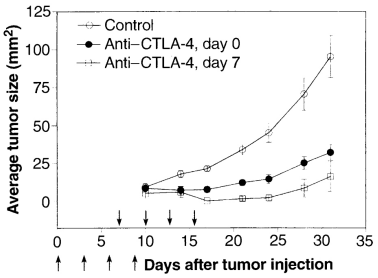
Blocking CTLA-4 promotes tumor rejection: CTLA-4 limits immune responses to tumors



Administration of antibody that blocks CTLA-4 in tumor-bearing mouse leads to tumor regression

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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?

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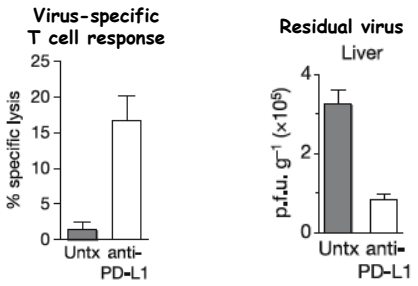
Inhibitory role of PD-1 in a chronic infection



In a chronic viral infection in mice, recognition of virus by specific T cells leads to PD-1 engagement, inhibition of T cell responses, and persistence of the virus. Blocking the PD-1 pathway releases the inhibition, enhances the T cell response, and leads to viral clearance.

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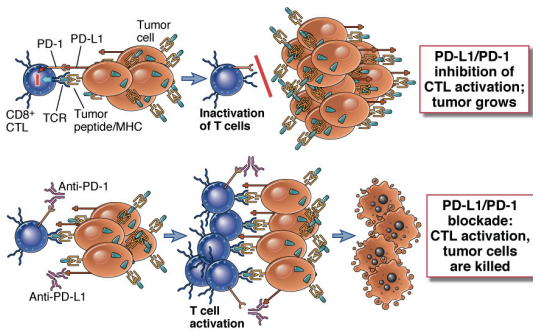
PD-1 limits T cell responses to tumors



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Actions of PD-1

- PD-1 attenuates TCR signaling in responding T cells
  - Limits harmful consequences of chronic stimulation with persistent antigen (self, tumors, chronic viral infections)
- Greater role in CD8 than in CD4 T cells
- Also expressed on follicular helper T cells; function?

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Functions of CTLA-4 and PD-1

	CTLA-4	PD-1
Major site of action	Lymphoid organs	Peripheral tissues
Stage of immune response suppressed	Induction	Effector phase
Main signals inhibited	CD28 costimulation (by reducing B7)	Chronic antigen receptor stimulation
Cell type suppressed	CD4+ > CD8+	CD8+ > CD4+
Inflammatory reactions following antibody treatment	More severe	Milder

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Inhibitory receptors of T cells

- Prevent reactions against self antigens (their physiologic function)
- Suppress immune responses to some tumors, chronic infections (HCV, HIV)
- Similar roles are established for both CTLA-4 and PD-1

Take home messages

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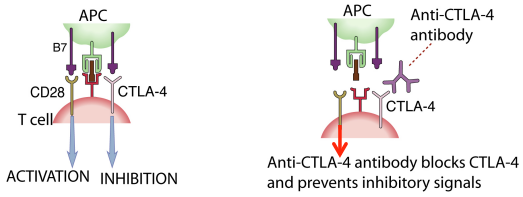
Therapeutics based on inhibitory receptors
2. Removing the brakes on the immune response



Anti-CTLA-4 antibody is approved for tumor immunotherapy (enhancing immune responses against tumors)
Even more impressive results with anti-PD-1 in cancer patients

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Risks of blocking CTLA-4 or PD-1

- Blocking a mechanism of self-tolerance leads to:

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Risks of blocking CTLA-4 or PD-1

- Blocking a mechanism of self-tolerance leads to:

- Autoimmune reactions
  - Prostatitis, vitiligo, other inflammatory disorders, often affecting site of cancer
  - Severity of adverse effects has to be balanced against potential for treating serious cancers
  - Less severe with anti-PD1 antibody

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The emerging paradigm for cancer therapy

- Signaling (e.g. Kinase) inhibitor to block oncogenic pathways in tumor cells

+

- Immune modulator
  - Inhibiting endogenous regulators allows the host to mount an effective immune response (let the immune system do the work itself)
  - May be more effective than vaccination and other approaches for stimulating immunity
  - Anti-PD1 may be more effective than anti-CTLA4 (less toxic, greater effect on CTLs)