ADVANCES IN Cancer IMMUNOTHERAPY™

Mechanisms of Immune-Related Adverse Events

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures: None

I will not be discussing non-FDA approved treatments/indications during my presentation today

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Outline

- Basic principles of immunological tolerance and autoimmunity
- Differential roles of CTLA-4 and PD-1 in maintenance of tolerance
- Mechanisms of breakdown of tolerance by checkpoint blockade

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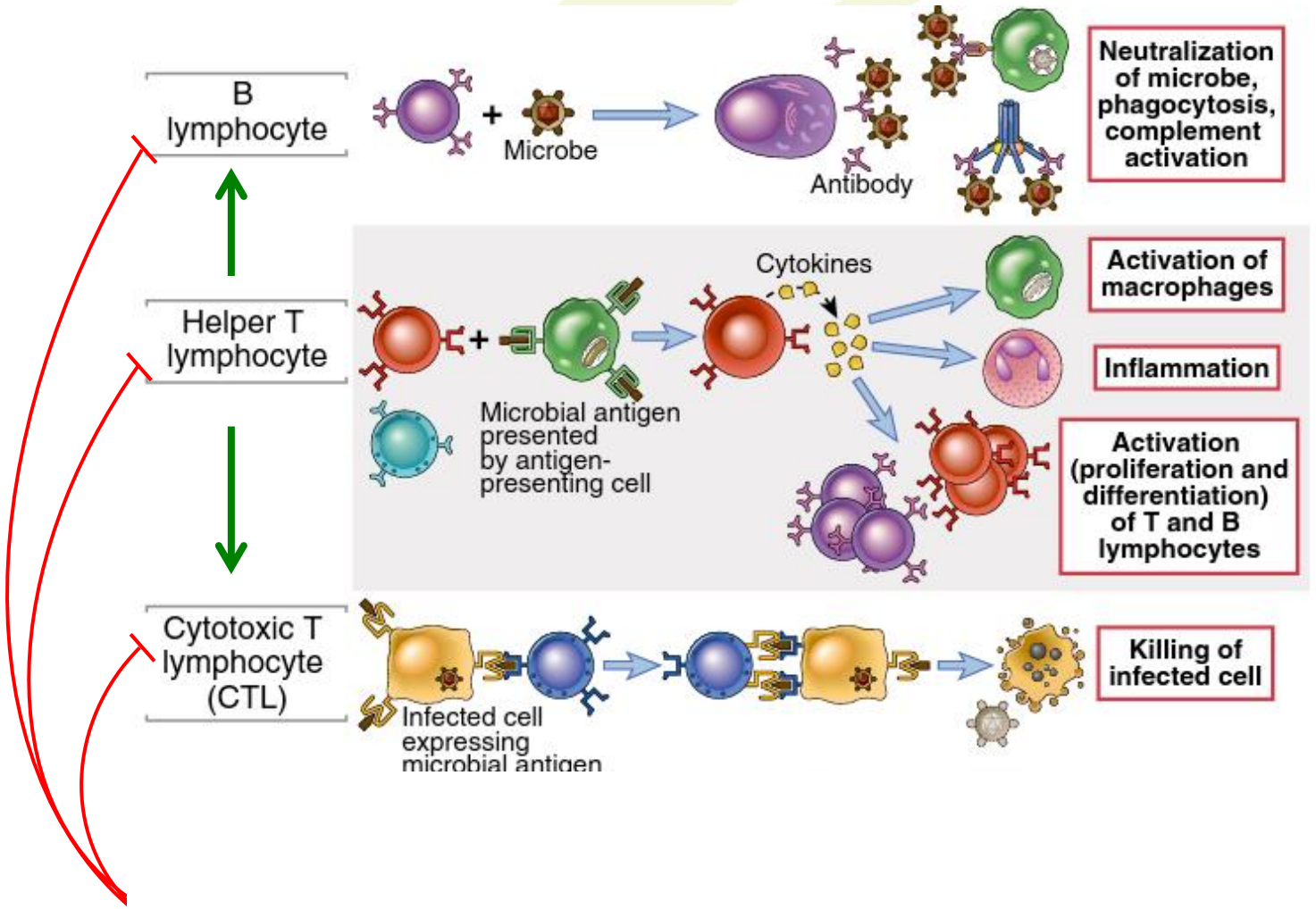
Major Effector Cells of the Immune System



Pemphigus
Myasthenia Gravis
Graves' Disease
AIHA/ITP

Rheumatoid arthritis
Inflammatory bowel disease
Multiple Sclerosis
Celiac Disease
Addison's Disease
Psoriasis

Type I Diabetes
Polymyositis

Loss of function leads to autoimmunity

Abbas, Lichtman, Pillai; Basic Immunology 4th ed.

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Most Autoimmune Diseases are due to Failure of T cell Tolerance

Immunologic Tolerance:
unresponsiveness of T cells to self antigens

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HLA (or MHC) is the strongest genetic factor for susceptibility to autoimmune disease

HLA-associated risk factors for autoimmune disease				
Disease	HLA allotype	Frequency (%)		Relative risk
		Patients	Control	
Ankylosing spondylitis	B27	> 95	9	> 150
Birdshot chorioretinopathy	A29	> 95	4	> 50
Narcolepsy	DQ6	> 95	33	> 40
Celiac disease	DQ2 and DQ8	95	28	30
Type 1 diabetes	DQ8 and DQ2	81	23	14
Subacute thyroiditis	B35	70	14	14
Multiple sclerosis	DQ6	86	33	12
Rheumatoid arthritis	DR4	81	33	9
Juvenile rheumatoid arthritis	DR8	38	7	8
Psoriasis vulgaris	Cw6	87	33	7
Addison's disease	DR3	69	27	5
Graves' disease	DR3	65	27	4
Myasthenia gravis	DR3	50	27	2
Type 1 diabetes	DQ6	< 0.1	33	0.02

Figure 13.24 The Immune System, 3ed. (© Garland Science 2009)

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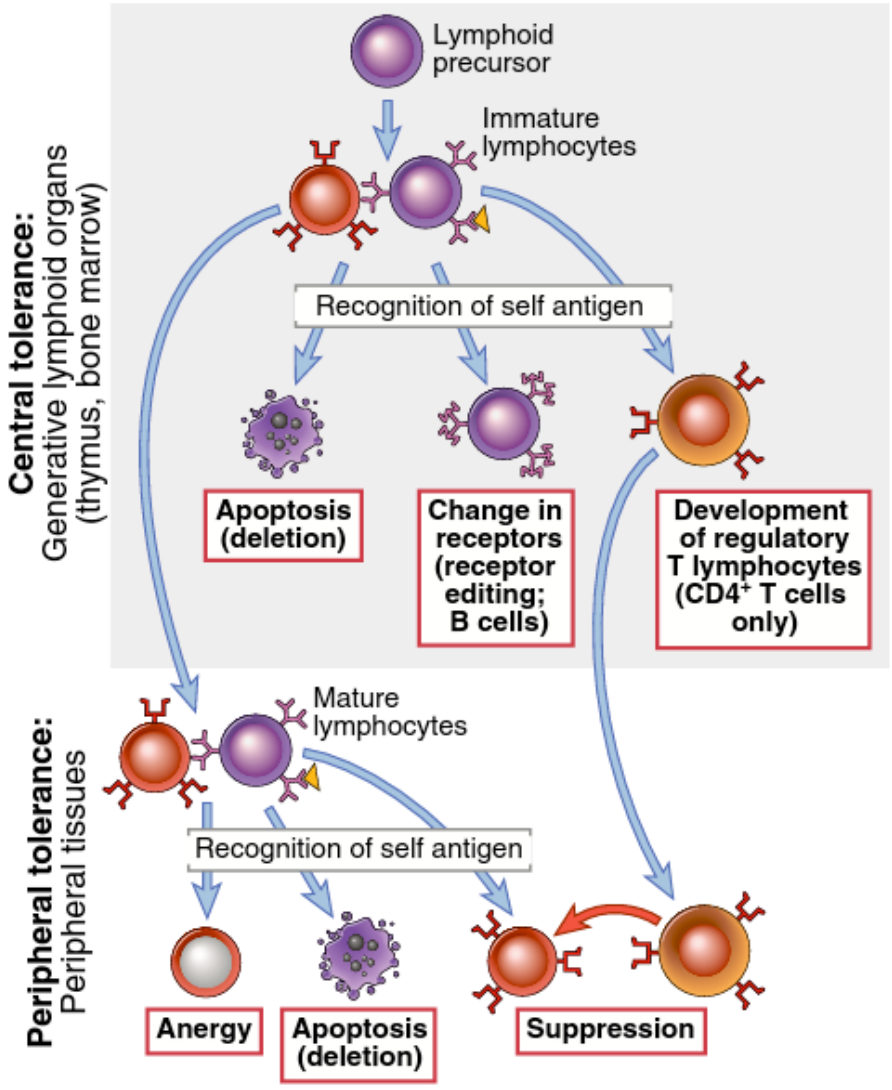
Central and Peripheral Tolerance



Abbas, Lichtman, Pillai; Basic Immunology 4th ed.

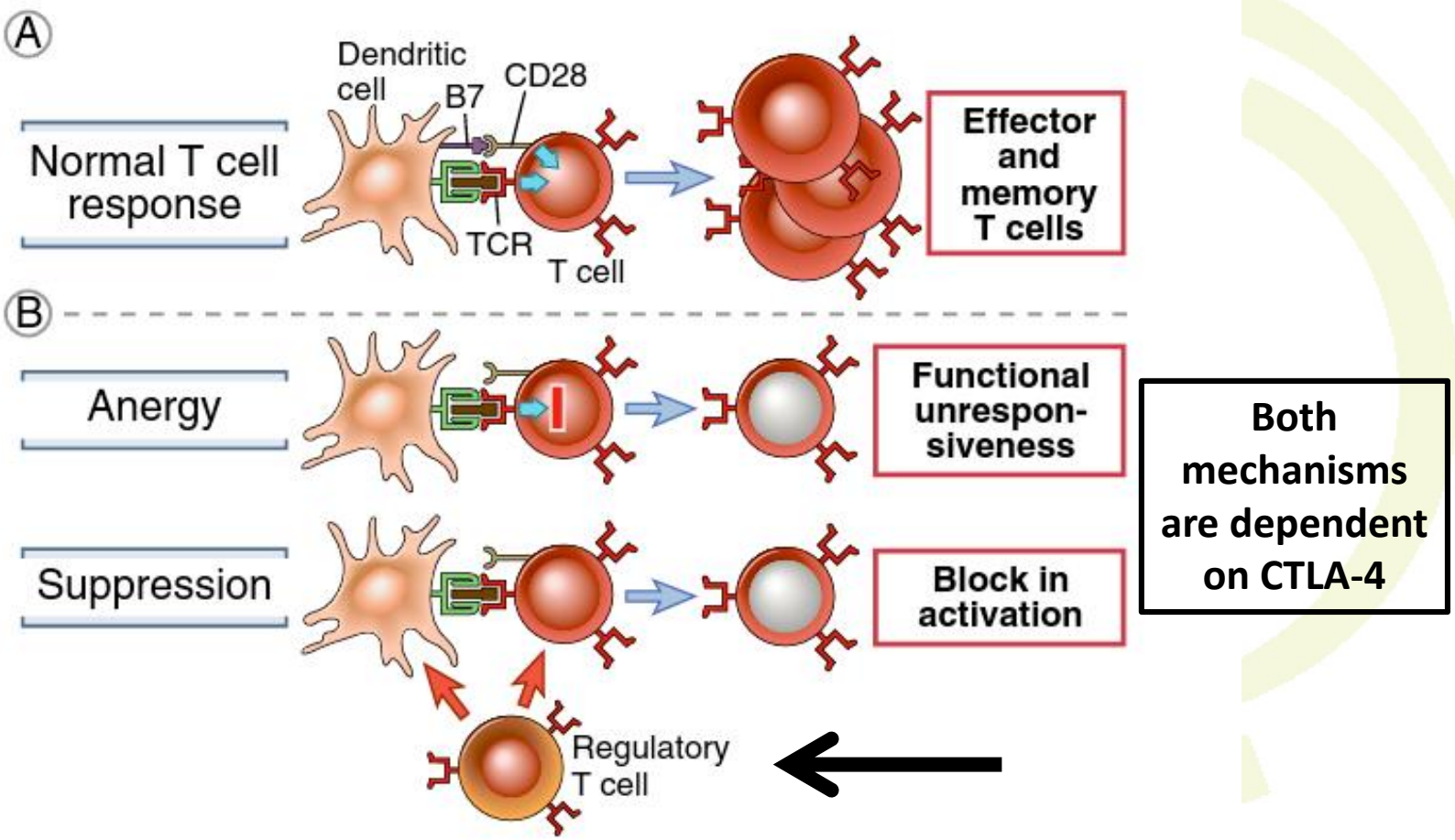
Central Tolerance

- For T cells it occurs in the thymus
- Fate of most self-reactive T cell is death (deletion) and removal from T cell pool
- Some survive as regulatory (suppressor) T cells while others escape to peripheral tissues

Peripheral Tolerance

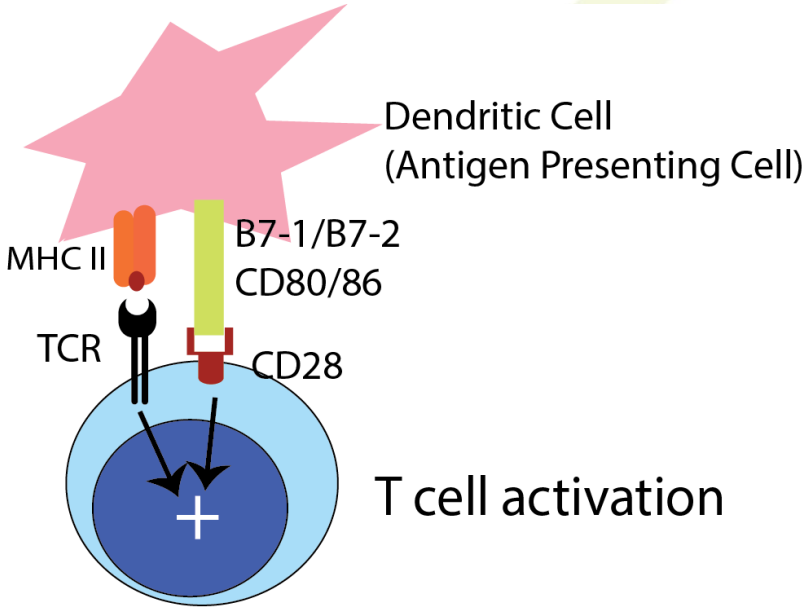
- Self-reactive T cells are suppressed by regulatory T cells
- CTLA-4 and PD-1, among other molecules play a role in maintaining self-reactive T cells from becoming activated (anergic)

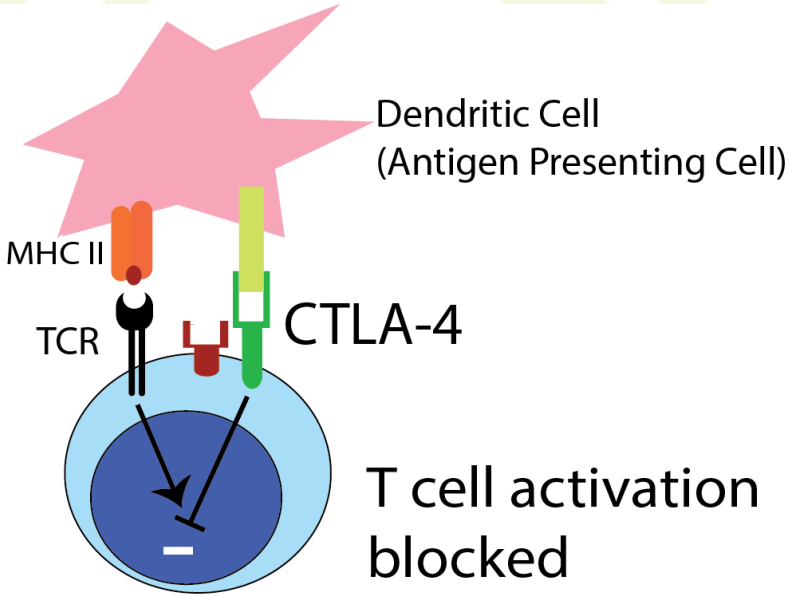
Peripheral tolerance occurs in the absence of CD28 dependent co-stimulation



Abbas, Lichtman, Pillai; Basic Immunology 4th ed.

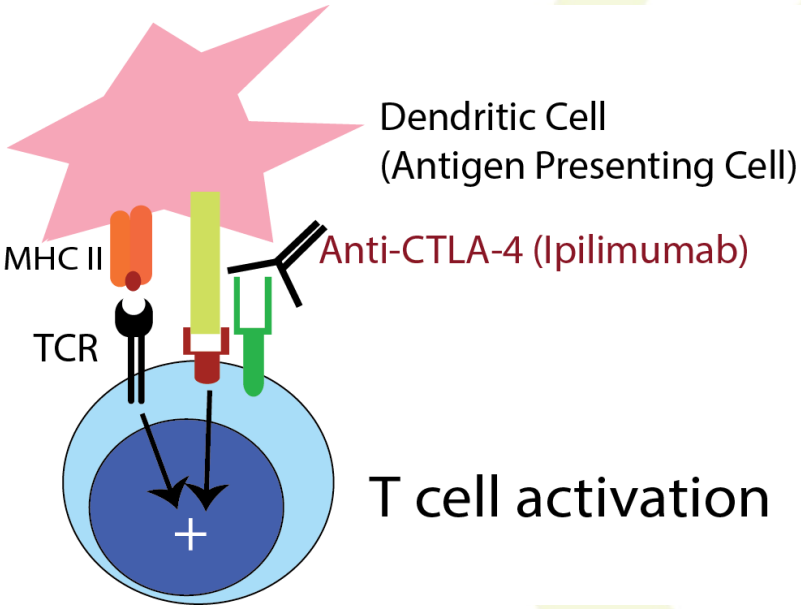
CTLA-4 inhibits co-stimulation by blocking interaction between CD28 and B7 molecules



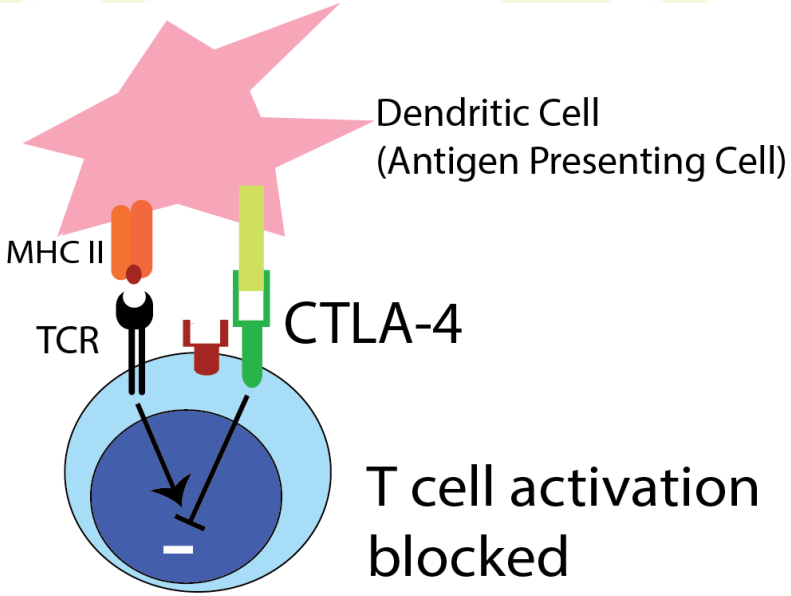


Mary Nakamura

Anti-CTLA-4 can lead to breakdown of peripheral tolerance by restoring co-stimulation

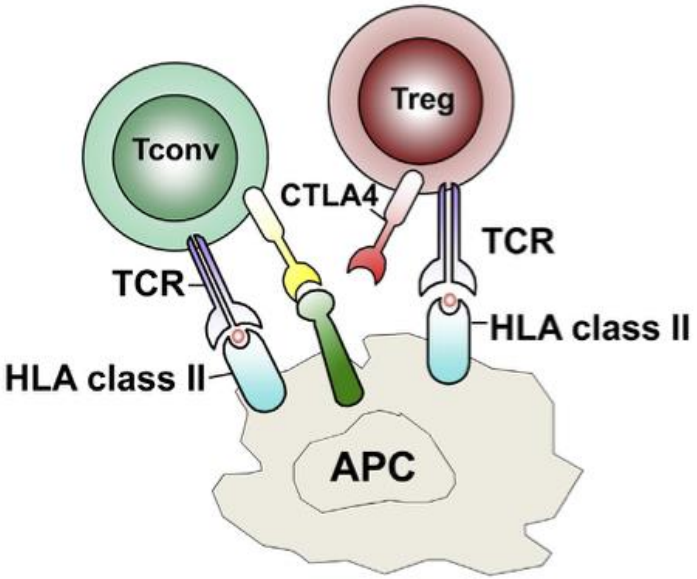


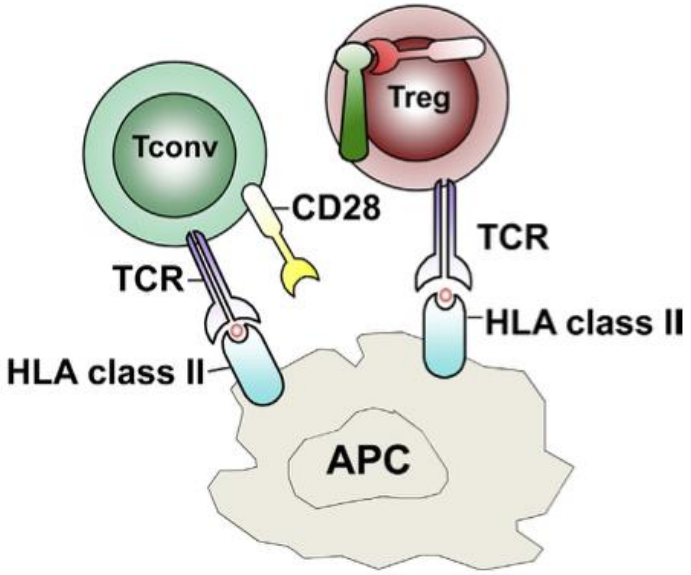
Breakdown of peripheral tolerance leading to activation of self-reactive T cells



Mary Nakamura

Regulatory T cells (Tregs) use CTLA-4 to remove B7 molecules from surface of antigen presenting cells to prevent activation of self reactive T cells

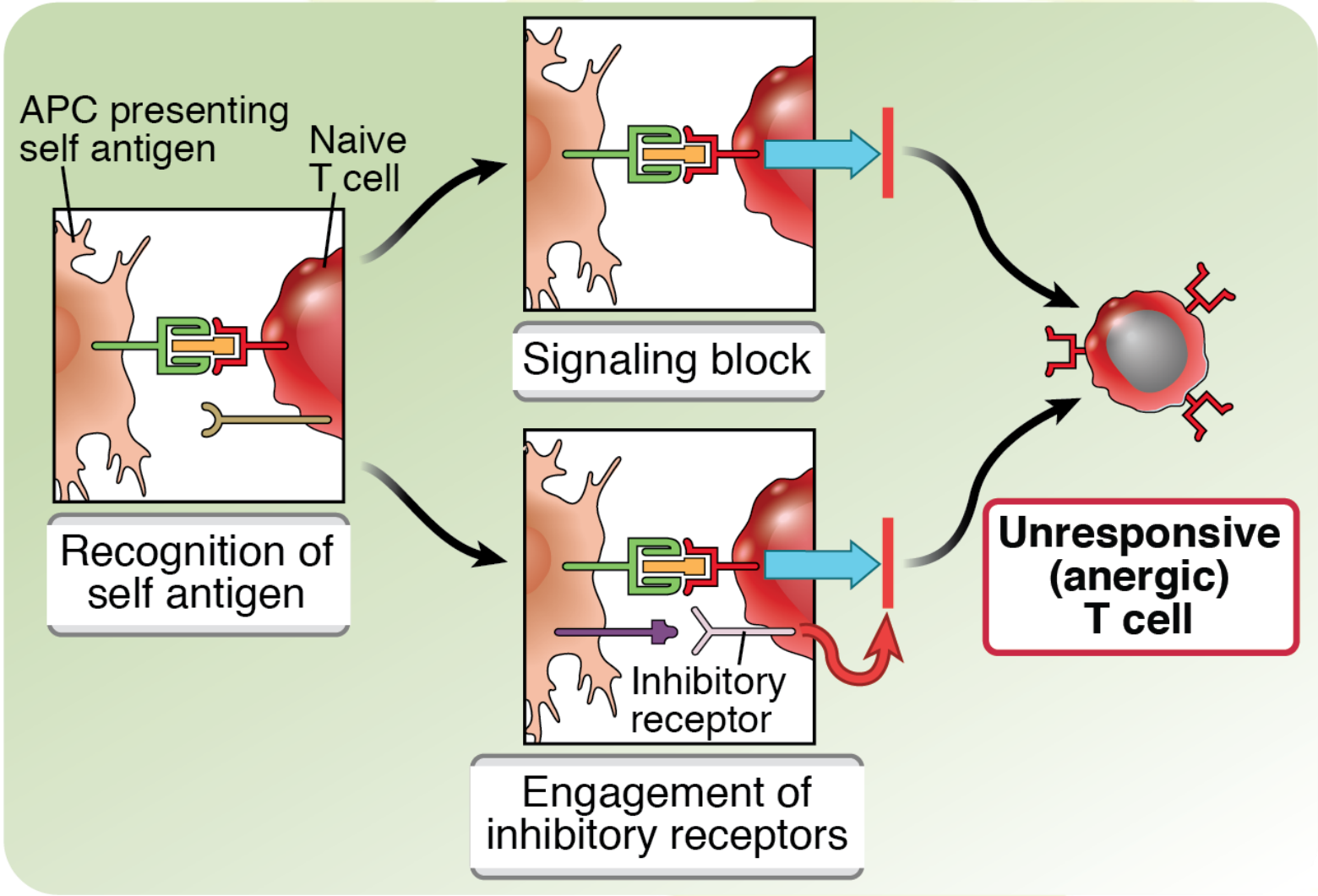




Anti-CTLA-4 (Ipilimumab) may interfere with inhibitory function of Tregs

Walker, L.; *Immunology Letters*; 2017; **184**:43

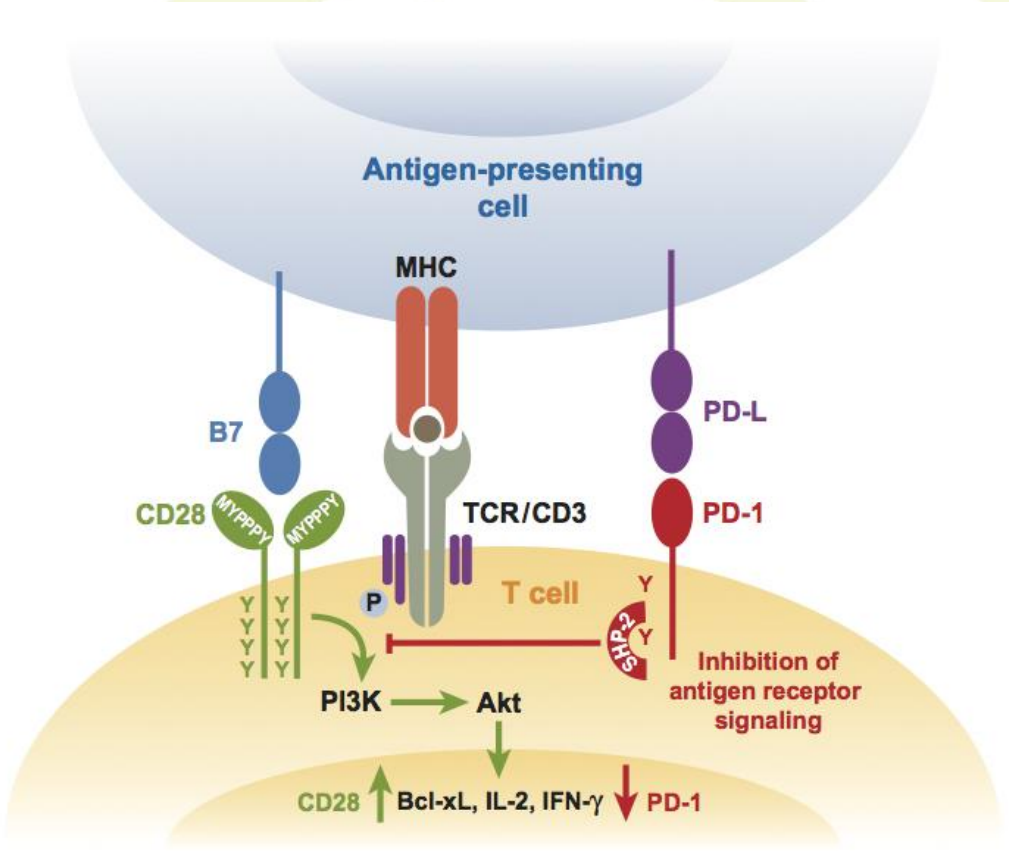
Inhibitory receptors provide a second mechanism for maintenance of tolerance



Abbas, Lichtman, Pillai; Basic Immunology 4th ed.

Interaction of PD-1 with its ligands, PD-L1/PD-L2 inhibits CD28 signaling in T cells

- PD-1 is upregulated on T cells after activation
- PD-L1 is found on both immune and non-immune cells in peripheral tissues
- PD-L2 is mostly found on immune cells in response to inflammatory stimuli
- In contrast, CTLA-4 and its ligands are only found on immune cells
- Mice deficient in PD-1 have delayed development of autoimmune disease compared to CTLA-4 deficient ones



Keir M. *et al*; *Ann. Rev. Immunol.*; 2008; **26**:677

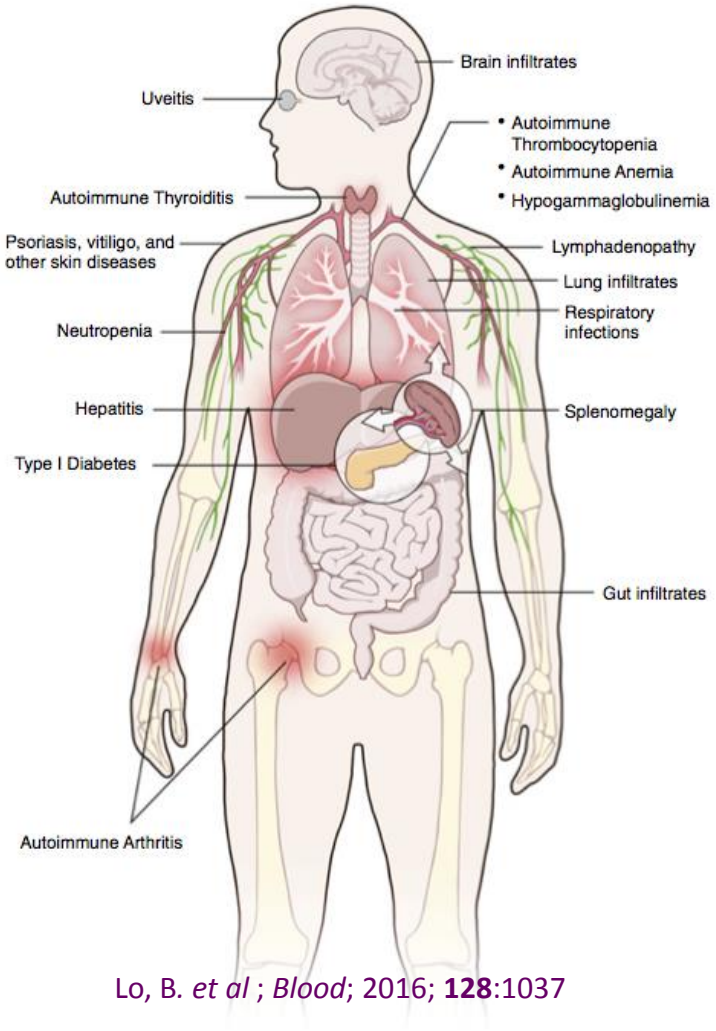
Polymorphisms in CTLA-4 and PD-1 genes have been linked to human autoimmune diseases

Autoimmune Disease	Polymorphism
Thyroiditis, Graves' disease, Hashimoto's disease	CTLA-4
Diabetes mellitus	CTLA-4
Celiac disease	CTLA-4
Myasthenia gravis	CTLA-4
Lupus	CTLA-4; PD-1
Rheumatoid Arthritis	CTLA-4; PD-1
Addison's disease	CTLA-4

Adapted from Michot JM, *et al* ; *European Journal of Cancer*; 2016; **54**:139

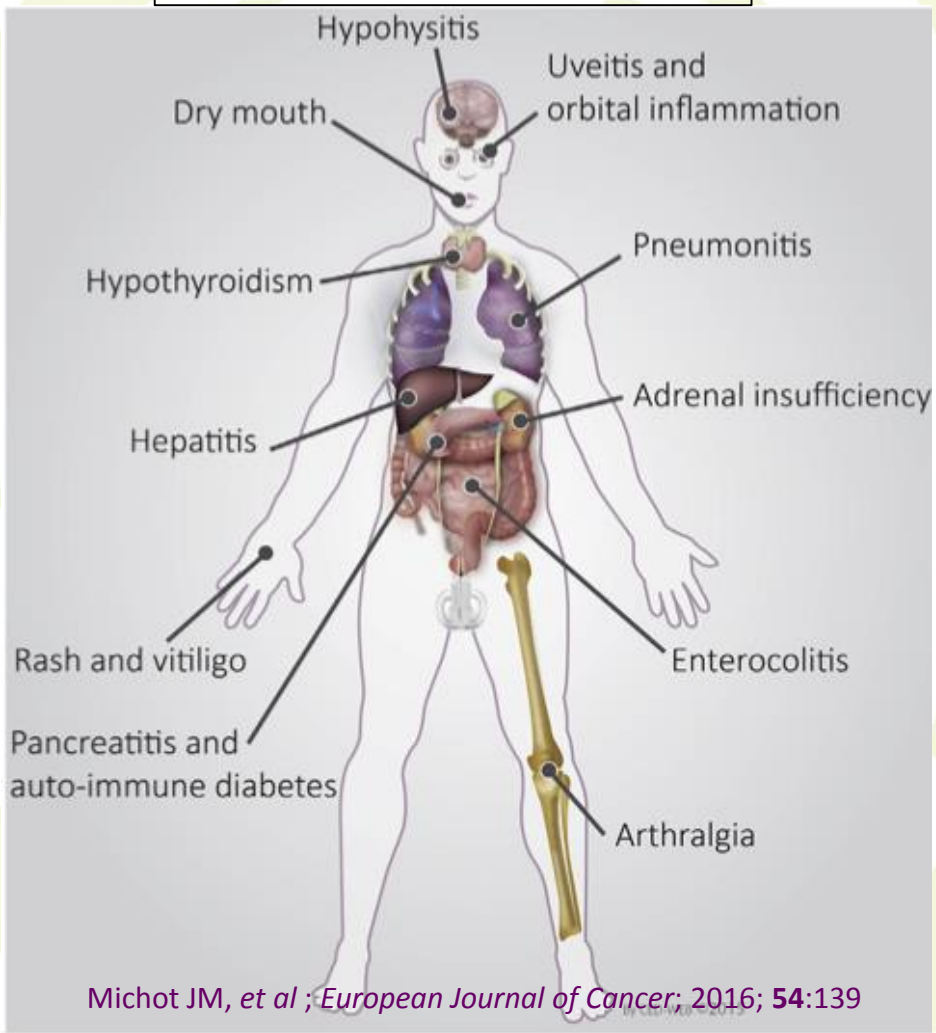
People with CTLA-4 haploinsufficiency develop a spectrum of autoimmune diseases similar to the irAEs observed with ipilimumab

CHAI/LATAIE Phenotype



Lo, B. *et al* ; *Blood*; 2016; **128**:1037

Ipilimumab irAEs



Michot JM, *et al* ; *European Journal of Cancer*; 2016; **54**:139

Early and late irAEs may occur by distinct mechanisms

Early and common

Mucosal
Colitis
Rash
Pneumonitis

Global Regulatory T cell dysfunction

↓

Activation of Effector T cells (Th_{17})

↓

Recruitment of inflammatory cells (neutrophils)

Late and rare

Specific organ
Hypophysitis
(other adrenal)
Myocarditis;Neurologic
Arthritis; Vitiligo

Breakdown of organ specific tolerance

↓

Activation of tumor specific T cells that recognize antigen shared between tumor and healthy tissue: vitiligo, myocarditis

Activation of tissue specific anergic T cells that recognize antigen distinct from the tumor

T cell or antibody mediated tissue destruction

Summary: CTLA-4 and PD-1 are important in maintenance of peripheral immune tolerance

- CTLA-4 expression on effector and regulatory T cells prevents co-stimulation through CD28 and maintains T cell anergy and peripheral tolerance
- Activation of PD-1 on activated T cells by its ligands renders them non-functional
- PD-1 activates regulatory T cells to maintain peripheral tolerance
- Humans with CTLA-4 haploinsufficiency develop a spectrum of autoimmune manifestations similar to irAEs seen after treatment with Ipilimumab