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# Tolerance – 2. Regulatory T cells; why tolerance fails

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## Lecture outline

- Regulatory T cells: functions and clinical relevance
- Pathogenesis of autoimmunity: why self-tolerance fails
- Therapeutic approaches for immunological diseases

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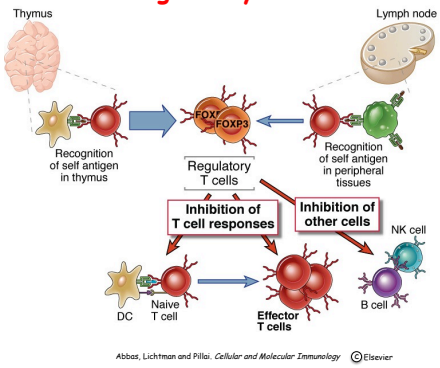
## Regulatory T cells




Abbas, Lichtman and Pillai. *Cellular and Molecular Immunology* ©Elsevier

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## Properties of regulatory T cells

- Phenotype: CD4+, high IL-2 receptor (CD25), low IL-7 receptor, Foxp3 transcription factor; other markers
- Significance: Foxp3 mutations --> autoimmune disease (IPEX); in mice, disease can be corrected by providing normal Foxp3+ cells
  - Common autoimmune diseases may be associated with defects in or resistance to Tregs; inconclusive evidence

*Take home messages*

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## Populations of Tregs

- Thymic (natural)
  - Induced by self antigen recognition during T cell maturation
- Peripheral (adaptive)
  - In response to antigen exposure in the periphery; contribution to preventing inflammatory disease?
- Induced (in vitro; sometimes called Tr1)
  - Culture with TGFβ + IL-2; therapeutic options
- There are no reliable markers for distinguishing these Tregs in a "bulk" population

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## 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
- Inhibitory cytokines produced by Tregs (TGF-β, IL-10, others?) suppress immune responses (DCs, Macs, T cells)
  - IL-10 deletion in Foxp3+ cells results in colitis
  - IL-10 is also produced by Foxp3- cells
- Consumption of IL-2

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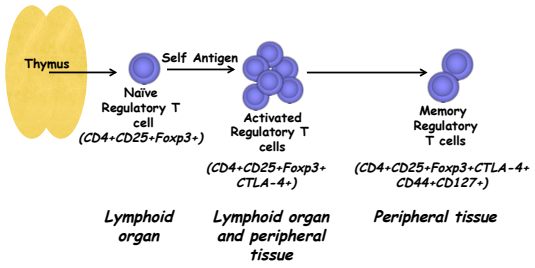
## The life history of regulatory T cells: the concept of regulatory memory




*Rosenblum, Gratz, Paw, Marshak-Rothstein and Abbas. Nature 480:538, 2011.*

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## Regulatory memory

- Inflammation is followed by the activation and generation of Tregs
- Some of these Tregs survive as memory cells in tissues and suppress subsequent inflammatory responses
- Implications:
  - reduced disease flares with chronic or repeated antigen exposure?
  - defect in regulatory memory underlies chronic or remitting/relapsing autoimmune disease?
  - role in peptide-specific immunotherapy (desensitization)?

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## Role of memory Tregs in fetal tolerance

- In evolution, the ability to stably express FoxP3 in peripheral Tregs coincides with placentation (Rudensky lab, *Cell* 2012)

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- **Paternal antigens expressed in the fetus induce long-lived (memory) antigen-specific Tregs**
- **Replacement of fetal antigen-specific Tregs with polyclonal Tregs in mice results in fetal resorption (SS Way lab, *Nature* 2012)**

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## Role of memory Tregs in fetal tolerance

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

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## 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**

*Take home messages*

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## 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 show it is safe, and has some (modest) benefit
- Challenges:
  - Non-specific immunosuppression
  - Stability of Tregs
- Administer antigen or antigen mimic in ways that preferentially induce Tregs?
  - Weak stimulus (peptide antigen, anti-CD3); + IL-2?

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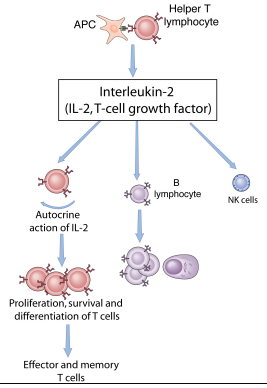
## Functions of Interleukin-2: the dogma

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## 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?

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## 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

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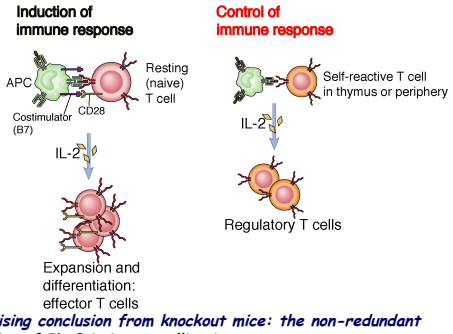
## Dual roles of IL-2 in T cell responses




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

*Take home messages*

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## Therapeutic potential of IL-2: a revision

- IL-2 was originally used to boost immune responses in cancer, HIV infection (promoting effector and memory T cells)
  - Inconsistent clinical results

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## Therapeutic potential of IL-2: a revision

- IL-2 was originally used to boost immune responses in cancer, HIV infection
- **IL-2 treatment can increase number and functional activity of Tregs**
- **Low-dose IL-2 used to treat steroid-resistant chronic GVHD, vasculitis**

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## Therapeutic potential of IL-2: a revision

- IL-2 was originally used to boost immune responses in cancer, HIV infection
- IL-2 treatment can increase number and functional activity of Tregs
- **The challenge: IL-2 activates both effector and regulatory T cells**
  - **Forms of IL-2 that preferentially activate one population**
  - **Combination therapy with agents (e.g. rapamycin) to block effector responses and preserve Tregs**

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## 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**

## Autoimmunity

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- Definition: immune response against self (auto-) antigen, by implication pathologic
- Much of our knowledge of immunological disorders is based on mouse models
- Elucidating the causes of these diseases has been a challenge
  - Initiating triggers generally unknown
  - Complex interactions between genes and environment
  - Unclear which mechanisms of tolerance fail in any disease

## Pathogenesis of autoimmunity

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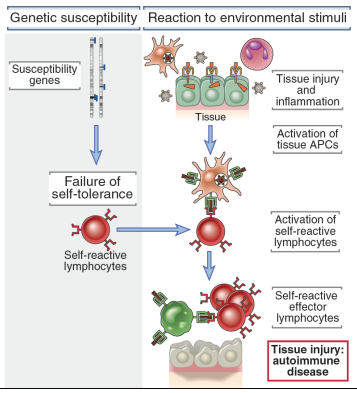


## Genetic basis of autoimmunity

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- Multiple genes are associated with autoimmunity
  - Most human autoimmune diseases are multigenic
  - Single gene defects reveal pathways of self-tolerance and why it fails (e.g. AIRE, Fas, Foxp3, many others) but are not involved in most, common autoimmune diseases
- Genes include HLA, many others
  - Each gene individually makes a small contribution
  - Little predictive value

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## Genetics of autoimmunity: challenges

- Relating complex genotypes to phenotypic and functional abnormalities, to better understand pathogenesis
  - Complex interactions between genes and environment, often difficult to define
- Predictive value of genetic polymorphisms
  - Unlikely because of low odds ratios
- Using polymorphisms to identify therapeutic targets
  - Difficult because any one gene makes a small contribution

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## Infections and autoimmunity

- Infections trigger autoimmune reactions
  - Clinical prodromes, animal models
  - IBD is dependent on gut commensals
- Some autoimmune diseases are prevented by infections (type 1 diabetes, multiple sclerosis, others? -- increasing incidence in developed countries): mechanism unknown
  - The "hygiene hypothesis"
- The role of the microbiome?

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## Other environmental influences

- Hormones
  - Gender bias of autoimmune diseases
  - Mechanisms still not defined
- UV exposure
  - SLE

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## Autoimmune diseases

- Experimental models are revealing pathways of immune regulation and why it fails
- Improving technologies for human genetic and phenotypic analyses are enabling studies of patients
- Challenges:
  - Defining which mechanisms of immune tolerance fail in different autoimmune diseases
  - Using this knowledge to develop therapies

*Take home messages*

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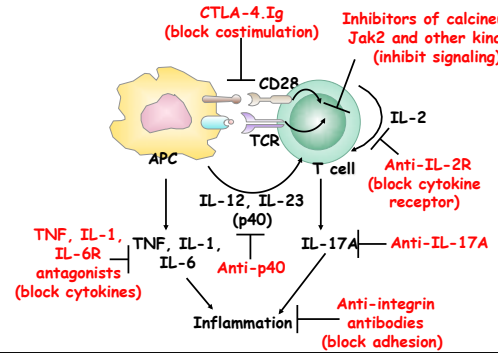
Therapy of immune disorders: rational approaches target lymphocyte activation and subsequent inflammation

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## Molecularly targeted therapies for immunological diseases: the rational approach

- Target the molecular basis of lymphocyte activation and effector functions: rationally designed therapies
  - Based on understanding of lymphocyte biology
  - Risks -- reactivation of infections
- Induce antigen-specific immunological tolerance: requires identification of target antigens
  - Being tried in MS, type 1 diabetes (in which the major autoantigens are known)
  - Based on successes in allergic diseases

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## Understanding autoimmunity

- Animal models have limited value for understanding etiology and pathogenesis of human diseases
  - They are invaluable for studying mechanisms and for discovery research
- Need technologies for studying patients
- Emphasis must be on antigen-specific immune responses