Regulation and termination of T cell responses; immunological tolerance

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Lecture outline

• Principles of immune regulation

• Self-tolerance; mechanisms of central and peripheral tolerance

• Regulatory T cells
**Balancing lymphocyte activation and control**

**Activation**
- Effector T cells
  - Normal: reactions against pathogens
  - Pathologic: inflammatory disease, e.g. caused by reactions against self

**Tolerance**
- Regulatory T cells
  - No response to self
  - Controlled response to pathogens

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*
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

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

Consequences of self antigen recognition in thymus

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

AIRE (autoimmune regulator) 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.
Central tolerance

- Lymphocytes that see self antigens before they are mature are either eliminated or rendered harmless.
- Probably continues to occur at some level throughout life (as new lymphocytes are produced from bone marrow stem cells).
- Unlikely that it will be possible to manipulate these processes for therapy.

Take home messages

Peripheral tolerance

Normal T cell response

Anergy

Deletion

Suppression

Functional unresponsiveness

Apoptosis (activation-induced cell death)

Block in activation
Multiple mechanisms demonstrated in different experimental systems

No clear evidence that natural self antigens induce anergy in humans

Therapeutic potential: can we administer antigens in ways that induce T-cell anergy?

Take home messages
"Activation-induced cell death": death of mature T cells upon recognition of self antigens

Both pathways cooperate to prevent reactions against self

ALPS Patient 2: An unusual mutation

Healthy female - at 18 months developed cervical adenopathy. Biopsy showed ‘reactive hyperplasia’ Pt developed anemia with hypersplenism, hematuria, proteinuria and renal insufficiency due to mesangial glomerulonephritis, then primary biliary infiltration. Evaluation at NIH: lymphadenopathy persists, ANA (+) 1:320, CD4/CD8 cells 25% of αβ T cells, increased B cells; Fas surface expression is normal Heterozygous Fas splice mutation resulting in loss of exons 3, 4 (AA 52-96)
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); many autoimmune diseases may be associated with defects in or resistance to Tregs
- **Mechanisms of action:** multiple
  - secretion of immune-suppressive cytokines (TGFβ, IL-10; IL-35?)
  - inhibition of APC function (role of CTLA-4?)

Take home messages
Populations and markers 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)**
  - Culture with TGFβ + IL-2; therapeutic options
- **Others?**

- **Markers**
  - CD4, CD25, Foxp3, low CD127 (IL-7 receptor)
  - Foxp3 may be transiently induced on many activated T cells, stable in Tregs (importance of DNA methylation assays?)

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*
The therapeutic potential of regulatory T lymphocytes

- Cell transfer of autologous Tregs to treat autoimmune disease, transplant rejection, graft-vs-host disease
  - Purify patient's own Tregs, expand ex vivo
  - Induce Treg (Tr1) cells from naïve T cells
  - Ongoing trials in GvHD, transplantation
- Challenges:
  - Adequate cell numbers
  - Stability (value of assays for Foxp3 demethylation?)
  - Specificity (transduction of antigen-specific TCRs?)
- Risks:
  - Non-specific immune suppression
  - Conversion to pathogenic T cells

Induction of regulatory T cells in vivo

- Administer antigen or antigen mimic in ways that preferentially induce Tregs
  - Trials of weakly activating (non-FcR binding) anti-CD3 antibody in early onset type 1 diabetes (Bluestone); risk of reactivating memory cells
  - Other approaches for preferentially activating Tregs in vivo?
  - The unexpected potential of interleukin-2
Functions of Interleukin-2: the dogma

Interleukin-2 (IL-2, T-cell growth factor)

- APC
- Helper T lymphocyte
- Autocrine action of IL-2
- Proliferation, survival, and differentiation of T cells
- Effector and memory T cells

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

- APC
- Costimulator (CD28)
- IL-2
- Expansion and differentiation: effector T cells

Control of immune response

- Resting (naive) T cell
- IL-2
- Self-reactive T cell in thymus or periphery
- Regulatory T cells

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

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
  - Difficult to extrapolate concepts to therapy

- Challenges:
  - Complexity: multiple connected pathways
  - Often limited molecular definition
  - Can best (only?) be studied in vivo
  - Reliance on experimental (animal) models