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AIRE, or Autoimmune Regulator, is a protein that plays a crucial role in the immune system, particularly in the development of self-tolerance. It is primarily expressed in the thymus, where it influences the maturation of T cells.

Functions of AIRE:

1. **Expression of Tissue-Specific Antigens**: AIRE promotes the expression of a variety of tissue-specific antigens in thymic epithelial cells. This process allows developing T cells to encounter a broad range of self-antigens.
2. **Negative Selection of T Cells**: By presenting these self-antigens, AIRE facilitates the negative selection of T cells. T cells that recognize self-antigens with high affinity are induced to undergo apoptosis (programmed cell death), preventing them from causing autoimmune responses.
3. **Prevention of Autoimmunity**: Proper functioning of AIRE is essential for preventing autoimmune diseases. Mutations or deficiencies in AIRE can lead to autoimmune conditions, such as Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED), where the immune system attacks the body's own tissues.

FOXP3 ((Forkhead box P3) is a transcription factor belonging to the forkhead/winged-helix family) is a protein that plays a crucial role in the immune system, particularly in the regulation of immune responses and the development of regulatory T cells (Tregs). **FOXP3 gene**: located on **X chromosome**.

Expression and Induction

- Expressed mainly in **regulatory T cells ($CD4^+CD25^+$)**.
- **Signals inducing FOXP3 expression:**
  - **TGF-β** (activates SMAD2/3 → FOXP3 transcription).
  - **IL-2** (via STAT5 signaling → stabilizes FOXP3 expression).
  - **Co-stimulatory molecules** (e.g., CD28, CTLA-4) also influence induction.

❖ **Functions** essential for **differentiation and stability of Tregs** in the thymus (FOXP3 is induced when TCRs recognize **self-antigen with intermediate affinity**) and periphery (regulate **inflammation and responses to non-self antigens** (e.g., gut microbiota, allergens, vaccines)), which help maintain immune tolerance and prevent autoimmune diseases by suppressing excessive immune responses and autoreactive T and B cell responses.

❖ **Molecular Functions of FOXP3**

FOXP3 acts as a **transcriptional repressor and activator**:

- **Upregulates**:
  - **CD25 (IL-2Rα)** → enhances IL-2 sensitivity.
  - **CTLA-4, IL-10, TGF-β** → immunosuppressive molecules.
- **Downregulates**:
  - Pro-inflammatory cytokines like **IL-2, IFN-γ, IL-17**.

This ensures Tregs **suppress effector T cell responses** and maintain immune homeostasis.

❖ **Clinical Importance**

- **Loss-of-function mutations** in FOXP3 cause **IPEX syndrome** (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked), a severe autoimmune disease in infants.
- Reduced or dysfunctional FOXP3 expression is linked to **autoimmune diseases** (e.g., type 1 diabetes, multiple sclerosis).
- Enhanced $FOXP3^+$ Tregs are found in the **tumor microenvironment**, where they suppress anti-tumor immunity.

PD-1, or Programmed Cell Death Protein 1, is an immune checkpoint receptor found on the surface of T cells and other immune cells. It plays a pivotal role in regulating immune responses(by balance between immune activation and tolerance), particularly in the context of maintaining self-tolerance and preventing autoimmunity.

Its function by inhibition of T Cell Activity**: When PD-1 binds to its ligands, PD-L1 or PD-L2 (expressed on various cells, including tumor cells and antigen-presenting cells), it delivers an inhibitory signal that reduces T cell proliferation and cytokine production. This helps to limit T cell activity and prevents excessive immune responses.**

In Cancer Immunotherapy Target: PD-1 is a significant target in cancer immunotherapy. Monoclonal antibodies that block PD-1 and can enhance T cell responses against tumors.

Caspases are a family of cysteine proteases that play essential roles in programmed cell death (apoptosis), inflammation, and cellular processes such as differentiation and proliferation. The name "caspase" is derived from "cysteine-aspartic protease," indicating their specificity for cleaving substrates at aspartic acid residues. They exist as inactive proenzymes (procaspases) and are activated in response to various apoptotic signals, leading to the morphological and biochemical changes associated with apoptosis (some time apoptosis associated with inflammation).

Caspases are a family of proteases classified as initiator, executioner, or inflammatory based on their function in programmed cell death and inflammation. Initiator caspases (e.g., caspases -2, -8, -9, -10) start the process of apoptosis, while executioner caspases (e.g., caspases-3, -6, -7) carry out the widespread degradation of cellular components. Inflammatory caspases (e.g., caspases-1, -4, -5, -11) do not directly cause apoptosis but instead trigger inflammatory responses and cell death, such as pyroptosis.

Caspases are vital for maintaining immune homeostasis and regulating immune responses. Dysregulation of caspase activity can contribute to various diseases, including cancer, autoimmune disorders, and neurodegenerative diseases.

Fas and Fas ligand (FasL) are important proteins involved in regulating programmed cell death (apoptosis) and maintaining immune system balance.

Fas (CD95) is a receptor found on the surface of various cells, including immune cells. When it binds to its ligand (FasL is mainly expressed on activated immune cells, like certain T cells), it sends a signal into the cell that triggers apoptosis, leading to cell death. This is important for getting rid of cells that are damaged, infected, or no longer needed.
This helps regulate the immune response, ensuring that potentially harmful or unnecessary cells are removed.
Importance in Immunology
Immune Regulation: The interaction between Fas and FasL helps control the number of immune cells, preventing excessive immune responses that could damage healthy tissues.

Acquired (or induced) tolerance is the process of deliberately teaching the immune system not to attack a specific antigen. This can be achieved by modulating the activation and maintenance of lymphocytes. Acquired tolerance is induced by either retraining lymphocytes to ignore a target antigen (anergy, deletion, regulation) or removing/controlling autoreactive cells, often by mimicking natural tolerance mechanisms.

The main strategies are:

1. Antigen-Specific Approaches

- **Receptor editing or modulation**: Altering B- or T-cell receptors so they no longer recognize self-antigens.
- **Low-dose or high-dose antigen exposure**:
  - *Low, repeated doses* (especially oral/nasal) promote regulatory T cells (Tregs) and anti-inflammatory cytokines (IL-10, TGF-β).
  - *High continuous doses* may cause deletion or anergy of autoreactive T cells.
- **Low-avidity ligands**: Weak antigen–receptor interactions induce T- or B-cell anergy instead of activation.

2. Manipulating Immune Signaling

- **Blockade of costimulation**: Preventing CD28–B7 signaling (e.g., with CTLA4-Ig/abatacept) stops full T-cell activation, leading to anergy or apoptosis.
- **Cytokine modulation**: Promoting tolerogenic cytokines (IL-10, TGF-β) or blocking proinflammatory ones (IL-6, TNF-α) skews the response toward tolerance.

3. Cell-Directed Therapies

- **Targeting autoreactive cells**: Using monoclonal antibodies (e.g., anti-CD20) to eliminate autoreactive B or T cells.
- **Adoptive transfer of regulatory cells**: Expanding patient-derived Tregs or tolerogenic dendritic cells ex vivo and re-infusing them to suppress autoimmunity.

4. Immunosuppressive Drugs

- Drugs such as cyclosporine, tacrolimus, or corticosteroids reduce T-cell activation and inflammatory cytokine production.
- When carefully dosed, they selectively dampen autoimmunity, though excessive use leads to generalized immunosuppression.

Mucosal Tolerance

Mucosal tolerance is the state of **immune unresponsiveness to antigens encountered through mucosal surfaces**, particularly the gut. It prevents unnecessary reactions against harmless substances such as food proteins or commensal microbes.

Mechanisms

1. **Dose-Dependent Effects**
   - **High doses** → induce T-cell anergy or deletion (cells become inactive).
   - **Low doses** → favor induction of **regulatory T cells (Tregs)**.
2. **Antigen Processing**
   - Ingested proteins are taken up in **Peyer's patches** and mesenteric lymph nodes.
   - Antigen-presenting cells stimulate **Tregs**, which release **IL-10** and **TGF-β** to suppress effector T-cell responses.
3. **Nasal Antigen Delivery**
   - Nasal antigens can activate **γδCD8+ cells**, which help shift immune responses from pro-inflammatory **Th1** to less aggressive **Th2** pathways.
4. **Role of Tregs**
   - Activated Tregs circulate systemically and suppress inflammatory responses at sites of autoimmune activity.
5. **Bystander Suppression**
   - Cytokines (IL-10, TGF-β) from Tregs can suppress not only antigen-specific T cells but also nearby effector T cells responding to unrelated antigens.

The mechanisms that allow a fetus to be tolerated by the mother's immune system—often referred to as "fetal-maternal immune tolerance"—are a unique immunological phenomenon. Given that the fetus is genetically distinct from the mother (inheriting genes from both parents), it could theoretically be targeted by the maternal immune system as "foreign" tissue. However, a complex interplay of immunological adaptations allows for a peaceful coexistence, involving several key mechanisms:

1. **Placental Barrier**: The placenta serves as a physical and immunological barrier between the mother and fetus. It limits the direct exposure of fetal antigens to maternal immune cells, helping to reduce immune reactions. The syncytiotrophoblast layer (outer layer of the placenta) lacks MHC (Major Histocompatibility Complex) class I and II molecules, which are usually involved in presenting antigens to immune cells, making it less recognizable to the maternal immune system.
2. **Downregulation of Maternal Immune Responses**: During pregnancy, the mother's immune system undergoes a shift from a pro-inflammatory (Th1-dominant) response to a more anti-inflammatory (Th2-dominant) state, which is less likely to attack the fetus. This shift is partially mediated by regulatory T cells (Tregs), which play a crucial role in suppressing maternal immune responses against fetal tissues.
3. **Production of Immunosuppressive Molecules**: The placenta and fetus produce molecules that suppress immune responses. For example:
   - **Human Leukocyte Antigen-G (HLA-G)**: This non-classical MHC molecule is expressed on placental cells and can inhibit natural killer (NK) cells and other immune cells.

- **Indoleamine 2,3-dioxygenase (IDO)**: This enzyme is produced by the placenta and depletes tryptophan, an amino acid required for T-cell activation, reducing maternal immune activity against the fetus.
- **TGF-β and IL-10**: These cytokines promote immune tolerance and are secreted by the placenta and maternal immune cells.

4. **Expansion of Regulatory T Cells (Tregs)**: Regulatory T cells increase in number during pregnancy, particularly in the uterine lining (decidua). Tregs are critical for suppressing immune responses that could target the fetus and help maintain tolerance.
5. **Maternal Immune Cell Adaptation**: Certain maternal immune cells, such as uterine natural killer (uNK) cells, adapt to support pregnancy rather than initiate an immune response. These uNK cells play a role in promoting placental development and vascular remodeling, which is necessary for fetal nutrient supply.
6. **Microchimerism**: Fetal cells can cross into maternal circulation, and some of these cells persist long-term, creating a phenomenon known as microchimerism. This low-level presence of fetal cells may contribute to tolerance by "educating" the maternal immune system about the fetus over time.

Together, these mechanisms create a local immunosuppressive environment at the maternal-fetal interface and induce systemic changes in the mother's immune system to protect and support the fetus throughout pregnancy.

Termination of Tolerance:

Tolerance, which helps prevent the immune system from attacking the body's own cells, can be lost if autoreactive T cells become reactivated. Some ways this activation can occur:

- ✓ **Molecular Mimicry:**

If an anergic (inactive) T cell encounters an antigen that resembles a tolerogen (a substance that induces tolerance), it can become activated. This can trigger T helper (Th) cells that provide signals to autoreactive B cells or Th1 cells, leading to an immune response against the tolerogen.

- ✓ **Restoration of Costimulatory Signals:**

Anergic T cells can be reactivated if they receive proper stimulation. For example, in certain transgenic mice that express a viral protein in their pancreas, T cells remained inactive until the mice were infected with the virus. This infection provided the necessary signals to activate these previously dormant T cells, which then attacked the pancreas and led to diabetes.

- ✓ **Infections with Superantigens:**

Some infections produce superantigens that can activate many T cells at once by binding to MHC-II molecules. This strong stimulation can wake up previously anergic autoreactive T cells, leading to an active autoimmune response.

- ✓ **Changes in T-Cell Balance:**

The survival and activation of T cells depend on a delicate balance. If this balance is disturbed, such as during conditions like lymphopenia (low T cell count), it can lead to a breakdown of tolerance and trigger autoimmunity.

The immune response to autoimmune diseases in general follows several stapes:

The immune response in autoimmune diseases generally involves Initiation, where environmental factors and genetic susceptibility trigger the breakdown of immune tolerance, activating autoreactive immune cells; Amplification, where these cells release cytokines and recruit more immune cells, leading to chronic inflammation; and Resolution, a dynamic phase where regulatory mechanisms attempt to control the response, resulting in alternating periods of disease remission and exacerbation (flares) that cause tissue damage.

1. Initiation Phase

- **Breakdown of Immune Tolerance:**
  A combination of genetic predisposition and environmental triggers (like infections) causes the immune system to lose tolerance to its own tissues.
- **Activation of Autoreactive Cells:**
  This loss of tolerance leads to the activation of autoreactive T cells and B cells, which are normally suppressed.
- **Self-Antigen Recognition:**
  These activated cells begin to recognize and target the body's own healthy cells and tissues as if they were foreign.

2. Amplification Phase

- **Cytokine Release:**
  Activated autoreactive cells release signaling molecules called cytokines, which promote and sustain the inflammatory response.
- **Immune Cell Recruitment:**
  Cytokines attract other immune cells, such as neutrophils and macrophages, to the site of inflammation, amplifying the tissue damage.
- **Self-Perpetuating Cycle:**
  The immune response becomes self-perpetuating, creating a chronic cycle of inflammation, cytokine release, and immune cell activation.
- **Pathogenic Effector Mechanisms:**
  This phase involves the production of autoantibodies by B cells and T cells driving tissue damage, leading to irreversible cellular and tissue injury.

3. Resolution Phase (Relapse and Remission)

- **Regulatory Mechanisms:**
  The body activates intrinsic and extrinsic mechanisms to try and control the autoimmune response, including the action of T regulatory cells (Tregs).
- **Relapses and Flares:**
  This phase is characterized by an ongoing struggle between the destructive effector responses and the regulatory mechanisms.
- **Disease Manifestations:**
  When the effector response overcomes the regulatory mechanisms, the patient experiences a symptomatic "flare" or relapse, leading to renewed tissue damage and clinical symptoms.
- **Remission:**
  Periods when the regulatory mechanisms regain control, leading to a temporary decrease in symptoms, are known as remission.

This dynamic process can result in chronic inflammation and tissue damage, leading to the varied symptoms of different autoimmune diseases.

The immune response in autoimmune diseases is complex and varies **depending on the specific disease and its target tissues**. For example, in rheumatoid arthritis, both humoral and cell-mediated responses contribute to joint inflammation, while systemic lupus erythematosus primarily involves antibody-mediated damage through immune complexes.

Autoimmune Disease	Immune Stimulus	Target Site	Type of Immune Response	Key Immune Cells Involved	Clinical Manifestations	Steps of Immune Response
Rheumatoid Arthritis	Joint inflammation	Synovial joints	Humoral and Cell-Mediated	T helper cells, B cells, Macrophages	Joint pain, swelling, stiffness	1. Synovial antigen recognition 2. T-cell activation 3. Macrophage recruitment 4. Cytokine release 5. Joint damage
Systemic Lupus	Diverse antigens	Multiple organ	Humoral	T helper cells, B cells	Fatigue, rashes, organ damage	1. Antigen recognition 2. B-cell activation 3.

Erythematosus		systems				Autoantibody production 4. Immune complex formation 5. Tissue inflammation
Multiple Sclerosis	Myelin proteins	Central nervous system	Cell-Mediated	CD4+ T cells, CD8+ T cells	Neurological symptoms, paralysis	1. Antigen recognition 2. T cell activation 3. Demyelination 4. Neurological symptoms
Type 1 Diabetes	Beta-cell antigens	Pancreas	Cell-Mediated	CD8+ T cells, B cells	Hyperglycemia, ketoacidosis	1. Antigen recognition 2. T cell activation 3. β-cell destruction 4. Insulin deficiency
Hashimoto's Thyroiditis	Thyroid antigens	Thyroid gland	Humoral	T helper cells, B cells	Fatigue, weight gain, cold intolerance	1. Antigen recognition 2. Autoantibody production 3. Inflammation 4. Hypothyroidism
Graves' Disease	Thyroid-stimulating antibodies	Thyroid gland	Humoral	B cells, T helper cells	Hyperthyroidism, weight loss	
Celiac Disease	Gluten	Small intestine	Cell-Mediated	CD4+ T cells, B cells	Diarrhea, malabsorption	
Psoriasis	Unknown triggers	Skin	Cell-Mediated	Th17 cells, CD8+ T cells	Red, scaly patches on skin	