OLLI SG 492
Human Immune System

Session 8 - April 27, 2022

Today’s Meeting

- Recap - Natural Killer (NK) Cells, Stress, and Ageing.
- Regulatory T cells.
- Autoimmunity - (potential) causes, role of regulatory T cells, and (potential) cures.

Basics of the Immune System

Natural Killer (NK) Cells

- NK cells have receptors to detect molecules on the surface of viruses and bacteria (AKA activating receptors), and receptors to detect MHC class 1 proteins (AKA inhibitory receptors).
- “Missing Self Hypothesis/Missing Self Recognition”:
  - Microbes (viruses and bacteria) lack MHC 1 proteins on their surface.
  - Healthy self-cells display MHC 1 proteins.
  - Infected, damaged or distressed cells display MHC1 with antigens (focus of T cells) or down regulate the production of MHC 1 (**low levels of expression** of MHC 1).
  - NK cells can distinguish between healthy self cells and cancerous, damaged, infected, etc. cells, and take action against the latter.

Basics of the Immune System

Natural Killer (NK) Cells

- Cancer cells have ligands/molecules on their surface detectable by activating receptors on NK cells.
- Cancer cells down regulate production of MHC 1 proteins to avoid detection by cytotoxic T cells.
- Inhibitory receptors of NK cells detect the low level of MHC 1, or lack of MHC 1, on cancer cells.
- This activates the NK cell to attack the cancer cell.

Basics of the Immune System

Natural Killer (NK) Cells

- On detection of infected/distressed or cancer cells, NK cells release cytotoxic granules containing perforin and proteases - granzymes.
- Perforin opens pores in the membrane of the target cell.
- The proteases initiate apoptosis (programmed cell death), or result in lysis (disintegration) of the target cell.

Stress

Fever and the Immune System

- Benefits of fever in fighting infection:
  - Virus replication decreases 200-fold at temperatures of 40^{o}C (104^{o}F).
  - Increases the number of immune cells in the bloodstream.
  - Increases the flow of immune cells to the site of an infection.
  - At the site of an infection, macrophage are better at engulfing pathogens, B cells produce more antibodies, dendritic cells are better at switching on T cells, etc.

Stress

Stress and the Immune System

- When stressed, the adrenal glands produce hormones, most importantly cortisol.
- Cortisol in stressful situations has many effects:
  - Prepares the body's fight-or-flight response.
  - Prepares the body's muscles for immediate action by increasing blood sugar levels and dilating blood vessels.
  - Quiets the immune system.
- Cortisol affects the activity of 20% of the 23,000 human genes.

Time

Ageing

- “Inflamm-ageing”:
  - Cytokines, clotting factors, and inflammatory molecules are found at higher levels in the elderly without overt signs of infection.
  - May result from accumulation of damaged or senescent cells.
  - Effect is that immune system is less able to discriminate between pathogens and the body’s own cells and tissues.
  - Further effect is that immune system is weak at detecting novel pathogens.
- While it may be easier to trigger an immune response in the elderly, the response is less discriminating.

Time

Ageing

- The elderly have more memory immune cells leaving fewer immune cells to fight new infections.
- The thymus shrinks as we age.
  - Testing of new T cells declines.
  - Activity shrinks to 1-5% of childhood activity.
- Influence of experience on our immune system
  - Studies of identical twins.

Basics of the Immune System

Regulatory T Cells - Overview

- Basic Functions:
  - Modulate the immune system.
  - Maintain tolerance to self-antigens.
  - Prevent autoimmune disease.
- In general, they are immunosuppressive - down-regulate effector T cells (both cytotoxic and helper T cells).
- Similar to helper (CD4) T cells - hard to distinguish between them.
- Shut down immune response after successful elimination of pathogens.

Basics of the Immune System

Regulatory T Cells - Development

- Derived from lymphoid progenitor cells in bone marrow.
- Shuffle T cell receptor genes to produce unique T cell receptor.
- Tested in thymus - “Goldilocks process”, not too hot, not too cold, just right:
  - Strong affinity for self peptides results in apoptosis.
  - **Weak** affinity for self peptides results in selection as effector T cell.
  - Intermediate affinity for self peptides results in selection as regulatory T cell.
- Wikipedia Article on Regulatory T Cells.

Basics of the Immune System

Regulatory T Cells - Selection

- If selected as a regulatory T cell, Foxp3 is activated.
  - Improper functioning of Foxp3 gene results in autoimmune disease (e.g., IPEX).
  - Foxp3 is essential for the development and functioning of regulatory T cells.
  - The activity of this gene can change a “normal” T cell into a regulatory T cell, switching from boosting to dampening an immune response.
  - Foxp3 encodes for a protein that “controls” the activity of around 700 other genes.
  - A master control gene.

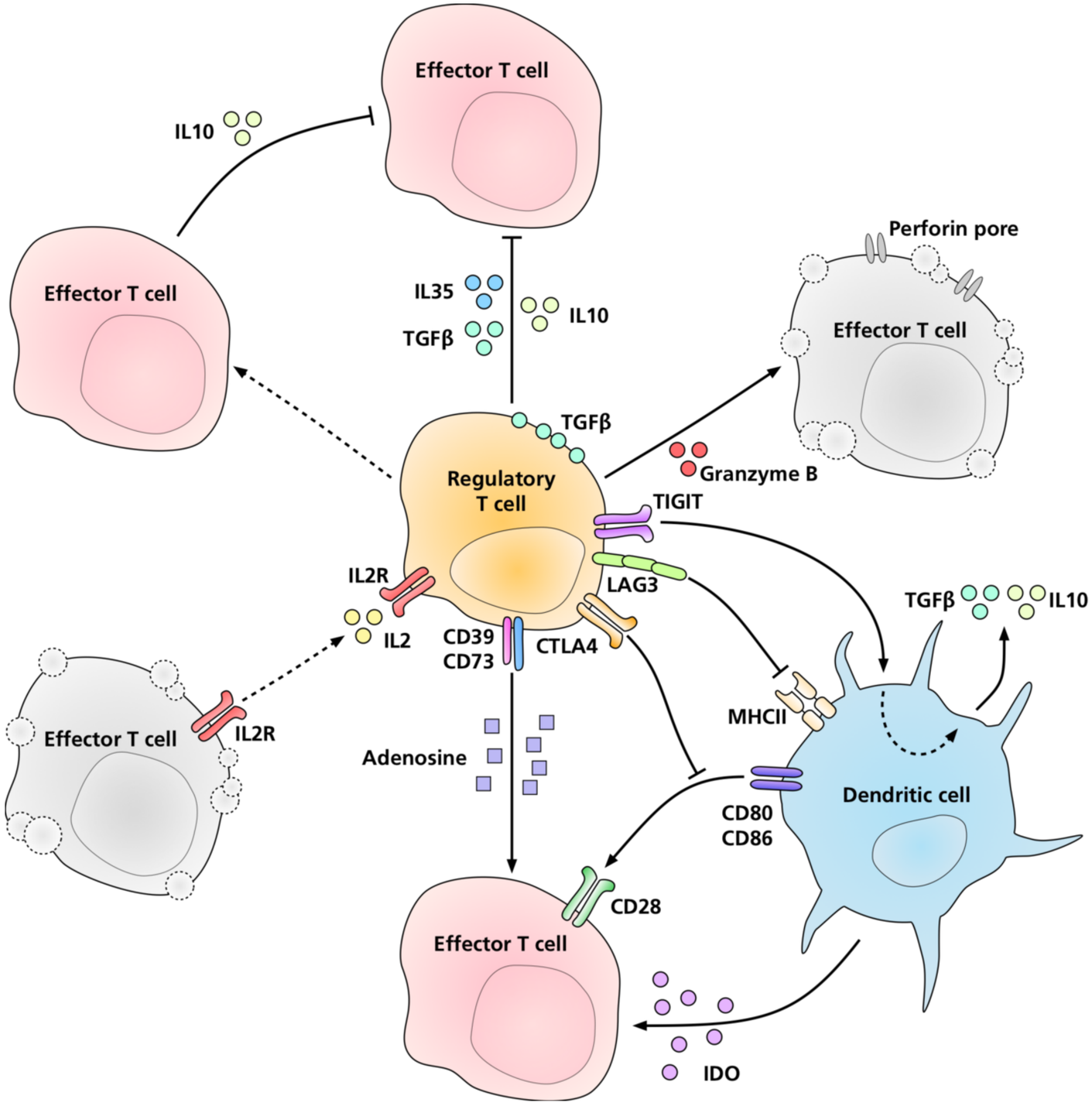
Basics of the Immune System

Regulatory T Cells - Operation

- Modes of operation:
  - Suppression by inhibitory cytokines.
  - Suppression by cytolysis.
  - Suppression by metabolic disruption.
  - Suppression by modulation of dendritic cell maturations or function.
- Recruited to site of infection in same manner as other T cells.

Basics of the Immune System

Regulatory T Cells - Operation



Basics of the Immune System

Regulatory T Cells

- Regulatory T cells are especially abundant in the gut.
- They have the difficult task of preventing any adverse reaction to the symbiotic bacteria resident in the gut - the gut microbiome.
- Metabolites from symbiotic gut bacteria dampen the sensitivity of immune cells.
- If metabolite levels from symbiotic bacteria fall, this cues the immune system to defend against harmful invaders.
- If alarmins are sensed, immune system is similarly activated.
- The immune system directly maintains the symbiotic relationship between us and our gut bacteria.

Autoimmunity

Causes - General Observations

- Difficult to discriminate between self and non-self. "The human body has invested heavily… to create a system as elaborate as anything else we know of in the universe. And **sometimes it fails**."
- There are large gaps in our understanding of how the immune system works, and how it can go wrong.
- Autoimmunity is "… something that happens to the immune system **in general**, a **weakening** of its ability to discriminate between healthy cells and harmful germs."

Autoimmunity

Causes - General Observations

- Some normal T cells are produced that can attack self cells, healthy cells.
- Regulatory T cells are central in autoimmunity - failure to suppress an immune response.
- Experiments in 1993 and by Sakaguchi in 1995, support the idea that an abnormality in suppressor (regulatory) T cells could be what underlies autoimmune disease.

Autoimmunity

Causes

- Experiments performed by two teams in 1993:
  - Subjects were mice genetically engineered to lack T cells.
  - T cells from (normal?) mice were extracted and separated into two types:
    - Naive T cells - had not yet encountered a germ.
    - Switched on T cells - had encountered a germ, memory T cells, and suppressor (regulatory) T cells.
  - Subjects injected only with naive T cells developed autoimmune inflammation.
  - Same subjects subsequently injected with switched on T cells had the autoimmune inflammation stopped.

Autoimmunity

Causes

- Polly Matzinger's "Big Idea":
  - Immune responses need only respond to germs that cause **damage**.
  - The "overarching principle": The immune system works by sensing damage to the body.
- Davis's big idea:
  - "… we must not expect everything the immune system does to fit any one overarching principle. The system discriminates between self and non-self, and it deters germs, and it responds to danger, and it does all these things concurrently - and messily. The immune system uses a collection of mechanisms which no single principle fully encapsulates."

Autoimmunity

Regulatory T Cells and the Microbiome

- Remember what triggers an immune response, and what restrains one, in the gut microbiome/immune system relationship - metabolites and alarmins.
- Diets high in fiber affect our immune system; stimulate the production of regulatory T cells.
- Reduction in the diversity of the bacteria in the “human” microbiome due to reduced exposure, reduces the number of regulatory T cells.
- Fewer regulatory T cells lead to less restraint on the immune system.
- Less restraint could account for increases in allergies and autoimmune disease.
- The “hygiene hypothesis”.

Autoimmunity

Regulatory T Cells and the Microbiome

- Comparison of Amish and Hutterite communities on incidence of allergies:
  - “…stimulation of the immune system by microbes found on small farms might be what protects Amish from asthma.”
- The effect of antibiotics:
  - Over use of antibiotics may change our microbiome.
  - Increases the risk of asthma.
- “Switching on an immune response early in life helps train the system to respond appropriately later in life.”

Autoimmunity

Regulatory T Cells and the Microbiome

- Dietary solutions for boosting regulatory T cell activity:
  - Prebiotics - vegetable fiber or supplements that encourage gut bacteria to multiply and hence improve the state of our immune system.
  - Probiotics - ingesting live bacteria, e.g., yogurt, with the same impact.
  - Probiotics using genetically modified bacteria - targeted production of molecules to boost activity of regulatory T cells aimed at stopping autoimmune diseases.

Autoimmunity

Causes - My Observations

- Some T cells have an affinity for self antigens.
- Performance of regulatory T cells affected by:
  - Genetic variations - Foxp3 and IPEX.
  - Age weakened immune system.
- The body may be subjected to prolonged, low-level damage with accompanying immune response (low level inflammation).
  - Prolonged stress.
  - Environmental contaminants and toxins.
  - Lifestyle - diet, smoking, alcohol, inactivity, obesity, etc.
- Immune system as a whole may lose coordination, suffer impairment of signaling between components.
  - Stress.
  - Age.

Autoimmunity

Cause - Davis's Observation

Before Sakaguchi's insight, "…the dogma was that immune cells capable of reacting against the body's own components were weeded out from the system, killed off in the thymus without ever reaching the bloodstream. But Sakaguchi and his contemporaries revealed the situation to be more complex than this. **The system specifically includes cells able to detect the body's own components**, which are there to safeguard against an immune reaction. We now know that this was just the tip of an iceberg because in fact, there are many types of T cell; far greater diversity than can be covered by the crude categories of 'normal' or 'regulatory' cells."

Autoimmunity

Nirvana on the Horizon?

“The reason that we’ve begun to triumph – why it is not hyperbole to suggest that we are at the dawn of a health revolution – is that we have now identified some of the hubs in the system: cells and molecules that, when targeted with drugs that boost or halt their activity, dramatically shift the behaviour of the system as a whole. We saw this with anti-cytokines. Blocking only one cytokine, TNF, for example, can alleviate the inflammation that underlies arthritis by halting an entire cascade of effects – in this case by severing the feedback loop in which immune cells keep triggering one another into action, leading to an autoimmune attack. When drugs, foods, prebiotics or probiotics are developed to impact the behaviour or numbers of regulatory T cells, which are undoubtedly also a hub in the system, we will have new treatments for allergies and other autoimmune diseases.”

Up Next

- Cancer and the immune system.
- Read - Chapter 8: Future Medicines.