OLLI SG 492
Human Immune System

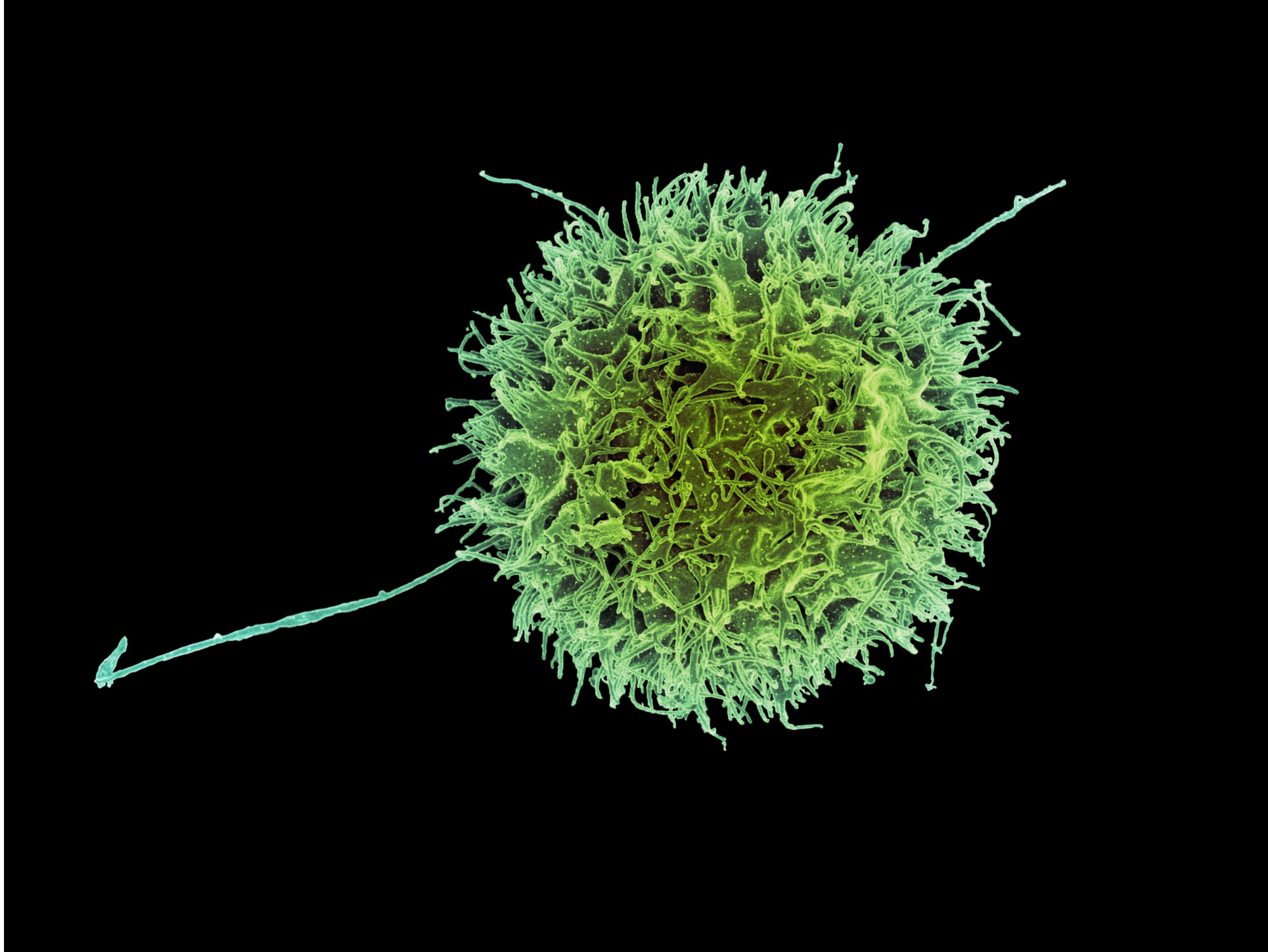
Session 7 - April 20, 2022

Today’s Meeting

- Comments, questions about last week’s topics - immune response scenario.
- Natural Killer (NK) Cells.
- Stress - effects on the body and the immune system.
- Ageing - variations over time, and the immune system gone “awry.”

Basics of the Immune System

NK Cell



Basics of the Immune System

Natural Killer (NK) Cells

- NK Cells are produced in the bone marrow by the lymphoid progenitor cells, a lymphocyte.
- Represent 5-20% of circulating lymphocytes in humans.
- Similar in function to cytotoxic T cells, but…
- Are part of the innate immune system - lack antigen specific receptors.
- Circulate in the blood and lymphatic systems.

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 (without antigens).
  - 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

MHC Class 1 Receptors

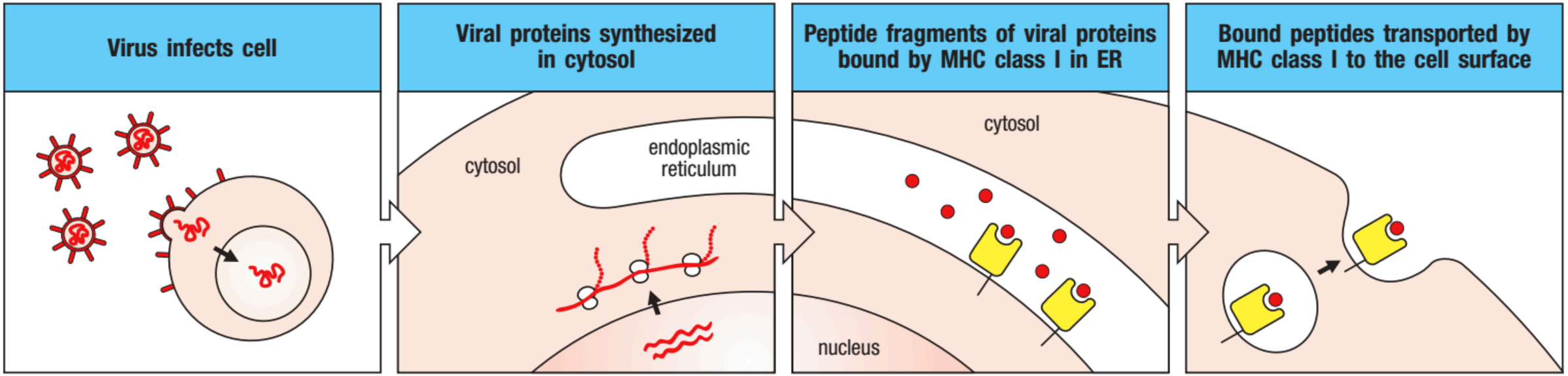
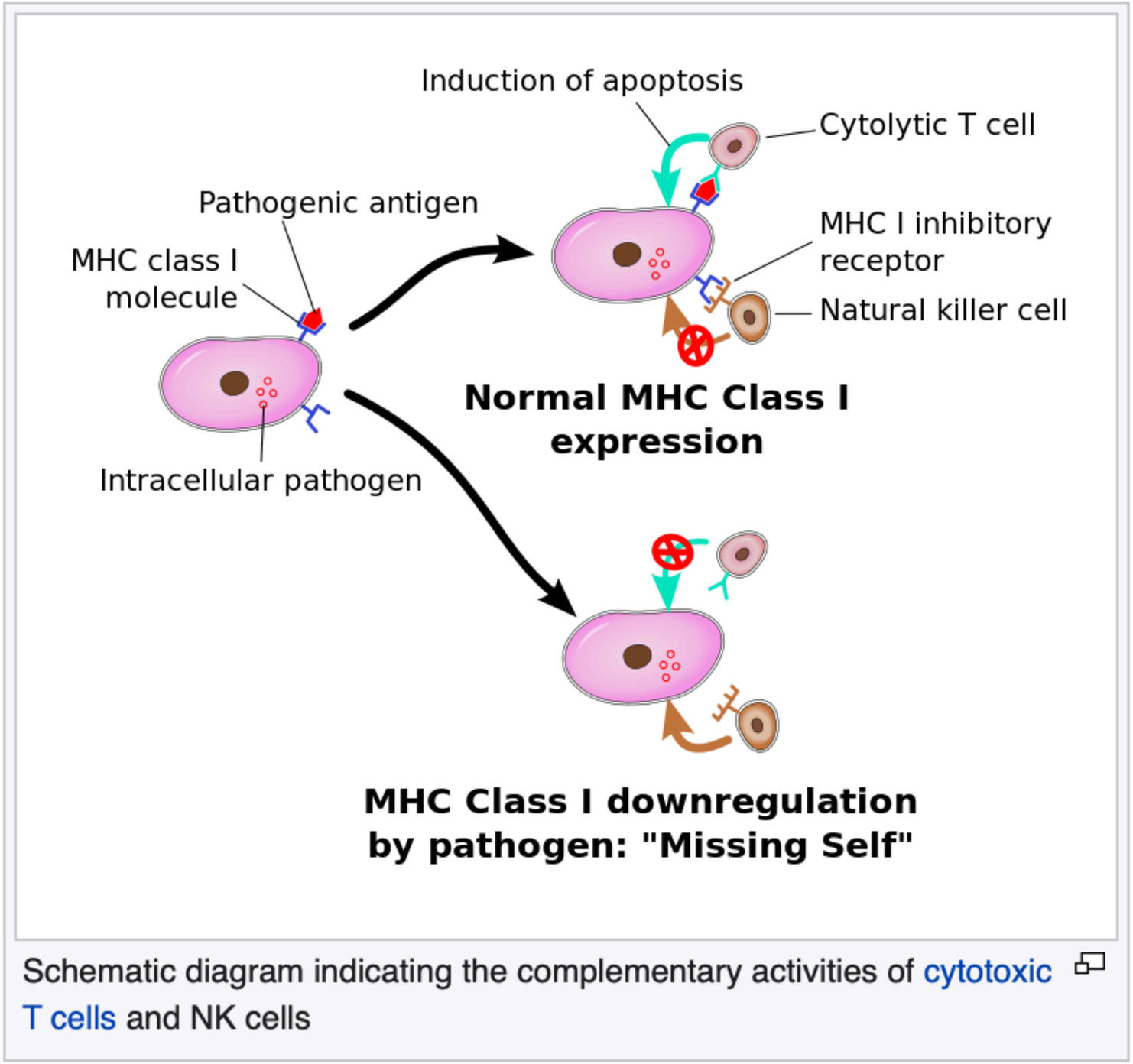


Fig. 1.30 MHC class I molecules present antigen derived from proteins in the cytosol. In cells infected with viruses, viral proteins are synthesized in the cytosol. Peptide fragments of viral proteins are transported into the endoplasmic reticulum (ER), where they are bound by MHC class I molecules, which then deliver the peptides to the cell surface.

Basics of the Immune System

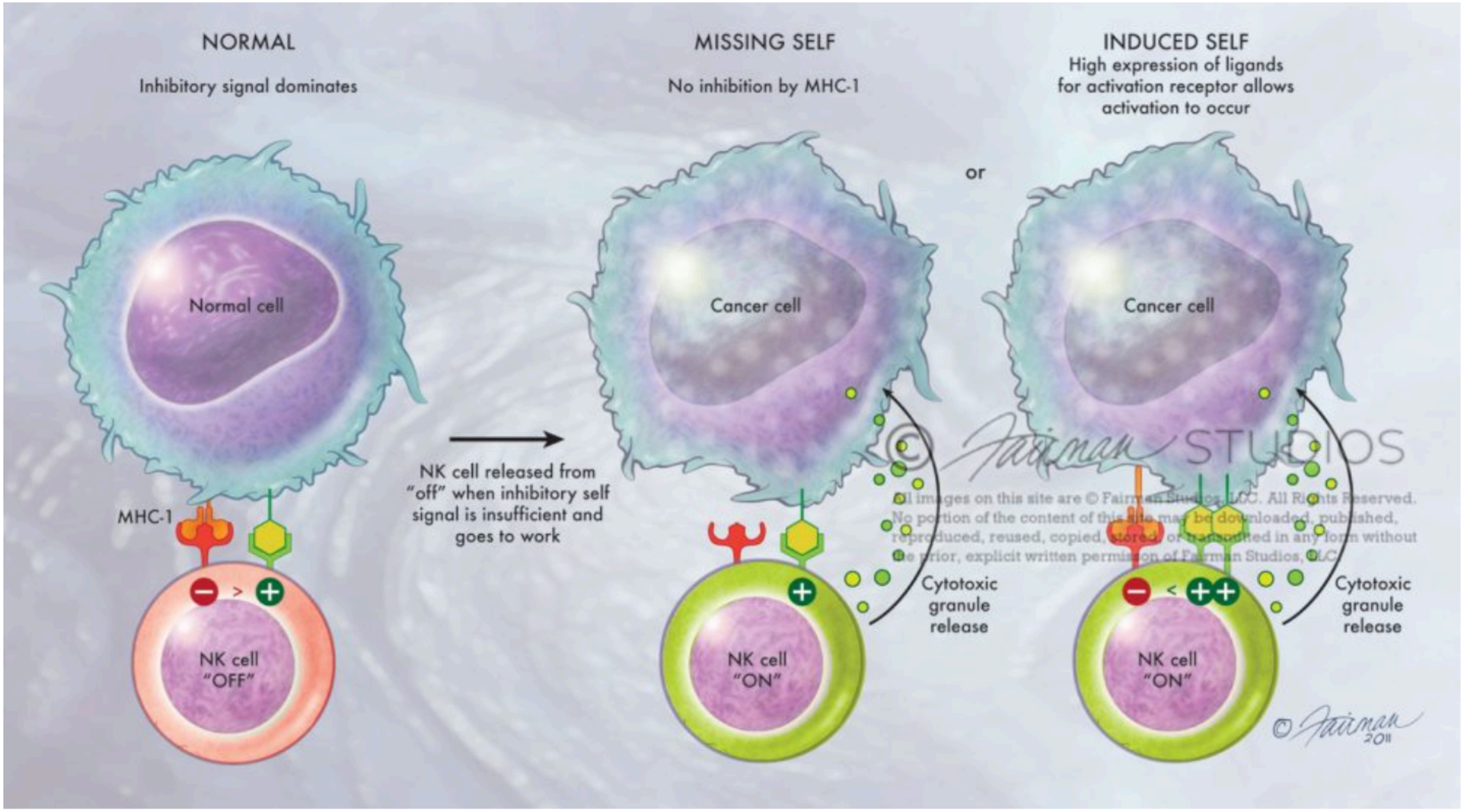
NK Cell Activity



Schematic diagram indicating the complementary activities of cytotoxic T cells and NK cells

Basics of the Immune System

NK Cell Activity



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.

Basics of the Immune System

NK Cell Activity

- Video on NK Receptors and Activity
- Video on Current Research With CAR NK Cells in Cancer Therapy
- Wikipedia article on Natural Killer Cells

Stress

Stress Response

- Cells that are damaged undergo a stress response.
  - Exposure to high temperatures can result in misshaped proteins.
  - UV light can damage a cells DNA.
  - Toxins can damage or interfere with normal functioning of cells.
- Cells exhibiting a stress response put up “stress-induced proteins” on their surface.
- If these proteins are detected by NK cells, the damaged cell is destroyed.

Stress

Cancer and Immune Response

- Some cancers can benefit from an immune response.
  - Cancer cells can take on features of immune cells, allowing them to respond to cytokines. This allows them to “hijack” the cues immune cells use to multiply and move around the body.
  - Solid tumors benefit from local inflammation that increases the supply of nutrients and oxygen. Some tumors can secrete proteins that attract immune cells, leading to inflammation; and some can secrete hormones that turn off immune cells attack capabilities while maintaining a local inflammation.
- A tumor that maintains a local inflammation is like “a wound that never heals.”

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

Fever and the Immune System

- Processes that produce a fever:
  - Macrophages release the cytokines TNF-alpha, IL-1beta, and IL-6; these are termed endogenous pyrogens.
  - These cytokines induce cells to produce the hormone prostaglandin E2, which acts on the hypothalamus; the hypothalamus stimulates the production of noradrenaline and acetylcholine.
  - This results in increased heat production through the metabolism of “brown fat”, heat retention through vasoconstriction, and muscle shivering.

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.

Stress

Effects of Cortisol/Cortisone

- Merck synthesized a version of cortisol, called cortisone.
- Cortisone quiets the immune system, suppresses the immune system.
  - Alleviates the symptoms of rheumatoid arthritis.
  - Not a cure for rheumatoid arthritis.
  - Effective treatment for asthma at lower doses.
- Derivatives of cortisol - hydrocortisone and dexamethasone - have been used to treat a wide range of ailments.

Stress

Stress and the Immune System

- Cortisol levels change dramatically with stress, dampening our immune system.
- If stress persists, the immune system may stay weakened.
- People under prolonged stress:
  - Suffer worse from viral infections.
  - Take longer to heal wounds.
  - Respond less well to vaccinations.
- The bad effect of stress on health is the best established link between lifestyle and the immune system.

Time

Temporal Variation of Immune Response

- Our immune system is stronger at night, while we rest. Cortisol is kept low at night.
- This variation in immune response may have evolved as a side effect of the need to optimize the body's use of energy, to regulate the body's metabolism.
- This temporal variation affects diseases like asthma, gout, and rheumatoid arthritis.
- Timed delivery of medicines would be a beneficial addition to current practice, as would "programable" delivery mechanisms.

Time

Ageing

- One of the greatest triumphs in the last century - increased lifespans.
- Our immune system becomes weaker as we age. “It somehow goes awry.”
- Effects of ageing:
  - Cell division slows down.
  - Epigenetic effects increase, affecting gene expression.
  - Telomeres shorten.

Time

Ageing

- The aged immune system:
  - Produces fewer immune cells.
    - Bone marrow stem cells lose their regenerative potential over time.
  - Poorer at detecting signs of disease.
  - Respond less efficiently to cytokines directing immune cells to infection sites.

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.

Up Next

- Autoimmunity.
- Read - Chapter 7: The Guardian Cells