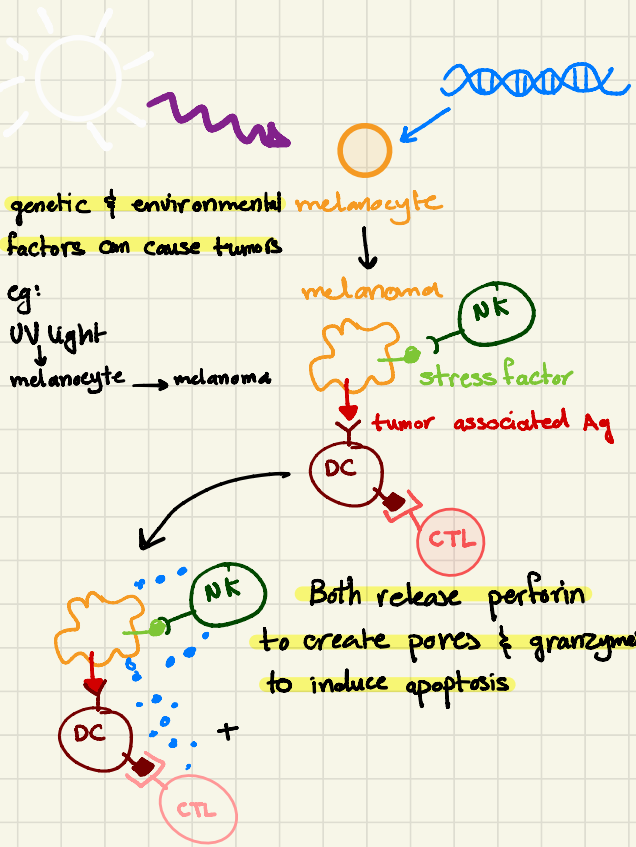
Different parts of the immune system:

Innate vs. Adaptive immunity

	Innate immunity	Adaptive immunity
Encoding of receptors	Germline	somatic
Distribution of receptors	Non Clonal (not specific)	Clonal (very specific)
Repertoire of receptors	Limited	Very large
Speed	Fast	Slow
Long-lasting memory	No	Yes

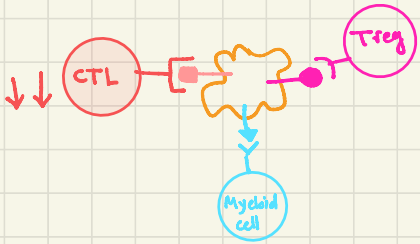
Tumors:



Both release perforin to create pores & granzymes to induce apoptosis

- T_H help DC activate CTL & produce IFNγ to activate NK cells

- Tumors are often heterogenous: Genetic changes occur to give tumor cells survival advantage, which mean they will stop expressing Ags that activate NK & CTL by immuno-editing.



- They also attract immune cells that suppress the activity of other immune cells and express inhibitory molecule PDL1 that binds to PD1 receptor on T cells to suppress them

- Chemotherapy: Drugs that induce cancer cells to die

- Immunotherapy: Using the body's own immune system to kill cancer (activating immune cells to recognize cancer as a foreign tissue)

- First used by William Coley

- Coley toxin: heat inactivated bacteria to induce inflammation

- Coley injected inactivated bacteria into tumors to induce an immune response there

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Four general strategies of immunotherapy

Non specific immune stimulation:

* **Injecting molecules:-**
  - to give immune system general boosts in vivo
  - activates APCs by binding to receptors that activate them to activate T cells

* **IL-2 & IFN α:-**
  - Cytokines are needed for full activation
  - treat some forms of cancer like melanoma
  - boost the activity of anti-tumor immune cells

* **BCG vaccine:-**
  - Live attenuated MB bovis
  - (this one is similar to Coley toxin)
  - cause inflammation ↑ # of immune cells around the tumor

Removing immune-checkpoint blockade:

(Blockades inhibit T cell activity to prevent collateral damage, to fight cancer they need to be removed)

* **CTLA-4:**
  - blocking them helps DC drive anti-tumor T cell response
  - The Ab Ipilimumab is used

* **PD1:**
  - use Ab that block it to switch off CTLs.

Adaptive immune transfer:

* **Tumor:-**
  - it's difficult to extract immune cells from tumor but the advantage is that the cells have already learned to recognize it

* **Blood:-**
  - Taking cells is easier
  - genetic engineering is needed to add tumor specific receptors
  - Cells are activated by cytokines and multiplied in petri dishes before reintroducing them to the patient

Vaccination

* **Viruses:-**
  - direct immune cells specifically to cancer tissue
  - Weakened HSV modified to produce an immune stimulating factor is being developed against melanoma & head and neck cancer

* **APC vaccination:-**
  - using persons immune cells
  - APCs taken from patient ↓ mature outside the body & loaded with tumor Ag ↓ reintroduced to patient to stimulate immune cells
  - (Provenge/Sipuleucel-T) first APC vaccination

* **Tumor cell:-**
  - extracted → irradiated to prevent spreading → engineered to secrete activating growth factors → injected to patient → growth factors alert immune system

* Immunotherapy :-

- Not all patients will respond to these immunotherapies and some responses will be delayed.
- Combining immunotherapy with chemotherapy or radiotherapy can lead to a better responses in some patients.
- Immunotherapies can themselves be combined.
- For example PD1 and CTLA-4 blockade can improve response when administered in combination.

- Since the introduction of ipilimumab (anti-CTLA-4) in 2011, the number of drugs approved for treatment of metastatic melanoma has expanded dramatically.
- Several drugs originally approved as monotherapies are now available as combinations which elicit greater clinical benefits.

* Risks :-

Activating the immune system has risks, some patients develop harmful side effects when their immune system attacks healthy cells.

Nevertheless there have been encouraging results from clinical trials.

Immunotherapies can be used to treat many different types of cancer

Types of immunotherapy

- **Passive immunotherapy:**
- Adminstration of monoclonal antibodies which target either tumour-specific or over-expressed antigens.
- **Active immunotherapies:**
- Cytokines- IL-2 / IFNs / TNFα
- Cancer vaccines
- Cell-based therapies
- tumour-specific CTL
- tumour-derived APC
- DC priming