Multipotent stem cells

'Adult'/tissue stem cells - replace tissue that have turned over throughout life:
Lose about 20 billion cells per day

- Needed for proper **tissue organisation** + response to demands of **growth/repair**
- Limits of adult stem cell growth set by **powerful molecular restraints** (by their niche)
    - **Heritable** during many rounds of cell division
    - Make sure they don't over-proliferate or remain too quiescent in repair
- Adult stem cells may show **relaxation** of these restrictions in an **altered environment**
    - Can account for **plasticity** (rare)

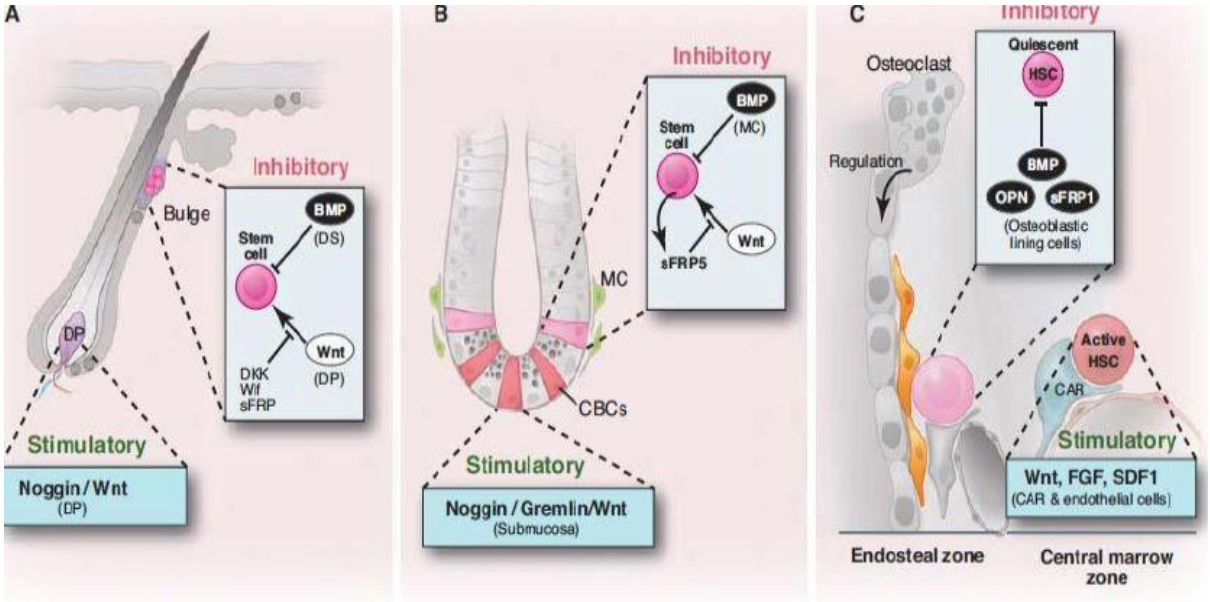
<u>Niches/Extrinsic signalling:</u>
Regulation of stem cell proliferation

Wnt/Noggin/Gremlin/FGF (BMP suppression) = **stimulatory**

BMP = **inhibitory** (makes them quiescent)

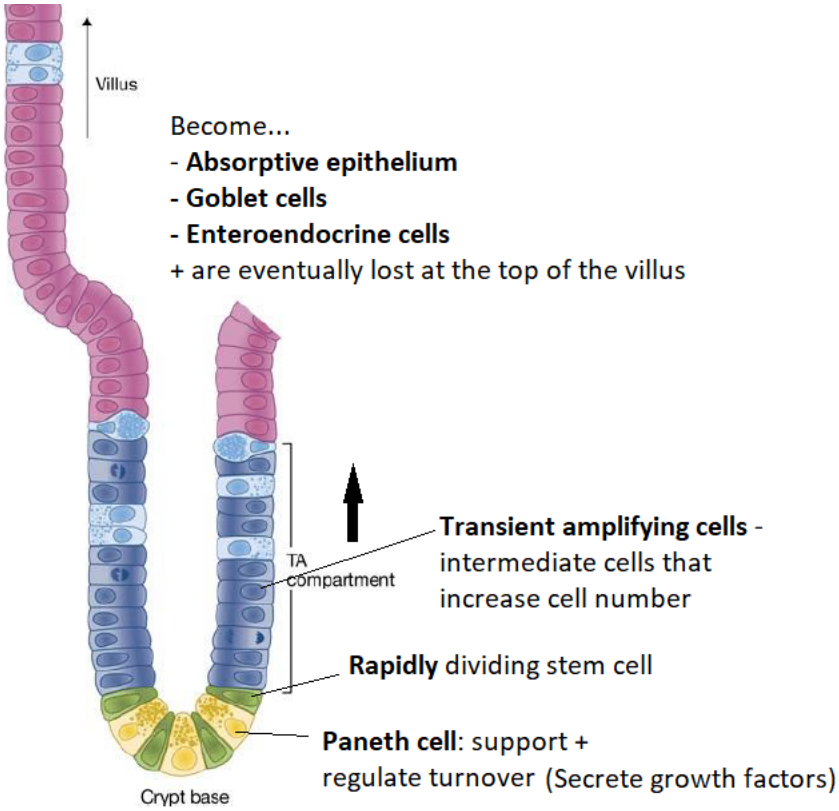
Will receive different signals depending on where the cell is – can **switch behaviour** of stem cells depending on environment

Balance of stimulation/inhibition regulates how quickly the cells turn over



<u>Tissues with stem cells</u>:

- Bone marrow
- Skin: Every 4 weeks a completely new epidermis generated
- Intestine: Lining replaced every 4 days



Cells move like a conveyor belt

Studied via **fluorescent tracing** – a single stem cell can give rise to **all** the epithelium on the sides of one villus

- Blood: RBCs only last 120 days (**can't divide** since no nucleus – blood stem cell that continues to produce them)
    - 1 HSC can repopulate **entire haematopoietic system**
    - Basis for bone marrow transplants in leukaemia treatment (transplant HSCs)
- Brain: Previously thought to be static/non-proliferative
    - Neurogenesis occurs in the **sub-ventricular zones + hippocampus**
    - SVZ – migrate out into the **olfactory bulb** (constant turnover of olfactory neurons)
    - Hippocampus – may have a role in learning + memory
    - Depression may decrease rate of making new neurons, exercise may increase rate of making new neurons
- Fat
- Muscle
- Bone

All have stem cells in them – some are more proliferative than others

e.g. hepatocytes – live for 300 days, cardiomyocytes – turn over 0.5% per year

<u>Facultative stem cells</u>

Where there is **massive injury**

e.g. in liver – generally no stem cells turning over

But if you have injury that drastically reduces no. hepatocytes, the **bile duct epithelium** will **trans-differentiate** into hepatocytes

i.e. they're **NOT stem cells** until there's a **catastrophe –**

The facultative stem cells then become hepatocytes

HOW? Because both the hepatocytes and bile duct epithelium are derived from the **same progenitor** (**oval cells**) – relatively small jump to switch gene expression

Application of adult stem cells

- Improve repair (e.g. repairing skin after injury) by understanding turnover (can promote proliferative repair process)
- **Mobilise** stem cells for harvesting + transplantation (HSCs)
    - e.g. mobilise HSCs so they come out of their niche and are circulating in blood – collect them by collecting blood
- Model diseases + screen for treatments
    - Make **organoids** (mini organs) derived from **epithelial stem cells** from the organ
    - Take small **biopsy** from these tissues, you can recreate a model of the organ in a dish (gel)
        - Model of the **specific patient**
        - **Test drugs –** very powerful tool for developing **personalised** treatments (especially for cancer)
        - Model **epithelial cancer**
    - Stimulating these stem cells can be done using the growth factor pathways

Mesenchymal stem cells

Another type of cell in bone marrow that was **mesenchymal** (not epithelial – no apicobasal polarisation)

- Can have **stromal potential** (helps with turnover of skeleton)
    - **Bone**
    - **Cartilage**
    - **Fat**
- Can **modulate** immune system
    - Immunosuppressive – produce factors that **reduce inflammatory state**
    - Immunoprotected – won't be rejected between individuals
        - Most clinical trials are testing this – given an MSC + transplant
        - For **graft vs host disease** and improved transplant outcome
        - This is **cell therapy** NOT stem cell therapy
            - Not expecting the MSC to turn into something – want them to modulate the immune system
- Only **lasts a few hours** after delivery
    - Whatever it's doing to modulate the immune system is **very rapid**

Pluripotent stem cells

- Can grow **indefinitely** in vitro
    - We **can't** grow most **adult stem cells** outside the human body
- Maintain **normal genetic makeup**
    - Can go through endless replications without accumulating mutations
    - Can make large numbers of stem cells to turn into tissue
- Capable of differentiation into a wide range of somatic tissues in vivo + in vitro at **high frequency** under a range of conditions
- Capable of **colonising all tissues** (including germ line) after **blastocyst injection** to give **chimeric** offspring (mice)
    - Will join the other pluripotent cells in the blastocyst and contribute to the organism (chimera)
- Not able to recreate an **entire organism** (won't make things in the right places)
- Can't generate **extra-embryonic tissue**

- May change in the future