L14 Pathogenesis of Myeloid Neoplasia

Leukaemic Stem cells

- Acute myeloid leukaemia accumulation of primitive stem cells in bone marrow
 - \circ $\;$ Transcription factors in myeloid development mutated in AML
 - o E.g. GATA
- Differentiation in stroma of bone marrow
 - If niche isn't right may develop a leukaemia
- Absence of certain transcription factors blood cell differentiation is blocked → can become a leukaemia cell
- Myeloid leukemic stem cells derived from stem cells or multipotent progenitors
- Myeloid dysplasia is a pre-cancer cells
 - MDS heterogeneous clonal disorder of blood cell production – acquisition of a number of heterogenous changes (genetic and epigenetic) that sequentially haemopoietic cell fate.
 - Partial block in differentiation + accumulation of immature cells

Normal blood cell development



Malignant blood cell development

- Different classes of mutation are required for the pathogenesis of AML
 - E.g. FLT3 mutations can be oncogenic
 - Some mutations are associated with each other. If you have one theother is more likely to be present of develop
- Clonal selection in disease progression from myeloty plast condrome to acute myeloid leukaemia
- Clonal evolution if you are treated nore than once the oplogy of the cells change those that
 - were not killed survive = if not wed 1st time will be harder to cure after each treatment.

Reprogramming of lacks mia

- Epigenetics
 - Turning genes on and off
 - DNA methylation
 - Switches off
 - In a lot of cancers there is a change in methylation pattern
 - Histone modification
 - Acetylation = on
 - methylation
 - phosphorylation
 - Non-coding RNAs
 - o Alters gene transcription, and hence expression profiles
 - \circ Can identify different types of AML by the pattern of methylation of genes

Acute myeloid leukaemia

- Malignant proliferation of poorly differentiated myeloid cells
- Genetic material can be moved from one chromosome to another
- Solid tumours have more genetic damage than leukaemia's
- There are many genetic changes that result in AML
- Single gene molecular abnormalities
 - o Gene has a mutation that switches it on or off or deletions