L14 Pathogenesis of Myeloid Neoplasia

Leukaemic Stem cells
- Acute myeloid leukaemia accumulation of primitive stem cells in bone marrow
  - Transcription factors in myeloid development mutated in AML
    - 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 heterogeneous changes (genetic and epigenetic) that sequentially haemopoietic cell fate.
  - Partial block in differentiation + accumulation of immature cells
- 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 the other is more likely to be present of develop
- Clonal selection in disease progression from myelodysplastic syndrome to acute myeloid leukaemia
  - Clonal evolution – if you are treated more than once the biology of the cells change those that were not killed survive → if not cured 1st time will be harder to cure after each treatment.

Reprogramming of Leukaemia Cells
- 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
  - Alters gene transcription, and hence expression profiles
  - 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
  - Gene has a mutation that switches it on or off or deletions