Multiple myeloma: epigenetic alterations
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Introduction
Multiple myeloma (MM) is the most common incurable haematological malignancy.
- Multi-step process: premalignant phase (MGSU) extramedullary aggressive form (PCL).
- Malignant plasma cells (PC) and bone marrow (BM) microenvironment interaction drug resistance.
- Manifestations: recurrent infections, anaemia, renal impairment, hypercalcemia, bone fractures and end-organ damage.

Epigenetics
- There are three altered epigenetic mechanisms that contribute to MM pathogenesis, by altering cell regulatory networks.

DNA methylation
- Distinguishes non-malignant from malignant MM phenotypes.
- Stage-specific DNA methylation pattern:
  - Global hypomethylation MGUS-MM transition
  - Gene-specific hypermethylation increasing throughout disease progression.

Histone modifications
- Mutations in histone-modifying enzymes oncogenes and TSGs.

Noncoding RNAs
- Mutations in non-coding RNAs (miRNAs)
- Effect on tumour suppressor genes (TSGs) and anti-apoptotic pathways.

Goals
- Understand the role of epigenetic abnormalities in MM and its effect in cell regulatory pathways.
- Highlight the potential use of an epi-drug therapy as future treatment for MM.

Tools
- Bibliographic databases (Scopus and Pubmed) to search information.
- Bibliographic manager (Mendeley) to organize the references.

Therapy
Understanding BM microenvironment
A. Immunomodulatory drugs
   - Thalidomide
   - Lenalidomide
   - Pomalidomide
   - Toxicity
   - Inhibitors of BM-MM cells interaction
B. Proteasome inhibitors Bortezomib
C. Other agents Heat shock protein 90 (HSP90), IL-6 blocking therapies

Epi-drugs
- Drugs acting by changing the epigenome under development.
  1. HDAC inhibitors effect through Histone modifications
  2. DNA demethylating agents
  3. Drugs targeting proteins for epigenetic marks recognition Ex. JQ1
  4. Synthetic miRNAs miR-29b and miR-34a

Conclusions
- Aberrant miRNA expression:
  - miRNAs dysregulation alteration of critical genes and epigenetic regulators
- Advantages in treatment drug resistance incurable.
  - Potential future therapy epigenetic agents.
  - Further studies novel biomarkers novel epi-drug strategies