Multiple myeloma: epigenetic alterations

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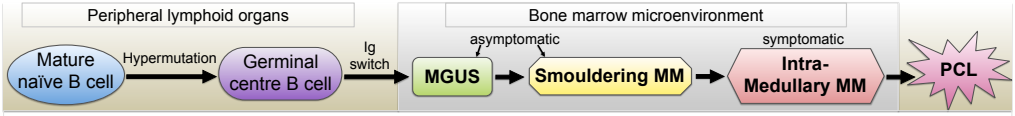
Introduction

→ Multiple myeloma (MM) is the most common incurable **haematological malignancy**.

- **Multi-step process**: premalignant phase (MGUS) → 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.



Multistep molecular process. Ig: Immunoglobulin; MGUS: monoclonal gammopathy of uncertain significance; PCL: plasma cell leukaemia

Goals

① Understand the **role of epigenetic abnormalities** in MM and its effect in cell regulatory pathways.

② 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.

Genetic alterations

Non-hyperdiploid cases (≈50%)
- Reciprocal translocations at 14q32 (*IgH*) → ⇧ D-type cyclins
- Copy number alterations (CNAs) → del(13) and add(1q)

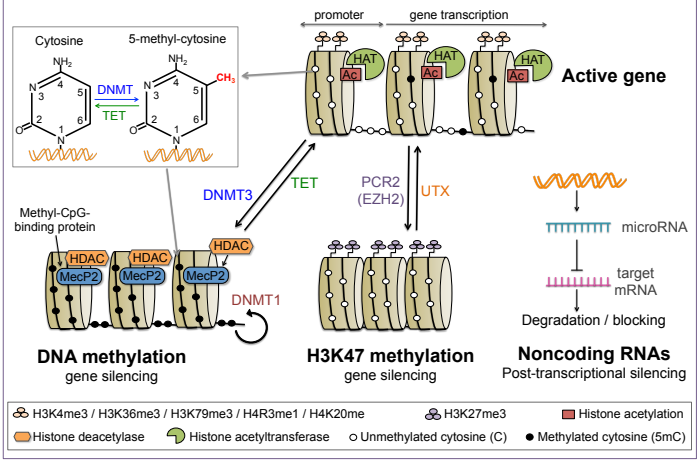
Hyperdiploid cases (≈50%)
- Trisomies: 3,5,7,9,11,15,19 and 21
- Infrequent 14q32 translocations

Secondary aberrations
- CNAs: del(1p), add(1q), del(13), del(17)
- Oncogene mutations: *RAS*
- Ig hypermutations
- Alterations in Rb pathway components
- ⇧ Dkk1 (Wnt signalling inhibitor)

Epigenetics

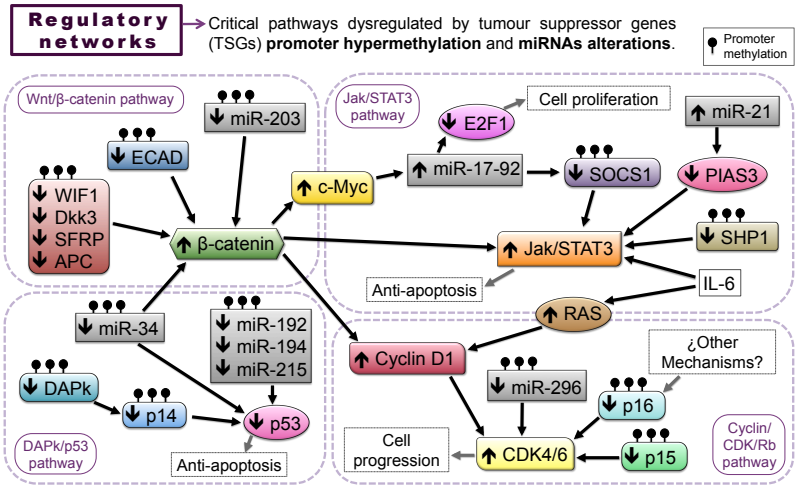
→ There are **three altered epigenetic mechanisms** that contribute to MM pathogenesis, by altering cell regulatory networks.

Molecular bases



Regulatory networks

→ Critical pathways dysregulated by tumour suppressor genes (TSGs) **promoter hypermethylation** and **miRNAs alterations**.



① DNA methylation

- Distinguishes non-malignant from malignant MM phenotypes.
- Stage-specific DNA methylation pattern:

Disease progression: PC → MGUS → SMM → IMM → PCL

Global hypomethylaton
⇧DNMT3a methylation → DNA demethylation
⇧ LINE-1, STAT-α and Alu demethylation → instability

TSGs promoter hypermethylation
⇧DNMT1

② Histone modifications

Mutations in histone modifying enzymes:

- ⇧***MMSET*** and ⇧***FSFR3*** → in t(4;14) cases
  - Methylates H3K36 and H4K20
  - Enhances HDACs function
  - → Oncogene activation
- ***UTX*** (histone demethylase) **deleted** / mutated
  - → ⇧histone methylation
- ⇧***ANP32E*** (HAT inhibitor) → in add(1q) cases
  - → ⇧histone methylation

③ Noncoding RNAs

MicroRNA (miRNA) dysregulation:

A. Downregulation → promoter hypermethylation
- *miR129-2* → ⇧oncogenes: *CDK6, SOX4*
- *miR-194*, *miR-34* → Annulation of *TP53* machinery

B. Upregulation
- *miR-21* → STAT3/IL-6 anti-apoptotic pathway
- *miR-17-92* → pro-apoptotic targets (PTEN)
- *miR-106-25* → *EF21* and *BCL2L11*

C. Interaction with critical epigenetic regulators
- *miR-29b* → DNMT3b
- *miR-106b-25* → PCAF

Therapy

Understanding BM microenvironment → **New drugs**

A. Immunomodulatory drugs
- ① **Thalidomide**
- ② **Lenalidomide**
- ③ **Pomalidomide**

(+ / - Toxicity)

- Apoptotic
- Anti-angiogenic
- Anti-inflammatory
- 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
- Transcription factors (HSP90)

② **DNA demethylating agents** → lysine demethylases and DNMT inhibitors

③ **Drugs targeting proteins for epigenetic marks recognition** → Ex: *JQ1*

④ **Synthetic miRNAs** → *miR-29b* and *miR-34a*

Conclusions

Epigenetic aberrations → critical pathways alteration → MM progression.

① **Stage-specific DNA methylation pattern**:
- Global hypomethylation → MGUS-MM transition
  - → ⇧repetitive elements demethylation → genome instability.
- Gene-specific hypermethylation → increasing throughout disease progression.

② **Alterations in histone-methylation patterns**:
- Mutations in histone-modifying enzymes → ⇧oncogenes and ⇩TSGs.

③ **Aberrant miRNA expression**:
- miRNAs dysregulation → alteration of critical genes and epigenetic regulators

Advantages in treatment → (but) **drug resistance** → incurable.
- Potential future therapy → epigenetic agents.
- Further studies
  - new biomarkers
  - novel epi-drug strategies