

## Multiple myeloma

### Clinics and Pathology

Disease	multiple myeloma (MM) is a malignant monoclonal plasma cell proliferation. Monoclonal gammopathy of unknown significance (MGUS) and smoldering myeloma (SMM) are premalignant states susceptible to transform in MM
Phenotype / cell stem origin	phenotype of mature terminally differentiated B-cell, but also with CD56 expression, which is not found in normal plasma cells; CD138+.CD38+ CD40+
Epidemiology	multiple myeloma's annual incidence: 30/10 <sup>6</sup> ; i.e. around 1% of malignancies in adults and 10% of haematologic malignancies; mean age: 62 yrs
Clinics	patients may be asymptomatic at the time of diagnosis; bone pain; susceptibility to infections; renal failure; neurologic dysfunctions
Pathology	MM staging: stage I: tumour cell mass < 0.6 X 10 <sup>12</sup> /m <sup>2</sup> ; Hb > 10 g/dl; serum calcium $\leq$ 120 mg/l; no bone lesion; low monoclonal Ig rate (IgG < 50 g/l, IgA < 30 g/l, BJ urine < 4 g/day); stage II: fitting neither stage I nor stage III; stage III: tumour cell mass > 1.2 X 10 <sup>12</sup> /m <sup>2</sup> ; Hb < 8.5 g/dl and/or serum calcium > 120 mg/l and/or advanced lytic bone lesions and/or high monoclonal Ig rate (IgG > 70 g/l, IgA > 50 g/l, BJ urine > 12 g/day)
Treatment	none before onset of symptoms; chemotherapy or BMT afterwards. Various new therapies, mainly acting by apoptosis induction in MM cells, are or will be involved in clinical trials (thalidomide, proteasome inhibitor PS-341, 2 methoxy estradiol, arsenic trioxide, TNF alpha).
Prognosis	evolution: multiple myeloma can evolve towards <a href="#">plasma cell leukemia</a> , where plasma cell count is greater than 2000/mm <sup>3</sup> ; survival is highly variable (median is around 3 yrs); prognosis is according to the staging and other parameters (such as age, serum albumin, b2 microglobulin, C-reactive protein, and plasma cell labeling index); the karyotype is emerging as an important prognostic factor: median survival in case of a normal karyotype could be 4 yrs vs 1 yr in case of -13/del(13q) and/or 11q rearrangements (the chromosome anomalies with the worst prognostic impact)

### Cytogenetics

Cytogenetics	cytogenetic information is limited, as the malignant cells have a low spontaneous proliferative activity; abnormal karyotypes are found in 30-50% of cases, more often in advanced stages than in newly diagnosed patients (is this because chromosome abnormalities are secondary events, or because malignant cells have an increased proliferative activity in advanced stages: see below); karyotypes are complex; hyperploidy is found in 2/3 of cases; karyotypes may evolve from normal to abnormal during course of the disease;
Morphological	- structural (and variable) <a href="#">anomalies of chromosome 1</a> are found in 30-

40% of cases, 14q rearrangements in 25% of cases, [11q abnormalities](#) in 20 %, [t\(11;14\)\(q13;q32\)](#) representing 10%; 6q anomalies represent 15% of cases; FISH is indicated, as metaphases are arduous to obtain in such a disease implicating mature cells, and tend to show that most cases bear chromosome anomalies, irrespective of the disease staging.

Cytogenetics All MM cells should express chromosome abnormalities, as strongly suggested by interphase FISH and CGH.  
Molecular Aneuploidy is detected in 67-90% of cases, allowing to define 2 prognosis entities:  
1) hyperdiploid sub-group with a significantly better overall survival, gains involving primarily [+3](#), [+5](#), +7, +9, +11, [+15](#), [+19](#), [+21](#) and infrequent structural abnormalities.  
2) hypodiploid group (+hypotetraploid cases by endoreduplication of a prior hypodiploid karyotype) strongly correlated with complex structural rearrangements, 14q32 translocations, [del\(13q\)/-13](#) and a more aggressive evolution.  
IG rearrangements: translocations involving 14q32 are found in at least 65-70% of patients, most of them result from short segments exchange and are detected quite exclusively by FISH. Five translocations involving IGH locus are particularly relevant and considered as very early primary events: [t\(4;11\)\(p16;q32\)](#), [t\(6;14\)\(p25;q32\)](#), [t\(11;14\)\(q13;q32\)](#), [t\(14;16\)\(q32;q23\)](#), [t\(14;20\)\(q32;q11\)](#). Other translocations involving IGH are rare or sporadic, they should be secondary and not mediated by specific recombination mechanisms.  
Del13q/-13: 13q14.3 deletions emerge as a major independent prognostic factor, underevaluated by conventional cytogenetics; found by FISH in 20-30% of patients; associated with a significant lower rate of response to conventional chemotherapy, and to a shorter survival.

## Genes involved and Proteins

### Gene Name [FGFR3](#)

Location 4p16

Note Involved in [t\(4;14\)\(p16;q32\)](#), approximately 15% of MM cases. FGFR3 (tyrosine kinase receptor) and MMSET (novel gene homologous to a Drosophila dysmorph gene, see below) are in opposite transcriptional orientation at 4p16. Both are involved in [t\(4;14\)](#). The translocation generates 2 fusion genes, IGH-MMSET on der(4) and FGFR3-IGH on der(14).

### Gene Name WHSC1 (MMSET)

Location 4p16

Note involved in [t\(4;14\)\(p16;q32\)](#) (see above)

### Gene Name CCND3 (Cyclin D3)

Location 6p21

Note Involved in [t\(6;14\)\(p21;q32\)](#) (3-5% of MM cases). Detected quasi exclusively by FISH.

### Gene Name [BCL1](#)

Location 11q13

Note BCL1 (also called Cyclin D1 or CCND1) is involved in [t\(11;14\)\(q13;q32\)](#) cases. Approximately 15-20% of cases. Same translocation as mantle

cell lymphoma but IGH breakpoint different (IGHS vs IGHJ)

**Gene Name** MAF

Location 16q23

Note basic zipper transcription factor, involved in t(14;16)(q32;q23) (5% of MM cases). Detected quasi exclusively by FISH

**Gene Name** MAFB

Location 20q11

Note MAF family basic region / leucine zipper transcription factor, involved in t(14;20)(q32;q11) (2% of MM cases)

**Gene Name** [C-MYC](#)

Location 8q24

Note Overexpression (mainly without rearrangement or amplification) correlated with increased tumour cell burden. RAS mutations (found in 20% of cases) and P53 mutations are associated with advanced disease

**Gene Name** [RB1](#)

Location 13q14

Note RB1 is deleted in more than 1/3 of cases. 13q14.3 deletions have been observed without RB1 loss, which should mean that RB1 is not the only critical locus of 13q14.3 sub-band. D13S25 and D13S319 appear as the more commonly deleted loci.

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