

Review Article

Molecular Biology of Multiple Myeloma

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Abstract

Multiple myeloma is a disease of malignant plasma cells in the bone marrow. Interaction of malignant plasma cells with the bone marrow microenvironment plays a key role in the pathogenesis of myeloma. Recognition of potential adverse cytogenetic and genomic abnormalities has led to identification of newer targets, translating to development of newer drugs. The introduction of two new such classes of molecules, namely immunomodulators (e.g. thalidomide, lenalidomide, pomalidomide), and proteasome inhibitors (e.g. bortezomib, carfilzomib), consolidation with high dose chemotherapy and autologous stem cell transplantation (ASCT) and improved supportive care has led to improved outcome, more so in younger patients (age <65 years). Frequent relapses despite initial responses to therapy remain a major clinical challenge. Identification of patients at high risk of relapse based on cytogenetics and comprehensive gene expression profiling is currently an active area of research. In this review we have made an attempt to cover the landscape of chromosomal abnormalities in myeloma and its clinical impact on outcome.

INTRODUCTION

Multiple myeloma (MM) is a neoplastic disease of the clonal plasma cells. Malignant plasma cells (PC) accumulate in the bone marrow and produce a monoclonal protein (immunoglobulin), usually IgG or IgA, referred to as M or Myeloma protein. MM is a heterogeneous disease whose treatment outcome is driven by the genetic-biologic characteristics. Monoclonal gammopathy of uncertain significance (MGUS) (with a limited number of clonal plasma cells) is considered to be the preceding event in the pathogenesis of MM. Individuals with MGUS are asymptomatic with no evidence of end-organ damage but have an annual risk of 1% of progression to myeloma [1,2]. Improved understanding of biology of myeloma, its molecular genetics and of bone marrow microenvironment have led to the development of new molecules with better outcomes. An aggressive approach has been suggested for a subset of patients with high-risk cytogenetics detected on FISH/ gene expression profile.

The origin of the myeloma clone

The developmental evolution of B-cell is marked by the immunoglobulin (Ig) heavy (IgH) and light chain (Ig λ genes (V_H -N-D_H-J_H on chromosome 14 and V_L -N-J_L on chromosomes 2 and 22 for κ and λ light chain respectively) rearrangements. This involves one of about fifty functional V_H , another of thirty D, and one of six J_H genes and, one of thirty V_L and one of four J_L genes. The unique IgH and IgL rearrangement process starts in the early pre-B-cell stage. Plasma cell, the myeloma cell precursor is a terminally differentiated B-lymphocyte that appears to have passed the normal steps with its immunoglobulin genes

having undergone the crucial stages of antigen selection, isotype switching and somatic hypermutation in germinal center. Extensive hypermutations are also evident in IgH gene sequences in MM with no apparent evidence of intra-clonal variations [3]. The first genetic "event" of a multi-step neoplastic process could take place by the random acquisition of translocations to the IgH locus on chromosome 14q32 or less frequently to the IgL locus (λ light chain on chromosome 22q11; κ light chain on chromosome 2p12) [4].

Bone marrow microenvironment

Interaction of malignant plasma cells with bone marrow (BM) micro-environment plays a key role in myeloma pathogenesis and progression. The cellular components of the BM microenvironment include- hematopoietic progenitor and stem cells, immune cells, BM stromal cells, BM endothelial cells, osteoclasts and osteoblasts. Non cellular components provide a niche for plasma cell expansion (Figure 1). Direct interaction of malignant plasma cells with these components and growth factors/cytokines secreted by either plasma cells or stromal cells or both, support growth, survival, migration of malignant myeloma cells and possibly confer drug resistance [5]. The non-cellular compartment provides adhesion for MM cell [6,7]. This is accompanied by production/secretion of urokinase type plasminogen activator, metalloproteinase-2, and metalloproteinase-9. The liquid milieu/fluid in the BM niche primarily comprises of cytokines and growth factors such as interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), insulin like growth factor-1 (IGF1), members of the tumor necrosis factor (TNF) super family, transforming growth factor

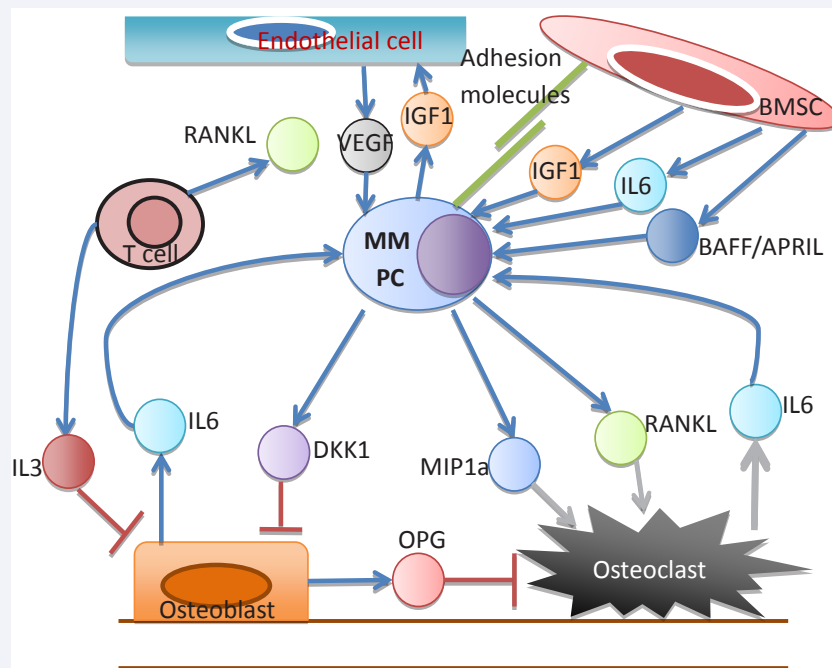


Figure 1 Bone marrow microenvironment in multiple myeloma- roles for cellular and non-cellular components.

beta-1(TGFβ1), chemokine ligand 3(CCL3), stroma-derived factor-1(SDF-1), hepatocyte growth factor (HGF), and interleukin 10(IL-10) [8]. Further, adhesion of myeloma cells to fibronectin confers protection from apoptosis, while binding of myeloma cells to bone-marrow stromal cells induces transcription and secretion of cytokines, including IL-6, IGF-1, and TNF, VEGF, and stroma-derived factor-1 [5]. In the cellular bone marrow compartment, MM cells interact with hematopoietic and non-hematopoietic cells; these interactions translate into immune suppression and lytic bone lesions. Bone marrow stromal cells have been shown to signal multiple myeloma cell growth, survival, migration, and drug resistance (directly through cell-cell contact or indirectly through secretion of soluble factors) [9]. Interleukin-6 secreted by bone marrow cells enhances the production and secretion of VEGF by malignant plasma cells and vice versa. The abnormal structure of multiple myeloma tumor vessels has been observed due to induction of pro-angiogenic molecules (e.g. VEGF), enhancer of micro-vascular density in the bone marrow. Typical established mosaic blood vessels primarily consist of endothelial cells, highly proliferative circulatory endothelial progenitors, hematopoietic stem/progenitor cells, monocytes and macrophages, and tumor cells (e.g. multiple myeloma cells) [10]. Studies have revealed correlation of the increased micro-vascular density with disease progression and poor prognosis in myeloma. Reports further suggest specific endothelial cell phenotype in MM, but, whether these are disease intrinsic or modulated by healthy endothelial cells by tumor cells is still unclear. Currently this is an active area of research [11]. The medullar microenvironment of the bone marrow is affected by the functionally distinct cortical bone. These complications are possibly caused by increased osteoclast formation/activity, reduced numbers of osteoblasts and development of hematopoietic and multiple myeloma stem cells [12]. Therapies

directly targeting the bone marrow microenvironment in MM currently are under active investigations [13].

Cytogenetic abnormalities in Myeloma

Cytogenetic abnormalities are universally present in the myeloma cells [14,15]. MM is characterized by marked karyotypic instability. This genomic complexity as well as the lack of specific methods in earlier reports to study these changes in low proliferating plasma cell clone hindered the understanding of genetic basis of MM. The development of methods such as interphase fluorescent in situ hybridization (iFISH), multicolor FISH, comparative genomic hybridization (CGH) and microarray technologies later enabled the investigators to unveil the biological consequences of some of the genetic abnormalities [16-19] (Table 1).

Deletion of Chromosome 13

Deletion of chromosome 13/13q14 is noted in about 15% of patients by conventional cytogenetics [18] and in 40-to 50% by iFISH [20-23]. The most common deleted region is 13q14, [23]. This locus harbors the retinoblastoma gene (RB1), a tumor suppressor gene involved in cell cycle regulation, and could therefore be a potential player in the pathogenesis of MM.

Deletion of chromosome 13/del13q14 was the first reported chromosomal abnormality consistently associated with poor prognosis in MM [24-26]. Earlier studies have reported association between the presence of del.13 and a shorter event-free (EFS) as well as overall survival (OS) [24-26]. This association was independent of treatment type (conventional chemotherapy, high-dose therapy, single or tandem autologous transplantation, and mini allogeneic transplant) and stage (newly diagnosed or pretreated patients). A number of studies have also suggested the role of del.13 in prognostication [23, 27-32]. Desikan et al (2000)

Table 1: Major chromosomal abnormalities and their frequency by conventional cytogenetics and Interphase FISH (adapted from ref.

Abnormality	CC (%)	FISH (%)
1p,1q amplification	-	40-70%
del13	10-15	40-55
t(4;14)(p16.3;q32)	None	10-15
t(6;14)(p21;q32)		3-4
t(11;14)(q13;q32)	2	15-20
t(14;16)(q32;q23)	None	3-6
del17p13	5	5-15
Hypodiploid	9-14	30-35
Hyperdiploid	30	50

Abbreviations: CC: Conventional Cytogenetics, FISH: Fluorescence In Situ Hybridization

reported inferior 5-year event free survival (EFS) for patients having del.13 abnormality ($P < 0.0001$) and an inferior 5-year overall survival (OS), 16% vs. 44%, ($P < 0.0001$) in a cohort of 1,000 autologous stem cell transplantation (ASCT) recipients [29]. Recent reports suggest del.13 detected by iFISH is an independent prognostic variable [19]. Zojer et al (2000) reported lower response rate ($P = 0.009$) and shorter OS ($P < 0.005$) for

patients having del 13 abnormality on iFISH [20]. In the French Myeloma Group study del.13 (by iFISH) was one of the most powerful adverse prognostic factor in patients receiving ASCT [33]. This study further reported the presence of del.13 and a high $\beta 2m$ (>2.5 mg/L) as unfavorable prognostic factors; median OS of 25.3 ± 3.2 months for patients with both factors, 47.3 ± 4.6 months for those with one factor, or median not reached at 111.1 months, ($P < 0.0001$) for those with no unfavorable factor. Recent studies [34-45] have also confirmed the impact of the del13q14 on survival (Table 2).

IgH Translocations

Translocations involving the IgH gene are common events in MM pathogenesis [46]. The prevalence of this abnormality is closely related to the detection method used. In MGUS and MM, the IgH translocations are identified in ~10-20% by conventional cytogenetics and in 50% by iFISH. The prevalence increases significantly in more advance stages of the disease, seen in up to 80% of PCL cases and of 90% in HMCLs [46]. Primary immunoglobulin translocations are believed to be an initiating event in MM pathogenesis for 50% of cases [47]. The most frequent partners of primary IgH translocations in MM are 11q13 (CCND1 gene, identified in 15% of patients); 4p16.3 (MMSET and FGFR3, 15%); 16q23 (C-MAF, 6%); 6p21 (CCND3, 3%) [48].

Table 2: del13q14 abnormality and its impact on outcome:

Study /Year (Ref)	Patients (n)	Therapy	Frequency (%)	Overall survival (deletion present vs absent)
Gao et al. 2012 [34]	60	NA	63.3	NA
Lim et al. 2013 [35]	525	BD/TD/HDCT	55	21.3 vs. 50.3 months ($P = 0.001$)
Klein et al. 2011 [36]	92	LD/HDCT	59	5.1 vs. 14.4 months ($P = 0.009$)
Neben et al., 2010 [37]	315	HDCT	46	72 vs. 82% ($P = 0.037$)
Chiecchio et al., 2006 [38]	729	CC	48	29 vs. 47 ($P = 0.001$)
Van Rhee et al., 2008 [39]	169	CC	25	HR=2.76; 95% CI: 1.85-4.10 ($P = .001$)
Schilling et al., 2008 [40]	101	CC+ASCT	61	38% vs. 56% ($P = 0.31$)
Knop et al., 2009 [41]	69	CC	41	HR: 1.35; 95% CI: 0.89, 2.05 ($P = 0.152$)
Konigsberg et al., 2000 [42]	89	CC	45	24.2 vs. 88.1 months ($P = 0.008$)
Reece et al., 2009 [43]	130	CC	41.5	HR= 1.43 ($P = 0.15$)
Gutiérrez et al., 2007 [16]	260	CC+HDCT	42	34 vs. 51 months ($P = 0.0001$)
Paul et al., 2009 [44]	193	CC	54	58 months vs. NR ($P = 0.006$)
Avet-Loiseau et al., 2010 [45]	207	CC	41	10.4 vs. 17.4 months ($P = 0.001$)
Fonseca et al., 2002 [25]	351	HDCT	54	34.9 vs 54 ($P = .021$)
Worel et al., 2001 [28]	28	HDCT	39	29 months vs NR ($P = 0.012$)
Jagannath et al., 2007 [24]	138	HDCT	29	NR
Chiecchio et al., 2009 [27]	400	CC	47	NA

Abbreviations: Freq: Frequency; HDCT :High-Dose Chemotherapy; CC :Conventional Chemotherapy; ASCT : Autologous Stem Cell Transplant; TD/LD/MPT :Thalidomide + Dexamethasone/Lenalidomide + Dexamethasone/Melphalan + Prednisolone + Thalidomide; BD: Bortezomib + Dexamethasone; Del13q14 : Deletion Of 13q14; T(14q32) : Translocations Involving The Region 14q32; OS : Overall Survival; HR : Hazard ratio; CI : Confidence Interval; NR : Not Reached; NA : Not Available

t (4;14)

The t (4; 14) is present in approximately 15% of MM patients by iFISH analysis; this chromosomal abnormality is not detected by conventional karyotyping. This chromosomal translocation results in the simultaneous dysregulation of the fibroblast growth factor receptor 3 gene (FGFR3) on der(14) and the multiple myeloma SET domain gene (MMSET) on der(4), with all the breakpoints occurring in the IgH locus switch region and dissociation of the intronic enhancer from the 3' enhancer [49]. FGFR3 is one of the high-affinity tyrosine kinase receptors for the FGF family of ligands. Both FGFR3 and MMSET genes are not normally expressed in plasma cells but are over expressed as a result of the t (4;14) translocation. Gene expression profiling and RT-PCR analysis have shown that 75% of the MM with t (4; 14) displays a simultaneous over expression of MMSET and FGFR3. In the remaining 25% of cases only MMSET is up regulated while lack of FGFR3 expression is linked in most cases to loss of the FGFR3 gene on der (14) [50,51]. It has been suggested that MMSET may be the critical transforming event in MM harboring the t (4; 14). In some cases (10%), the trans located FGFR3 contains activating mutations that may be involved in MM progression [52].t (4; 14) is more prevalent among patients with IgA myeloma as well as in patients with aggressive clinical features [50,53].

The t (4; 14) detected by iFISH is associated with poor OS independent of treatment type [50, 53-55]. In a French study, among 936 ASCT recipients, EFS was 20.6 months for patients with t (4; 14)(p16.3;q32) compared to 36.5 months for those without the abnormality (P < 0.001).The median OS was 32.8 months versus not reached for patients without the abnormality. Expected overall survival at 80 months was 22.8% vs 66%; P = 0.002) in this study [22].

Similar observations were reported in a study of 153 ASCT recipients from Mayo Clinic [54]; time to progression was shorter (8.2 vs.17.8 months< 0.001) and median OS was 18.8 months vs. 43.9 months (P < 0.001) for patients with t(4;14)(p16.3;q32) [54]. Thus, presence of the t(4;14)(p16.3;q32) translocation, therefore identifies high-risk patients who do not benefit from conventional chemotherapy or even ASCT [54-56].

t (6;14)

The t(6;14) has been reported in a low proportion (3%) of MM. Microarray based gene expression profiling analysis have revealed high levels of cyclin D3 mRNA in myeloma patients t(6;14) as detected by iFISH [57].

t (11;14)(q13;q32)

The t(11;14)(q13;q32) is common translocation , detected in 15-20% on iFISH. This translocation is similar to as t(11;14) in mantle cell lymphoma. In this translocation, the PRAD-1 (CCND1) proto-oncogene at 11q13 is juxtaposed to the immunoglobulin heavy chain gene at 14q32, resulting in over expression of the protein product, cyclin D1 [58]. This is generally associated with CD20 expression, lympho-plasmacytic morphology, hypo secretory disease, lambda light chains and higher frequency of IgM disease. Cyclin D1 detected by immune histochemistry identifies MM patients with the t(11;14) [59]. Patients with t(11;14) have outcome (PFS and OS) inferior to those with normal cytogenetics but superior to those with high risk cytogenetics / iFISH [60,61].

t(14;16)

The frequency of t(14;16) in MM is between 5 and 10%. The breakpoints on16q23 occur over a region 550-1350 Kb centromeric to CMAF. For this translocation, the distance between the enhancer and the oncogene CMAF is considerably longer than in other IGH translocations. CMAF is the cellular homologue of v -MAF, the transforming gene in the avian MAF retrovirus, and it is expressed at high level in MM cells with a 16q23translocation. Microarray and quantitative RT-PCR data have demonstrated that the over expression of CMAF is observed in half of myeloma cases. This proportion is much more frequent than was expected from the low prevalence of the t(14;16). Interestingly, the oncoprotein CMAF increases the expression of integrin β7, an adhesion molecule that heterodimerises with integrin αE to bind to E-cadherin on the surface of BM stroma cells. This finding suggests that CMAF enhances the adhesion of myeloma cells to BM stroma through the integrin αEβ7/E-cadherin pathway [62].

t(14;20)

MAFB is a B-zip transcription factor like CMAF, but in contrast to t (14; 16), MAFB translocation have structural features that indicate they are secondary translocations [14].

Deletion 17p13

TP53 tumor suppressor gene p53 is the target of the deletion17p13 and is implicated in the regulation of cell proliferation, differentiation, and apoptosis. Although, the deletion 17p13 is a rare event and is detected in only 5 -10% of MM patients at diagnosis, but it becomes more frequent (20-40%) in advance stages of disease [63-65].

Table 3: Chromosomal abnormalities by conventional cytogenetics.

Study	Patients (n)	Therapy	Freq. (%)	Comments
Chiecchio et al., 2006 [38]	555	CC	38	Presence of abnormal karyotype associated with inferior OS; 24 vs 45 months (P =0.001)
Shaughnessy et al., 2003 [32]	231	HDCT + ASCT	33	Presence of hypodiploid karyotype showed inferior OS with HR =2.33; (95% CI: 1.5-3.5) (P = 0.001)
Van Rhee et al., 2008 [39]	169	CC	47	Presence of numerical abnormalities had impact on OS with HR=3.07; (95% CI 2.15-4.38). (P =.001)
Desikan et al., 2000 [29]	1000	CC	34	Presence of monosomy 13 was associated with inferior outcome; 16vs. 44 months. (p < 0.001)

Abbreviations: CC: Conventional Chemotherapy; ASCT: Autologous Stem Cell Transplant; HDCT: High-Dose Therapy. OS: Overall Survival; HR: Hazard Ratio; CI: Confidence Interval

This chromosomal abnormality has been associated with many poor clinical manifestations like hypercalcemia, extramedullary disease, central nervous system involvement, high-serum creatinine levels, and plasmacytomas [54,56, 66,67]. Chromosome 17 deletions are an important negative prognostic factor, irrespective of the detection method [54]. Patients with this abnormality generally have a shorter EFS and OS after conventional chemotherapy and ASCT [56,67]. Response rates with conventional chemotherapy are low [63].

1q21 Amplification

Amplifications of the 1q21 or copy number gains in this locus are among the most commonly reported genetic abnormalities seen in MM [68]. CKS1B is a putative target of this amplification, which promotes the degradation of p27, an inhibitor of cell cycle progression. iFISH has been efficient to detect copy number gains of 1q21 in around one third of MM patients [68-69]. Patients with 1q21 gains have a higher prevalence of deletion13 and t(4;14)(p16.3;q32). Zhan et al (2007) reported that this region is involved in the development of myeloma growth and survival in aggressive disease [70].

Aneuploidy

MM patients may be grouped into two major categories according to ploidy status assessed by conventional karyotyping: the hyper diploid group (greater than 46/47 chromosomes) and the non-hyperdiploid group, composed of hypodiploid (up to 44/45 chromosomes), pseudo diploid (44/45 to 46/47) and near tetraploid (more than 74) cases [15, 59]. The non-hyperdiploid MM is characterized by a very high prevalence of IGH translocations involving the five recurrent partners [59, 71]. Likewise, monosomy/deletion13 occurs predominantly in non-hyperdiploid MM. By contrast the hyperdiploid group is associated with recurrent trisomies involving odd chromosomes (3, 5, 7, 9, 11, 15 and 19) and with a low incidence of structural chromosomal abnormalities [72].

Among numeric abnormalities the most common monosomy is 13. Indeed, deletions of chromosome 13 identified by iFISH usually denote monosomy 13 and only occasionally represent an interstitial deletion. Patients with hyper diploid MM are older males with IgG kappa myeloma and symptomatic bone disease [73]. Hyper diploid patients who also harbor IgH translocations appear to have a more aggressive clinical course. Among the patients with hyper diploid MM, presence of deletion 13 carries no significant prognostic implication, while deletion17p13 remains an important predictor of outcome [66] (Table 3).

Recent studies have reported the favorable outcome for patients with trisomies, even when concurrently present with high-risk cytogenetics [74,75]. International Myeloma Working Group recently reported a comprehensive analysis on a database of 12,137 patients treated worldwide for myeloma. At diagnosis 2309 patients had cytogenetic studies and 5387 had analyses by iFISH. Using the comprehensive iFISH data (on 2642 patients), combining both t(4;14) and deletion (17p), along with ISS stage, significantly improved the prognostic assessment in terms of EFS and OS. These studies elicit the clinical utility of combining iFISH data with ISS staging to significantly improve risk assessment in myeloma [74].

Gene Expression Profiling (GEP) of MM

Microarrays profiling based studies have led to better

understanding of molecular biology of MM. Comparison by gene-expression profiles of CD138*enriched plasma cells from the bone marrow of healthy donors and of patients with MGUS, newly diagnosed MM, and end-stage MM have provided potential clues to the molecular pathogenesis of MM- disease specific changes on gene expression level [27].

Unsupervised clustering of these early global gene-expression data showed that MM could be divided into four distinct molecular subgroups, MM1-MM4; with MM1 being more similar to MGUS and MM4- related to myeloma cell line (plasma cell leukemia). The MM4 group also had a higher incidence of cytogenetic abnormalities and high serum levels of β 2-microglobulin, clinical features historically linked to poor prognosis. Genes distinguishing MM4 from the other groups were related to cell proliferation. More advanced microarray technologies and larger sample sizes have now further divided MM into seven disease classes (MS, MF, CD-1, CD-2, HY, LB, and PR). These results have provided the evidence that MM is likely to be harboring numerous molecular entities that presumably use different molecular mechanisms to get to a tumor with a common histology [76,77].

To get insights into the molecular characterization of plasma-cell dyscrasias and to investigate the contributions of specific genetic lesions to the biological and clinical heterogeneity of MM, Mattioli et al. (2005) compared the GEP of plasma cells isolated from 7 cases of MGUS, 39 of MM, and 6 of plasma-cell leukemia [78]. MM was heterogeneous at the transcriptional level, whereas MGUS was distinguished from plasma-cell leukemia and the majority of MM cases by differential expression of genes involved in DNA metabolism and proliferation. The clustering of MM cases was mainly driven by the presence of one of five recurrent translocations involving the immunoglobulin heavy-chain (IGH) locus [79]. Over expression of CCND2 and genes involved in cell-adhesion pathways was observed in cases with t (14; 16) and t (14; 20), whereas up-regulated genes showed apoptosis-related functions in cases with t (4; 14). The peculiar finding in cases with t (11; 14) was the down-regulation of the α -subunit of the interleukin-6 receptor (IL6R). Finally, cancer-testis antigens were specifically expressed in a subgroup of patients characterized by aggressive clinical evolution of MM [78]. To further decipher the differences between malignant and normal plasma cells, recently, a study focused on 58 genes linked with extrinsic and intrinsic apoptotic pathways, caspases and inhibitor of apoptosis proteins. B-cell differentiation was associated with change in the expression of pro-apoptotic and anti-apoptotic genes with TRAIL being up regulated, whereas FAS, APAF1, and BNIP3 were down-regulated in MM cells compared with normal bone-marrow plasma cells [80].

GEP and Cyclin D dysregulation in MM

Dysregulated expression of cyclin D is one of the potential universal event in myeloma pathogenesis. Relative to plasma cells from bone marrow of healthy donors, myeloma plasma cells exhibit increased and/or dysregulated expression of either CCND1, CCND2, or CCND3 [77]. IGH-mediated translocations can directly activate CCND1 (11q13) [81] or CCND3 (6p21); [82] MAF (16q23) - or MAFB (20q11)-activating translocations lead to their trans-activation of adhesion molecules and CCND2, which is elevated in t (4; 14)-positive tumors [74]. Bi-allelic dysregulation of CCND1 occurs in nearly 40% of tumors, most of which are

hyper diploid [73]. Elevated levels of CCND2 and the absence of IGH translocation spikes characterize a novel form of MM discovered through GEP of primary disease [76]. Interestingly, elevated expression of CCND2 is not an adverse prognostic factor in this setting [83].

GEP based validated molecular classification of MM

Using a supervised classification approach that uses prior knowledge of the disease, a classification schema based on GEP spikes of the five recurrent translocations was developed. Reducing the complexity of the microarray from over 50000 probes to <30 genes, eight translocation/cyclin D (TC) groups have been identified. These have been termed as the 11q13/TC1, 6p21/TC2, 4p16/TC3, MAF/TC4, D1/TC5, D1+D2/TC6, D2/TC7, and none/TC8 classes [84]. These classes exhibited significant, uniform differences in global gene-expression profiles and clinical features, such as prevalence of bone disease, frequency, distribution at relapse, and progression to extra-medullary tumor growth [79]. GEP class-prediction model have been adopted and applied on purified plasma cells in a study with 50 MM cases. The TC1, TC2, TC4, and TC5 groups were characterized by 112 probe sets, but TC3 samples showed heterogeneous phenotypes and no gene biomarkers [83]. The TC2 group, with extra copies of the CCND1 locus and no IGH translocations or 13q deletion, has been characterized by over expression of genes involved in regulation of protein translation. The failure to validate all TC classes may very well be related to the small sample size. Another possibility may have been lack of robustness of the TC classification. Thus, improved methods of classification are required when dealing with large GEP datasets [83,84].

GEP and risk stratification

Although most cases of MM initially respond to treatment, a subset exhibits resistance to therapy from the outset, and most develop resistance during the course of treatment over time. Therefore, long-term survival in patients with MM can vary considerably, and it is difficult to predict outcome. High-risk MM is routinely defined by laboratory parameters alone or in combinations as in the Durie-Salmon staging system and International Staging System (ISS). Presence of abnormal metaphase or interphase cytogenetics, high plasma cell labeling index, and a recently defined flow-cytometry based test on minimal residual disease have also improved our understanding [85]. Importantly, understanding the molecular mechanisms by which plasma cells develop resistance from initial drug responsiveness will contribute to more robust prognostic strategies.

To determine whether GEP might provide a better measure of risk stratification, one recent study correlated microarray data with outcome in two independent cohorts, permitting identification and validation of a high-risk gene-expression signature present in approximately 15% of newly diagnosed disease [86]. The high-risk signature is evident in a subset of all molecular classes and negatively influences regardless of class. The '70/17-gene model' based on expression patterns of 70 genes, reducible to 17 genes predominantly increased expression of genes from the q arm and reduced expression of genes from the p arm of chromosome 1- has further been confirmed by whole-

genome microarrays and high-resolution comparative genomic hybridization[86].

When subjected to multivariate analysis including the ISS and a gene-expression-based proliferation index, the 70/17-gene model remained a significant predictor of outcome. Another study used U133A microarray data to develop response and survival classifiers for relapsed disease treated with single-agent bortezomib or high-dose dexamethasone that were significantly associated with outcome [87]; a modified version of the 70/17-gene model also predicted poor outcome in relapsed disease [88]. U133A data from newly diagnosed disease validated the 70/17-gene model, but also showed that the t (4; 14) translocation remained a significant variable for poor outcome [89]. In addition to its ability to predict the outcome of newly diagnosed MM patients, a recent study showed that the 70-gene model as an independent and the most significant prognostic factor in an analysis of post-relapse survival in relapsing MM [89]. Another study used a custom cDNA microarray to define a 15-gene model of high risk related to cell proliferation, with a hyper diploid signature being related to a better survival. Multivariate analysis comparing the 70/17-gene model with the 15-gene model revealed the 70/17-gene model as significant predictor in all datasets tested, but the 15-gene model remained significant in bortezomib trials only [90].

A "critical-gene" model independently predicts overall survival

Agnelli et al [91] have recently reported 100 genes, which are identified to have characteristics which make them good candidates as being central to the clinical outcome in MM based on their shared relevance within transcriptional networks. Furthermore, association between gene expression and OS in the three datasets with associated prognostic information has further been tested, including 351, 264 and 247 samples, respectively. Analysis revealed a significant correlation between expression levels and OS in two of the three independent datasets [91]. These findings have further been validated by a recent report on the initial genome sequence analysis where distinct set of genes (related to B cell development) have been identified differentially expressed in myeloma [92].

CONCLUSION

Improved insights in the myeloma disease biology suggest the pivotal role of the bone marrow microenvironment in addition to the genetic heterogeneity of the disease. This further becomes more intriguing with the fact that a substantial percentage of patients receiving novel molecules (immunomodulators, proteasome inhibitors) and/or peripheral blood stem cell transplant eventually relapse even after achieving a complete response. Future studies with more evolved and stringent staging system coupled with cytogenetics and comprehensive gene expression profiling are likely to be used to develop risk adapted treatment.

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