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Editorial

# P53 and Molecular Genetics of Multiple Myeloma

**Benedetta Lucani, Giulia Papini, Monica Bocchia and Alessandro Gozzetti***

Department of Hematology, University of Siena, Italy

***Corresponding author:** Alessandro Gozzetti, Hematology, Policlinico "Santa Maria alle Scotte", VialeBracci 16, 53100, University of Siena, Italy, Fax: +39-0577586185; Email: gozzetti@unisi.it

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## Editorial

Multiple Myeloma (MM) is a clonal bone marrow disease characterized by the neoplastic transformation of differentiated B cells, accounting for 1% of all cancers and ~10% of all hematologic malignancies [1,2]. The median Overall Survival (OS) ranges from a few months to several years, a large fraction of disease heterogeneity can be determined by host factors (age, performance status, and comorbidities), stage, disease aggressiveness, response to therapy and myeloma cell biology [3,4]. Staging of myeloma using the Durie–Salmon staging [5] or the International Staging System [4,6] provides prognostic information but it is not helpful to guide treatment, while a risk stratification model could be useful for therapeutic decision-making [7]. In terms of survival, patients with standard risk myeloma have a median OS of 6–7 years, while those with high risk disease have a median OS of less than 2–3 years despite tandem Autologous Stem-Cell Transplantation (ASCT), being suitable for novel drugs in clinical trials [1]. This suggests the importance to discriminate cytogenetic and molecular characteristics of these patients. Genetic aberrations can be classified as primary events, contributing to plasma cell immortalization, or secondary events, contributing to disease progression. Overall MM is broadly divided into two major categories, hyperdiploid MM (h-MM) and non-hyperdiploid MM (nh-MM). Nonhyperdiploidy myeloma involves the translocation of Immunoglobulin Heavy chain alleles (IGH) at 14q32 with various partner chromosomes including 4, 6, 11, 16, and 20. Hyperdiploidy myeloma involves trisomies of the odd numbered chromosomes 3, 5, 7, 9, 11, 15, 19, and 21 coupled to a low prevalence of IGH translocations, has a tendency towards a more favorable outcome and is generally associated with better survival [8,9]. The t (4; 14) is observed in 15% of myeloma cases and has been associated with an adverse prognosis and poor survival [10-13], irrespective of the treatment choice [14,15]. The consequence of the translocation is increased expression of FGFR3 and Multiple Myeloma SET domain (MMSET) [16,17]. The t (11; 14) is more common, occurring in approximately 17% of myeloma patients and it directly up regulates a cyclin D gene in the form *CCND1* [10,18]. In most series tested, t (11;14) (q13;q32) seems to be associated with a trend toward a favorable outcome, yet not statistically significant [8]. The t (14;16) involving *maf* genes has been described in 5–7% of all MM cases, it has been associated with a higher frequency of chromosome 13 deletion and a more aggressive clinical outcome [12]. The t (6;14) and t (14;20) are the rarest translocations observed, resulting in a up regulation of the CCND3 and MAFB genes, respectively [10,19]. The secondary genetic events include loss of Chromosome 13/13q, Chromosome 1 abnormalities and Loss of 17p. The first is the most common cytogenetic alteration, observed in 50% of myeloma cases, resulting mainly from a constitute monosomy (85%) or less frequently form interstitial deletions (15%) [20-23]. To establish the prognostic impact of del (13/13q) is challenging due to its frequent association with other high risk lesions, such as t (4;14) whit whom it is concurrently present in approximately 90%of cases [8]. Regarding chromosome 1 we can find both 1q gain and 1p loss observed respectively in 35% and 30% of cases, both associated with a shorter survival [24-30].

The most important negative molecular cytogenetic factor for prognostication is the deletion of 17p13 [14,15,31]. This alteration is detected in 11% of newly diagnosed patients and in all series tested, 17p13 deletion, impacted very negatively on survival, with a median OS of 22 months [16,32]. Recently more detailed studies have analyzed the association between the percentage of plasma cells affected by this deletion and its prognostic value, demonstrating a short survival only in those in patients that have at least 60% of plasma cells with 17p13 deletion..

At the level of the band 17p13 is present the gene locus p53 tumor suppressor, which is lost in the case of deletion [14,15,31].

The p53 tumor suppressor is a critical regulator of tissue homeostasis, and its inactivation at the gene or protein level confers cellular properties conducive for oncogenesis and cancer progression [33]. The functional loss of the p53 protein (TP53) may take place with the deletion but also with the mutation. TP53 mutations are rare in multiple myeloma, only 3% of newly diagnosed patients while their prevalence increases with more advanced disease [34,35]. In particular this aspect was elaborated Chng et al. that showed that the presence of TP53 mutations was significantly associated with 17p13 deletion (56% of cases) and for the first time in 2007 reported the extremely negative prognostic significance of TP53 mutations, as the presence of TP53 mutations was associated with a survival of only one and half year [35]. Conversely, in 2011 Lode et al. demonstrated that the mutations in TP53 are exclusively associated with del (17p) and survival analyses did not reveal any difference, in patients with del (17p), between patients presenting additionally a TP53 mutation and those with a germ line TP53. However, the numbers are too small to draw any definitive inference [32].

In conclusion, the concomitance of TP53 mutations and del (17p) is relatively rare, being found at most in 13% of newly diagnosed MM [33], whereas the functional loss of the gene is found in a definitely higher percentage of cases; in addition according to the work of Lodè the vast majority (63%) of del (17p) are hemizygous patients, suggesting that in these non-mutated patients, normal and functional p53 protein is still present, potentially overcoming the poor effect of




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del (17p), albeit without clinical impact. So we can think that other modifications may occur and alter p53 pathway. The p53 pathway silencing might pass also through changes in the expression level or in the activation of p53 itself, regulated by several specific inhibitors and/or activators, such as MDM2, MDM4 has showed in a recent work [34]. Moreover other recent studies have shown epigenetic mechanisms, as well as deregulation of microRNA involved in the pathobiology of MM; Picchiorri et al. identified two related microRNA clusters located in regions considered important for MM (miR-194-2-192 at 11q13.1 and miR-194-1215 at 1q41.1) [5] associated with activation of the p53 pathway. Furthermore this work showed that the expression of these miRNAs changed during transition from normal PC, via MGUS to intramedullary MM resulting significantly down regulated in a cohort of newly diagnosed MMs; these result have defined a mechanism of p53 regulation through miRNAs acting on MDM2 expression. We believe that miRNAs in MM should be investigated in the future as potential mechanisms of resistance. This data could give information's not only about disease development and prognosis, but can also provide potential therapeutic targets.

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