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Review

An update on molecular biology and drug resistance mechanisms of multiple myeloma

Pelin Mutlu[a], Yağmur Kiraz[b], Ufuk Gündüz[c], Yusuf Baran[b,d,*]

[a] Middle East Technical University, Central Laboratory, Molecular Biology and Biotechnology R&D, Ankara, Turkey
[b] İzmir Institute of Technology, Department of Molecular Biology and Genetics, İzmir, Turkey
[c] Middle East Technical University, Department of Biological Sciences, Ankara, Turkey
[d] Abdullah Gul University, Faculty of Life and Natural Sciences, Department of Molecular Biology and Genetics, Kayseri, Turkey

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ABSTRACT

Multiple myeloma (MM), a neoplasm of plasma cells, is the second most common hematological malignancy. Incidance rates increase after age 40. MM is most commonly seen in men and African–American population. There are several factors to this, such as obesity, environmental factors, family history, genetic factors and monoclonal gammopathies of undetermined significance (MGUS) that have been implicated as potentially etiologic. Development of MM involves a series of complex molecular events, including chromosomal abnormalities, oncogene activation and growth factor dysregulation. Chemotherapy is the most commonly used treatment strategy in MM. However, MM is a difficult disease to treat because of its marked resistance to chemotherapy. MM has been shown to be commonly multidrug resistance (MDR)-negative at diagnosis and associated with a high incidence of MDR expression at relapse. This review deals with the molecular aspects of MM, drug resistance mechanisms during treatment and also possible new applications for overcoming drug resistance.

* Corresponding author at: İzmir Institute of Technology, Faculty of Science, Department of Molecular Biology and Genetics, Urla, 35430 İzmir, Turkey. Fax: +90 232 7507509.
E-mail address: ybaran@gmail.com (Y. Baran).

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1. Introduction

Multiple myeloma (MM) fits in the group of plasma cell disorders characterized by neoplastic proliferation of plasma cells which produce and secrete monoclonal antibodies, usually IgG or IgA isotypes (MacLennan, 1991). The monoclonal protein secreted by MM plasma cells is immunoglobulin or a component of immunoglobulin which is called M-protein or paraprotein. Due to the mutations in the genes that are responsible for immunoglobulin production in myeloma cells, the normal antibody function of the immunoglobulin is lost. Excess M-protein accumulates in the bloodstream and/or in the urine of the MM patients (Botallie and Harousseau, 1997; Kyle and Rajkumar, 2008; Palunbo and Anderson, 2011).

Plasma cells are the end-stage effector cells of the B-lymphocyte lineage that produce and secrete antigen-specific antibodies (MacLennan, 1991). In contrast with the distribution of normal plasma cells, MM plasma cells localize specifically within the bone marrow, produce M-protein and a number of cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF)-β and monocyte–macrophage colony stimulating factor activating stromal and accessory cells and also have osteoclast activating factor (OAF) activity leading to the typical punched out osteolytic lesions (Cozzolino et al., 1989; Mundy et al., 1974; Nakamura et al., 1989; Ross Garrett et al., 1987).

Bone marrow microenvironment of MM is well organized in terms of adhesive properties and production of the cytokines for growth and differentiation of plasma cells. A number of cytokines, including IL-1β and M-CSGF, are released from plasma cells and activate bone marrow stromal cells to produce IL-6, which stimulates the proliferation of plasma cells (Caligaris-Cappio et al., 1992; Jernberg et al., 1991; Kishimoto, 1989; Klein et al., 1989; Nilsson et al., 1990; Nordan and Potter, 1986; Zhang et al., 1989). Most recently, IL-6 has also been shown to enhance survival of MM cells by inhibition of apoptosis triggered by corticosteroids, serum starvation and anti-Fas (Hulkkonen et al., 2001; Humphries et al., 2001; Sfrent-Cornateanu et al., 2006). Elevated IL-6 serum levels are correlated with poor prognosis, higher tumor cell mass and also osteoclast activation in MM (DeMichele et al., 2003; Jerrard-Dunne et al., 2003; Jones et al., 2001; Sawczenko et al., 2005; Snoussi et al., 2005).

Multiple myeloma patients usually present with bone destruction, hypercalcemia, renal damage, increased susceptibility to infections and anemia (Kyle and Rajkumar, 2008; Morgan et al., 2002). There are no established risk factors for MM other than gender, age, ethnicity, family history of lymphatohematopoitic cancer (LHC) and monoclonal gammopathy of undetermined significance (MGUS). Annual risk of progression of MGUS to multiple myeloma is approximately 1% (Ries et al., 2005).

2. Epidemology

According to Multiple Myeloma Research Foundation, MM is the second most common blood cancer after non-Hodgkin's lymphoma and represents approximately 1% of all cancers in white individuals and 2% of all cancers in black individuals (Multiple Myeloma Research Foundation, 2015).

MM occurs more frequently in men than in women, and its highest incidence has been found in African–American population, being twice as high compared with white population. Incidence rates for most European countries, white Americans and Canadians are similar. The lowest incidence of myeloma has been found among Asian individuals (American Cancer Society, 2005; Parkin et al., 2002; Ries et al., 2005). Blacks may be two times more likely to develop multiple myeloma with respect to whites since they are more likely to have a precursor condition known as MGUS (Cohen et al., 1998; Landgren et al., 2006; Singh et al., 1990).

Increased risk for association between obesity and MM has been reported in a few epidemiologic studies (Blair et al., 2005; Pan et al., 2004). Findings for tobacco use and alcohol consumption do not support a causal association with multiple myeloma (Brown et al., 1992, 1997; Brownson, 1991; Mills et al., 1990; Nieters et al., 2006; Pan et al., 2004; Vlajinac et al., 2003). Although the incidence of MM is higher in males than in females, the studies suggest that hormonal influences do not play a significant etiologic role in MM (Altieri et al., 2004; Fernandez et al., 2003).

Table 1
Durie and Salmon staging system.

Criteria	Measured myeloma cell mass (myeloma cells in billions/m^2)
Stage I (low cell mass) All of the following: • Hemoglobin value >10 g/dl • Serum calcium value normal or <10.5 mg/dl • Bone X-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only • Low M-component production rates IgG value <5.0 g/dl IgA value <3.0 g/dl Urine light chain M-component <4 g/24 h	600 billion
Stage II (intermediate cell mass) Fitting neither Stage I nor Stage II	600–1200 billion
Stage III (high cell mass) • One or more of the following: • Hemoglobin value <8.5 g/dl • Serum calcium value >12 mg/dl • Advanced lytic bone lesions (scale 3) • High M-component production rates IgG value >7.0 g/dl IgA value >5.0 g/dl Urine light chain M-component >12 g/24 h Subclassification A: Relatively normal renal function (serum creatinine value <2.0 mg/dl) B: Abnormal renal function (serum creatinine value >2.0 mg/dl)	>1200 billion

3. Prognostic factors and staging

Diagnosis of MM is confirmed according to the growth rate of myeloma cells, production rate of monoclonal proteins and various cytokines. In 1975, Durine/Salmon staging system was developed as shown in Table 1 (Durie and Salmon, 1975). This is actually a functional system which serves to evaluate the prognosis using various types of clinical and laboratory tests. Durine/Salmon staging system is used worldwide since it provides the best direct correlation between individual patient clinical features and it differs from anatomic staging systems for solid tumors.

A new staging system was developed by the IMF-sponsored International Myeloma Working Group in 2005. In this staging system, serum β2 microglobulin and albumin levels provide a powerful and reproducible three- ekleyelim stage classification (Grepp and Durie et al., 2005). Myeloma can be further classified upon genetic factors using molecular fluorescence in situ hybridization (FISH) and cytogenetic analysis (Zojer et al., 2001).