Review

Functional significance of genetic abnormalities in multiple myeloma

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Abstract—Multiple myeloma (MM) is a B-cell neoplasm characterized by infiltration of the bone marrow with malignant plasma cells, synthesizing and secreting monoclonal immunoglobulin fragments. The malignant transformation of this terminally differentiated plasma cell is the result of a multistep transformation process. In spite of recent advances in this field, the cause and the exact molecular genetic basis of MM remain obscure. In this review, an attempt has been made to summarize the genetic alterations having functional significance in the generation and progression of MM, and also the existing relationship between genetic abnormalities and chemosensitivity, as well as the typical genetic alterations in various MM subgroups. Factors known to have a role in the conversion of monoclonal gammopathy of unknown significance (MGUS) to MM are also reviewed.

Key words: Multiple myeloma; genetic alterations; chromosomal abnormalities.

INTRODUCTION

Multiple myeloma (MM) is an incurable malignancy accounting for 2% of cancer-related deaths [1]. Clinically, it is manifested by malignant plasma cell infiltration of the bone marrow and the production of a paraprotein, leading to lytic bone lesions [2]. Unfortunately, since the mid-1970s there has been little improvement in the 5-year survival rate of 28% of MM patients. Although high-dose chemotherapy followed by autologous or allogenic stem cell grafting can achieve high response rates, most patients will end up with a relapse and few, if any, will be cured [3, 4].

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The plasma cells associated with MM are post-germinal centre B cells that have undergone immunoglobulin (Ig) gene somatic hypermutation, VDJ recombination, antigen selection, and isotype switch recombination [2]. Malignant transformation of this terminally differentiated plasma cell is the result of a multistep transformation process. Plasma cells may proceed through different phases: an inactive phase, where the tumor cells are nonproliferating mature plasma cells; an active phase, with a small percentage (< 1%) of proliferating plasmablastic cells; and a fulminant phase, with frequent extramedullary proliferation and an increase in the plasmablastic cell number mass. The malignant transformation process of plasma cells corresponds to the variant clinical forms of the disease. MM is best viewed as a heterogeneous disease with varying prognosis, clinical course, and response to therapeutic interventions in different subjects [5].

In the past few years, considerable progress has been made in identifying factors that may play a role in the neoplastic transformation and progression of the disease, and also regarding the background of the different clinical patterns, prognostic factors, and responsiveness to chemotherapy. Abnormal expression of cytokines, cytokine receptors, growth factors, and adhesion molecules appears to be critical for progression of the the disease.

The significance of karyotype abnormalities, dysregulation of different oncogenes, tumor suppressor genes, cell survival genes, and also the gene polymorphism of certain kinds of cytokines, growth factors, and their receptors are under investigation.

Despite recent advances in this field, the cause and exact molecular genetic basis of MM remain obscure. A clear understanding of the genetic background of MM is the key to improving therapy for this uniformly fatal disease [4].

CHROMOSOMAL ABNORMALITIES

While karyotypic changes have been identified in up to 50% of MM patients, recent molecular cytogenetic techniques have revealed chromosomal abnormalities in the vast majority of cases examined. Because of a low proliferation rate in plasma cell malignancies, the conventional Giemsa (G)-band methods have resulted in the detection of chromosomal defects in approximately only 20–60% of MM patients. Fluorescence in situ hybridization (FISH), which is capable of detecting chromosomal aberrations even in interphase cells, overcomes this weak point of the G-band method. Recent studies utilizing FISH showed that an aberration in the immunoglobulin heavy chain (IgH) gene structure, located on 14q32, occurred as a nearly ubiquitous event in MM patients [6].

Although there is no unique genetic abnormality in MM, a number of karyotypic alterations have been revealed: numerical chromosomal alterations (chromosome gain and loss), translocations (14q32 with different partner loci), mutations in the coding and regulatory regions of genes (p53, Rb-1, bcl-6), as well as aberrant expression patterns of several oncogenes (c-myc, N- and K-ras), tumor suppressor