Pathobiology and Diagnosis of Multiple Myeloma

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Objective: *To understand the role of the genetic changes and bone marrow microenvironment on the development, progression, and staging of multiple myeloma (MM).*

Data Sources: *Peer-reviewed articles and clinical guidelines.*

Conclusion: *The acquisition of genetic changes and the bone marrow microenvironment in which myeloma cells develop both influence the pathogenic potential of these malignant cells and is reflected in staging of the disease, risk of progression, and predicted response to treatment.*

Implications for Nursing Practice: *Treatment of multiple myeloma is largely dependent on risk factors in which specific genetic alterations play a large role. Clinicians should be aware of these genetic changes and how they may influence the individual treatment plan for each patient.*

Key Words: *multiple myeloma, cytogenetics, microenvironment, staging.*

Multiple myeloma (MM) is an incurable, biologically heterogeneous disease of the plasma cells. It is characterized by uncontrolled growth of monoclonal plasma cells in the bone marrow that leads to the overproduction of nonfunctional intact immunoglobulins or immunoglobulin chains. Accumulation of these immunoglobulins and interaction of the aberrant monoclonal plasma cells with other cells in the bone marrow lead to a host of problems including anemia, bone lesions, infections, hypercalcemia, renal failure, fatigue, and pain.[1] The World Health Organization classification system differentiates MM from other plasma cell disorders such as monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma of the bone, extraosseous plasmacytoma, and monoclonal immunoglobulin deposition diseases.[2]

MM is the second most common hematologic malignancy. The American Cancer Society predicts there will be 30,280 new MM diagnoses and 12,590 deaths related to the disease in the United States in 2017.[3] It has been estimated that in 2012, there were 89,658 people living with MM.[4]The risk of developing MM is higher in older age groups, whereas it is a much more uncommon diagnosis for patients under the age of 45.[1] The median age at diagnosis is 65 years and the current the 5-year survival is approximately 46.6%.[4,5]

Pathogenesis

Molecular and Cytogenetic Events

MM appears to progress almost universally from MGUS.[6] The molecular basis for the initial

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TABLE 1.
Risk Stratification, Ctyogenetics, and Affected Cell Function

Risk Category	Cytogenetic Abnormality	Chromosome/gene affected	Function affected
Standard	Trisomies	All odd chromosomes except 1, 13 or 21	Multiple
	t(11;14)	CCND1	Cyclin D1
	t(6;14)	FGFR-3; MMSET	Apoptosis; DNA methylation
Intermediate	t(4;14)[a]	CCND3	Cyclin D3
	Gain(1q21)	CKS1B; ANP32E	Cell cycle regulation; histone modification
High	t(14;16)[a]	MAF	Transcription factor: proto-oncogene
	t(14;20)	MAFB	Transcription factor: proto-oncogene
	Del(17p)[a]	Tp53	Tumor suppressor

[a]Denotes high risk in the Revised International Staging System for Myeloma. From Palumbo et al., 2015[19] and Rajkumar, 2016.[20]

transformation of normal plasma cells to the establishment of MGUS is unclear, but dysregulation of the family of cyclin D proteins (cyclins D1, D2, and D3) appears to be an abnormality present at the very early stages.[7] There are multiple mechanisms for this dysregulation, which include (1) translocations of *CCND1* (cyclin D1) and *CCND3* (cyclin D3) with the IgH gene, (2) specific cyclin D gene amplifications, (3) trisomies, and (4) other, as of yet uncharacterized, cytogenetic events.[8] Upregulation of cyclin D expression appears to be a necessary occurrence early in the establishment of an abnormal plasma cell, but it is not sufficient in itself to the drive the disease from MGUS to MM.

Based on karyotype, MM can be grouped into two subclasses that likely represent two distinct oncogenic pathways. The first of these is the hyperdiploid subclass, which is characterized by the presence of an extra copy (trisomies) of one or more of the odd chromosomes 3, 5, 7, 9, 11, 15, 19, and 21.[9] The basis of the non-random selection of odd chromosomes is unknown and this subclass represents approximately 40% of all MM cases. In contrast, the IgH-translocated subclass (30 % of MM cases) involves translocations between the IgH locus at 14q32 with one of several partner genes having oncogenic properties.[10] The two most frequent translocation partners are 11q13, which directly targets and upregulates the cyclin D1 gene, followed by 4p16, which targets both the *FGFR3* and *MMSET* genes and leads to dysregulation of cyclin D2. Other common partners include the transcription factors MAF and MAFB found at 16q23 and 20q11, respectively, that lead to overexpression of cyclin D2. Exchanges at the 6p21 locus lead to overexpression of the cyclin D3 gene (*CCND3*) found at that site.[11] While a small subset of patients (15%) present with both trisomies and IgH translocations, the two subclasses are generally considered distinct.

Following dysregulation of one or more of the cyclin proteins, additional genetic changes are required to enhance the growth potential of the "activated" abnormal plasma cells. Early on, this is mediated through secondary events that include loss of chromosome 13 (site of the retinoblastoma tumor-suppressor gene) and the acquisition of mutations that lead to the activation of the *MYC* and *RAS* oncogenes.[12-14] Accordingly, these activating mutations have been shown to be present at much lower levels in MGUS compared to MM.[15] Additional cytogenetic events occur later in the course of the disease and are generally associated with a poor prognosis. These include copy number changes of chromosome 1 (gain of the long arm and/or loss of the short arm) and cMyc activating rearrangements at the 8q24 locus.[14,16] The loss of tumor-suppressor TP53 activity is a particularly poor prognostic factor and occurs either by deletion of the short arm of chromosome 17 or by the presence of inactivating mutations.[17] Mutations that inactivate regulation of the nuclear factor kB (NF-kB) transcription factor pathway are common in late stage disease.[18] NF-kB regulates the expression of adhesion molecules involved in the interaction of MM cells with the bone marrow stroma. Loss of this regulatory control and subsequent MM- stromal relationship likely contributes to both the extramedullary growth of MM cells and the development of stromal-independent plasma cell leukemia (Table 1).[19,20]

Epigenetic Events

Modulation of gene expression leading to progression of MGUS to MM also occurs by mechanisms