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Prognostic Implications on Genetics of Multiple Myeloma

Lisandro Stepanov*

Department of Molecular Biology, University of Bergen, Norway

Description

Multiple myeloma (MM) is a disorder of the monoclonal plasma cells. It is the second most common hematologic malignancy in high-income countries and its global incidence is increasing. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM) are considered pre-malignant states of MM. Newer therapies have improved patient outcomes; however, MM remains an incurable disease and the majority of patients experience multiple relapses. MM disease initiation and progression are highly dependent on genetic alterations, including chromosomal translocations and other structural variants (SVs) such as deletions, duplications, and insertions.

Single-nucleotide variants (SNVs) that cause MM disease [1-3] progression and treatment resistance are also common. Next-generation sequencing (NGS) and other highly sensitive technologies have highlighted the complexity of MM genetics and opened up new perspectives on the timing, origins, and detection of MM, providing new insights into the mechanisms underlying MM progression and treatment responses. There are currently no targeted treatments available for multiple myeloma, but targeted treatment may be possible with further discovery and characterization of these genetic aberrations. This review will summarise what is currently known about genetic aberrations in MM and their pre-malignant states, how MM genetics affect prognosis and treatment response, and finally, the highly sensitive diagnostic workup of MM made possible by molecular techniques.

Primary events in MM are clonal events that occur early in the disease's pathogenesis. Immunoglobulin (Ig) translocations and hyperdiploidy (HRD), or the gain of odd-numbered chromosomes, are examples of primary events. Errors in VDJ recombination (a process of chromosomal breakage and rejoining in developing B-cells that begins in the pre-pro-B stage and ends in the pro-B stage) allow oncogenes to be controlled by strong enhancers (Ig heavy chain (IgH) loci). The aetiology of these primary events is unknown, but they appear early in the disease process. For example, in SMM patients, common MM Ig translocations may be present in one-third and HRD may be present in approximately half of SMM patients. IgH translocations increase with disease stage, occurring in roughly half of MGUS and SMM, 60-65 percent of intramedullary MM, and 70-80 percent of extramedullary MM.

Secondary genetic events in MM occur in the context of primary events and are frequently more complex, with additional copy-number abnormalities such as gains (duplications), losses (deletions), other translocations, and somatic mutations (deleterious single nucleotide variants), and are frequently associated with progression. Mutations in the driver genes, such as rat sarcoma virus (RAS) mutations, proto-oncogene MYC dysregulation via SVs, and a variety of mutations that inactivate the NFKB pathway, are some of the most common progression events in MM, but there are many other important genes that lead to progression. The evolution of MM has been described as a Darwinian process influenced by the bone marrow microenvironment. The use of NGS techniques has aided in determining the temporal evolution [4,5] of MM. A study used the concept of molecular time (through the integration of SVs, copy-number alterations (CNAs), and point mutations) to chronologically construct the driver events in MM, specifically the timing of aneuploidies. Although HRD is considered an early, primary event in MM, significant structural changes are likely to occur between diagnosis and relapse (sub clonal evolution).

The researchers discovered that there were significant changes in the underlying karyotype of any individual patient over time, including chromosome losses and gains. There was one extreme case of a patient who relapsed with entire whole-genome duplication. Gains of odd chromosomes and 1q were the most common aneuploidies in HRD patients. Chromothripsis and templated insertions also appeared early in the disease course as clonal events, whereas chromoplexy and focal deletions appeared later. The revised international staging system is based on tumour cell characteristics (measured by cytogenetics and fluorescence via in situ hybridization, FISH) and a laboratory evaluation of tumour burden (measured by 2 microglobulin, LDH, and albumin) (R-ISS). Historically, serum protein electrophoresis (SPEP), which detects and quantifies the monoclonal protein (M-protein), and immunofixation electrophoresis (IFE), which detects the M-protein isotype, were used to diagnose and monitor MM disease status. Serum light chain assays detect the presence of free kappa and lambda light chains in the blood.

NGS technologies have revealed the complexities of MM genetics, confirming that MM is a disease that is heavily reliant on underlying genetic abnormalities. Clonal, or primary, events occur early in development and are primarily made up of translocations or trisomy of odd chromosomes (HRD), but the acquisition of these primary events is unknown. Detecting these clonal events at extremely low levels (MRD) is now possible using NGS and NGF techniques, and MRD is now known to be a prognostic indicator. Secondary, or sub clonal, events are genetic aberrations that occur in the context of clonal events and are associated with disease progression.

Conflict of Interest

None.

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***Address for Correspondence:** Lisandro Stepanov, Department of Molecular Biology, University of Bergen, Norway, E-mail: LisandroStepanov30@gmail.com*

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