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Review Article

Role of Cytogenetics in Multiple Myeloma: Advancing Diagnosis, Prognosis, and Treatment

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Abstract

Multiple Myeloma (MM), a prevalent hematological cancer, remains a challenge due to its intricate nature and variable outcomes. Cytogenetics, the study of chromosome structure and function, has emerged as a critical tool in uncovering the genetic landscape driving MM. This article explores the transformative impact of cytogenetics on MM diagnosis, prognosis, and treatment.

Key Words: Multiple Myeloma; Cytogenetics, Diagnosis; Prognosis; Treatment; Karyotyping; Fluorescence in Situ Hybridization; Comparative Genomic Hybridization; Next-Generation Sequencing; Therapy; Personalized Medicine.

1. Introduction

Multiple Myeloma (MM), a malignancy arising from plasma cells, is the second most common hematological cancer worldwide [1, 2]. Despite significant progress in its diagnosis and treatment, MM remains a complex and heterogeneous disease with variable clinical outcomes [3, 4]. Cytogenetics, a branch of genetics focusing on the study of chromosome structure and function, has emerged as a vital tool in understanding the underlying genetic alterations that drive MM pathogenesis. By providing crucial insights into the genetic makeup of tumor cells, cytogenetics has revolutionized the way we approach the diagnosis, prognosis, and treatment of this challenging disease [5, 6].

1.1 Role of Cytogenetics in Diagnosis

The diagnosis of MM has undergone remarkable transformation due to advances in cytogenetic techniques. Traditionally, MM was classified based on morphological characteristics and the presence of monoclonal proteins [7]. However, cytogenetic studies have demonstrated that MM is a genetically heterogeneous disease, with various chromosomal abnormalities contributing to disease development and progression [7-10]. These genetic changes can be detected using methods such as conventional karyotyping, fluorescence in situ hybridization [FISH], and more recently, high-throughput technologies like array-based comparative genomic hybridization [aCGH] and next-generation sequencing [NGS] [8-14]. By identifying specific chromosomal aberrations, cytogenetics helps refine the diagnostic criteria, leading to improved accuracy and tailored therapeutic approaches.

Karyotyping and FISH have been pivotal techniques in the clinical diagnosis of MM for decades. Research, including our own findings, indicates that FISH exhibits greater sensitivity than Karyotyping in identifying genetic abnormalities associated with MM. This heightened sensitivity can be attributed, at least in part, to FISH's ability to detect subtle chromosome changes, such as microdeletions, which might not be easily discerned through Karyotyping alone. Notably, the application of plasma cell enrichment in FISH analysis has demonstrated even higher rates of detection for MM-related genetic anomalies compared to direct FISH [15-18]. Consequently, FISH offers distinct advantages over Karyotyping in the diagnosis of MM. Nevertheless, FISH's diagnostic efficacy remains constrained by its reliance on probes targeting known gene mutations, limiting its ability to identify all genetic variations detectable via Karyotyping. As such, both these approaches possess unique strengths and can synergistically complement each other [18].

The adoption of automated scanning systems, exemplified by Bioview and Meta System, has gained momentum in FISH and karyotyping analyses over recent years [19-22]. These systems have significantly enhanced work efficiency by substantially reducing labor requirements. However, it's worth noting that the use of current automated scanning systems for Karyotyping might tend to yield lower detection rates when compared to the expertise of seasoned cytogenetists.

This discrepancy arises from the automated systems' setting for not selecting cells' chromosomes with poor morphologies [poor spreading, short arms, and et al] for scanning, whereas genetic abnormalities associated with MM are frequently observed in cells with poor morphology due to the great variability of cancer cells in the reaction to hypo solution. Improving automated scanning systems' setting and training junior cytogenetists to better recognize and select target cells would be pivotal in boosting MM detection rates.

A noteworthy molecular cytogenetic technique, aCGH, facilitates the identification of chromosomal copy number changes on a genome-wide and high-resolution scale [23]. Rao PH [24] offers an in-depth discussion in his article outlining the procedures involved in aCGH, encompassing DNA labeling, hybridization, fluorescence microscopy, digital image analysis, data interpretation, and the limitations of the technique. Wang YF and colleagues' studies [25] underscore that array-CGH can outperform conventional MM examination methods, detecting more chromosome abnormalities and furnishing clinicians with greater cytogenetic insights. It is essential to acknowledge, however, that aCGH shares the common limitation of many genetic methods – its inability to identify genomic differences where no alteration in DNA copy number is present, such as balanced reciprocal chromosomal translocations, transpositions, inversions, and select triploidies [24, 25]. Furthermore, its utility is constrained by the scope and design of its probes, echoing the challenges encountered in FISH analyses.

Diverging from FISH and aCGH, which employ predetermined probes to identify gene abnormalities, NGS scrutinizes the sequence of nucleotides across entire genomes or targeted regions of DNA or RNA. NGS presents an ideal technology for MM diagnosis, albeit with the caveat of a higher cost. Apart from its relevance to MM cases featuring a heightened abundance of abnormal plasma cells, numerous studies underscore NGS's notable advantage in managing MM-related minimal residual disease, which pertains to instances wherein patients retain a small number of cancer cells in their bodies following treatment and these residual cells potentially posing a risk of MM relapse [26- 28].

1.2 Prognostic Implications of Cytogenetics

The prognostic implications of cytogenetics in MM play a crucial role in understanding the disease's behavior and tailoring treatment approaches. Cytogenetic abnormalities are genetic changes in the chromosomes of MM cells that can provide valuable insights into disease prognosis and guide therapeutic decisions [29].

MM is a complex and heterogeneous plasma cell neoplasm that arises from the bone marrow [1, 2]. Cytogenetic abnormalities are common in MM and have been extensively studied for their impact on disease progression, treatment response, and overall survival. These genetic alterations can encompass various structural changes, such as translocations, deletions, and amplifications, affecting key genes and pathways involved in cell growth, survival, and immune response.

One of the most well-known cytogenetic abnormalities in MM is the t (4; 14) translocation, which leads to the dysregulation of the fibroblast growth factor receptor 3 (FGFR3) and multiple myeloma SET domain [MMSET] genes. This alteration has been associated with poorer prognosis and resistance to certain treatments, making it a significant marker for risk stratification. Conversely, the t (11; 14) translocation involving cyclin D1 [CCND1] and immunoglobulin heavy chain (IGH) enhancer regions is generally linked to a more favorable outcome and better response to therapies [29-31].

Other cytogenetic abnormalities, such as del (17p) involving the tumor suppressor gene TP53, are associated with high-risk MM. Patients with del (17p) often exhibit aggressive disease behavior, resistance to treatment, and shorter survival. Detection of these high-risk markers through cytogenetic analysis enables clinicians to consider alternative therapeutic strategies, including novel targeted agents and combination therapies [32-34].

Advancements in technology, such as FISH and NGS, have improved the ability to detect cytogenetic abnormalities with higher precision and sensitivity. This has led to a deeper understanding of the genetic landscape of MM and the identification of new prognostic markers. For instance, the presence of specific chromosomal abnormalities, like gain (1q) and del (1p), has been associated with adverse outcomes and therapeutic challenges [35-38].

In recent years, the integration of cytogenetic information into risk stratification models, alongside clinical and biochemical parameters, has enhanced treatment decision-making [29]. Tailoring therapies based on a patient's cytogenetic profile can optimize outcomes by selecting the most appropriate treatment regimen [39]. Additionally, ongoing research aims to decipher the intricate interactions between genetic alterations and the bone marrow microenvironment, shedding light on the mechanisms driving disease progression and treatment resistance.

The prognostic implications of cytogenetics in MM have greatly deepened our understanding of the disease's heterogeneity and its impact on patient outcomes. Identifying specific cytogenetic abnormalities enables clinicians to personalize treatment strategies, offering patients the best chance of a favorable response and prolonged survival. As technology continues to evolve, the integration of genetic information into clinical practice will undoubtedly shape the future of MM management.

1.3 Implications for Treatment

The incorporation of cytogenetics into therapeutic decision-making has revolutionized MM management [40, 41]. Understanding the genetic basis of MM has led to the development of targeted therapies, such as proteasome inhibi-

tors, immunomodulatory drugs, and monoclonal antibodies. These treatments specifically target the molecular abnormalities identified through cytogenetic analysis, leading to more effective and better-tolerated therapies. Additionally, cytogenetics-guided therapies have opened the door to precision medicine in MM, where treatments can be tailored to each patient's unique genetic profile. Moreover, as new cytogenetic abnormalities are discovered, ongoing research holds the promise of uncovering further therapeutic targets and innovative treatment modalities [40-45].

Cytogenetics has also emerged as a pivotal tool in advancing the treatment landscape for MM, providing critical insights that guide therapeutic strategies and enhance patient outcomes. The intricate relationship between cytogenetic abnormalities and treatment response results in development of innovative MM management, leading to more personalized and effective interventions [40-43].

Cytogenetics, the study of chromosomal changes within cells, has unveiled a profound understanding of the genetic underpinnings of MM. By identifying specific genetic alterations associated with MM, such as translocations, deletions, and mutations, clinicians can tailor treatment approaches to target the disease's vulnerabilities. These insights have paved the way for precision medicine, where therapies are uniquely designed to address a patient's genetic profile, ensuring optimal results [42-45].

The integration of cytogenetic information into treatment decisions has led to the development of risk stratification models. High-risk cytogenetic markers, such as the t (4; 14) translocation or Del (17p) deletion, can indicate a more aggressive disease course and potential resistance to conventional therapies. Armed with this knowledge, clinicians can opt for alternative treatments, including novel agents and immunotherapies, to overcome treatment challenges posed by these high-risk markers [46-48].

Furthermore, cytogenetics has played a crucial role in guiding the choice of induction therapy. Tailoring initial treatment based on a patient's cytogenetic profile can significantly impact response rates and depth of remission. For instance, patients with t (11; 14) translocation often respond well to proteasome inhibitors, while those with t (4; 14) may benefit from agents targeting the FGFR3 pathway [49-53]. This targeted approach maximizes the therapeutic effect and minimizes unnecessary side effects.

Cytogenetic analysis also informs decisions regarding autologous stem cell transplantation [ASCT] [54, 55]. Patients with favorable cytogenetics may undergo ASCT early in their treatment course, while those with high-risk genetic markers might benefit from delaying transplantation until disease control is achieved through alternative therapies [56, 57]. This dynamic approach ensures that each patient receives the most appropriate treatment timing for their unique disease characteristics.

The evolution of cytogenetics extends beyond traditional techniques. NGS and other advanced genomic technologies allow for comprehensive profiling of MM genomes, uncovering rare and cryptic mutations that may impact treatment response [13, 14]. By detecting these subtle genetic changes, clinicians can devise customized treatment regimens that address both common and rare genetic alterations [56, 57].

As clinical trials increasingly incorporate cytogenetic data into their study designs, new therapies are emerging with targeted mechanisms of action. Cytogenetic profiling helps identify patient subgroups that are more likely to benefit from these novel agents, facilitating the development of more efficient and effective treatments. In this way, cytogenetics serves as a guiding compass, steering research efforts towards precision therapeutics [50, 57].

Therefore, the integration of cytogenetics into MM treatment strategies has ushered in an era of personalized medicine. By unraveling the genetic complexities of the disease, clinicians are empowered to make informed decisions about induction therapy, transplantation timing, and the use of novel agents. As our understanding of MM genetics deepens, the role of cytogenetics will continue to expand, fostering innovative approaches that redefine the standard of care and ultimately improve the lives of patients battling this complex malignancy.

2. Conclusion

Cytogenetics has emerged as an indispensable tool in the diagnosis, prognosis, and treatment of MM. By unraveling the genetic complexity of this malignancy, cytogenetics has ushered in an era of personalized medicine, where treatment strategies can be optimized to improve patient outcomes. As research continues to advance, the integration of cytogenetic findings with other omics data and innovative technologies will undoubtedly pave the way for even more targeted and effective therapies, ultimately bringing us closer to achieving better outcomes and improved quality of life for MM patients.

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