International Journal of
Translational Medicine

MDPI

Article

Copy Number Alterations Suggest a Functional Switch from Innate Immunity to DNA Repair and Drive Clinical Heterogeneity in Plasma Cell Dyscrasias

Igor Valentim Barreto [1,†], Wallax Augusto Silva Ferreira [2,†], Guilherme Passos de Morais [1], Jéssica Sousa Cavalcante [1,3], Caio Bezerra Machado [1], Flávia Melo Cunha de Pinho Pessoa [1], Leidivan Sousa da Cunha [1], Anna Karolyna da Costa Machado [1], Isabelle Magalhães Farias [1], Beatriz Maria Dias Nogueira [1], Deivide de Sousa Oliveira [1], Carolina Koury Nassar Amorim [3], Rodrigo Monteiro Ribeiro [4], Ana Paula Lopes Moreira [4], Kaira Mara Cordeiro de Albuquerque [4], Mateus de Paula Gomes [4], Maria Elisabete Amaral de Moraes [1], Manoel Odorico de Moraes, Filho [1], Edivaldo Herculano Correa de Oliveira [2], Daniel Pacheco Bruschi [5] and Caroline Aquino Moreira-Nunes [1,6,*]

1 Clinical Genetics Laboratory, Drug Research and Development Center (NPDM), Department of Medicine, Federal University of Ceará, Fortaleza 60430-275, CE, Brazil; barreto.igorv@gmail.com (I.V.B.); guilherpdmorais@gmail.com (G.P.d.M.); jessica_2704@yahoo.com (J.S.C.); caio.bmachado97@gmail.com (C.B.M.); flaviamelop@outlook.com (F.M.C.d.P.P.); biomedleidivan@gmail.com (L.S.d.C.); annakcm1.8@gmail.com (A.K.d.C.M.); isabellefariasbiomed@gmail.com (I.M.F.); bmdnogueira@gmail.com (B.M.D.N.); deividearmorial@gmail.com (D.d.S.O.); betemora@ufc.br (M.E.A.d.M.); odorico@ufc.br (M.O.d.M.F.)
2 Laboratory of Cytogenomics and Environmental Mutagenesis, Environment Section (SAMAM), Evandro Chagas Institute, Levilândia, Ananindeua 67030-000, PA, Brazil; wallaxaugusto@gmail.com (W.A.S.F.); edivaldodeoliveira@iec.gov.br (E.H.C.d.O.)
3 Faculty of Biomedicine, Unichristus University Center, Fortaleza 60430-275, CE, Brazil; carolinaamorim@iec.gov.br
4 Department of Hematology, Fortaleza General Hospital (HGF), Fortaleza 60150-160, CE, Brazil; rmonteiroribeiro@icloud.com (R.M.R.); anplopesm@hotmail.com (A.P.L.M.); drakairahematologista@gmail.com (K.M.C.d.A.); gomes988@gmail.com (M.d.P.G.)
5 Evolutionary Cytogenomics Laboratory, Department of Genetics, Federal University of Paraná (UFPR), Curitiba 81530-000, PR, Brazil; danielbruschi@ufpr.br
6 Genomics and Molecular Biology Laboratory, Clementino Fraga Group, Central Unity, Fortaleza 60115-170, CE, Brazil
* Correspondence: carolfam@gmail.com or carolfam@cnpq.br
† These authors contributed equally to this work.

Abstract

Background/Objectives: Multiple myeloma (MM) is a genetically complex hematological neoplasm driven by accumulating genomic events. Despite therapeutic advances, MM remains an incurable disease with a complex molecular picture. Characterizing copy number alterations (CNAs) represents a promising strategy to identify dysregulated biological pathways and reveal novel therapeutic targets. This study aimed to characterize the CNA profile across pre-malignant gammopathies, MM, and plasma cell leukemia, identifying the key molecular pathways involved in disease progression. Methods: Genomic analysis via array comparative genomic hybridization (aCGH) was performed on bone marrow samples from 21 patients representing all disease stages. Data were analyzed in CytoGenomics software version 5.3.0.14 utilizing the GRCh38/hg38 human genome. CNAs were identified with the ADM-2 algorithm, followed by functional enrichment analysis to determine significantly overrepresented pathways. Results: Pre-malignant evaluation suggested a potential functional switch from innate immunity and olfactory signaling in Monoclonal Gammopathy of Undetermined Significance (MGUS) to DNA repair mechanisms in Smoldering Multiple Myeloma (SMM), marking early genomic instability. In active MM, 280 CNAs were

Check for updates

Academic Editor: Ewa Grzybowska

Received: 1 April 2026
Revised: 28 April 2026
Accepted: 7 May 2026
Published: 12 May 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

detected. Low-risk (ISS-I) patients retained cell adhesion signatures, whereas high-risk (ISS-III) profiles exhibited extensive genomic instability affecting tissue remodeling and cytokine signaling. Conclusions: In summary, our descriptive findings suggest that early alterations in immune response and olfactory signaling pathways may emerge as potential triggers driving pre-malignant dyscrasias and active MM development.

Keywords: multiple myeloma; aCGH; monoclonal gammopathy of undetermined significance; smoldering multiple myeloma; leukemia; plasma cell

1. Introduction

Multiple myeloma (MM) is a heterogeneous hematological malignancy characterized by clonal proliferation of plasma cells in the bone marrow (BM) and marked production of monoclonal immunoglobulins [1]. Although its etiology has not been fully elucidated, it is generally accepted that MM evolves from earlier premalignant stages, known as Monoclonal Gammopathy of Undetermined Significance (MGUS), which has a progression rate of 1% per year and is present in about 4% of individuals over 50 years of age, and Smoldering Multiple Myeloma (SMM), whose progression risk varies significantly based on risk stratification, with high-risk SMM showing substantially higher progression rates [1,2].

At the more aggressive end of the spectrum of plasma cell neoplasms is plasma cell leukemia (PCL), a rare condition characterized by extramedullary involvement and an aggressive clinical course. PCL can present as primary or secondary (developing from pre-existing MM), with primary PCL showing significantly better outcomes than secondary PCL despite both having aggressive clinical courses [3,4]. In general, it is believed that the cell responsible for these malignancies originates from the germinal center of the lymph node, where initial genetic mutations occur. These premalignant clones with chromosomal abnormalities migrate to BM, where they initiate the clonal expansion that characterizes MGUS or SMM [5,6].

Among the initiating genetic events, translocations involving the *IgH* locus on chromosome 14 are notable; they are present in about 50% of patients and affect several loci such as 11q13, 4p16, and 16q23. In parallel, the occurrence of hyperdiploidy, characterized by trisomies of odd chromosomes, constitutes another fundamental initial milestone, compromising cell cycle regulation [7,8]. Although essential for pathogenesis, primary alterations alone are insufficient to define the malignant phenotype of MM. Tumor progression depends on the accumulation of secondary events, including the dysregulation of oncogenes such as *MYC* and *RAS*, alongside complex genomic instability characterized by copy number alterations (CNAs). Among these, del(1p), del(17p), and del(13q) are critical markers, particularly 1q21 gain or amplification, which is now incorporated into the R2-ISS high-risk criteria due to its significant prognostic accuracy [9–11].

To translate biological complexity into clinical stratification, the International Staging System (ISS) originally provided a framework based on serum beta-2 microglobulin (B2M) and albumin (ALB) levels [12]. While the original ISS remains a relevant benchmark for biochemical tumor burden, risk stratification has significantly evolved in 2024 and 2025. Modern systems, such as the R2-ISS, the Real-World ISS (RW-ISS), and Consensus Genomic Staging, now integrate these accessible parameters with advanced cytogenetic and genetic markers to provide a more precise prognostic landscape [1,13].

Despite substantial advances in understanding the biology of MM, clinical practice still faces extremely variable outcomes, often marked by early relapses and fatal progression. This prognostic disparity is widely attributed to the intense genomic heterogeneity of the

disease, supported by a vast repertoire of molecular rearrangements and chromosomal instability present in the malignant clone [14]. Given this instability, molecular characterization is essential for understanding clonal evolution and tumor aggressiveness. While emerging technologies such as single-cell sequencing, optical genome mapping, liquid biopsy, and integrated proteogenomics are increasingly employed in MM research, aCGH remains a robust and validated platform for comprehensive CNA detection [15–19].

Therefore, this study was conducted to understand the molecular mechanisms that drive the evolution of plasma cell dyscrasias such as MGUS, SMM, MM, and PCL, and to describe their CNAs by characterizing the profile of the biological pathways overrepresented in patients from each group. This characterization can help to better understand the initiating and progression mechanisms associated with these pathologies.

2. Materials and Methods

2.1. Patients and Ethical Issues

The study cohort comprised 21 patients, primarily consisting of MM cases (n = 17) stratified by the ISS into stages I (n = 6), II (n = 5), and III (n = 6). To provide a comprehensive overview of genomic alterations across the evolutionary spectrum of plasma cell dyscrasias, representative cases of MGUS (n = 1), SMM (n = 2), and PCL (n = 1) were also included. Their inclusion facilitates an exploratory, longitudinal-like analysis of CNAs, tracing the progression from precursor states to highly aggressive clinical manifestations. All participants were included only after understanding and signing a written informed consent form. All methods were conducted in accordance with the Declaration of Helsinki guidelines and regulations. This study received formal approval from the Research Ethics Committee (REC) of the Fortaleza General Hospital (HGF) via the national ethics platform (Plataforma Brasil), under CAAE number 010496/2022, approval date 4 May 2022.

2.2. Inclusion and Exclusion Criteria

Patients with a confirmed clinical and laboratory diagnosis of MGUS, SMM, MM, or PCL, seen at HGF or referred by the Ceará Municipal and State Health Departments, were eligible for inclusion. Conversely, patients were excluded if they presented with other onco-hematological diseases or if their clinical and laboratory findings did not meet the diagnostic criteria for plasma cell dyscrasias.

2.3. Patient Stratification

Patients diagnosed with MM were stratified according to the ISS criteria. Patients were classified as ISS I (serum B2M $<$ 3.5 mg/L and ALB $\geq$ 3.5 g/dL), ISS III (serum B2M $\geq$ 5.5 mg/L), or ISS II (values not meeting ISS I or III criteria). This system was selected due to the uniform availability of these biochemical markers across the cohort, ensuring a standardized baseline for all patients. Stratification was not applied to MGUS, SMM, and PCL cases, as the ISS is validated exclusively for symptomatic MM.

2.4. Genomic DNA Extraction

Bone marrow samples were collected, and genomic DNA (DNAg) was isolated using a PureLink Genomic DNA Mini Kit (Cat. #K182001, Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. DNAg concentrations were determined with a NanoDrop2000 spectrophotometer (ThermoScientific®, San Jose, CA, USA). The purity and integrity of the gDNA, indicated by the DNA Integrity Number (DIN), were determined using a D1000 ScreenTape (Cat. #5067-5582, Agilent Technologies, Santa Clara, CA, USA) on a 4200 TapeStation System (Cat. #G2991BA, Agilent Technologies, Santa Clara, CA, USA). For aCGH, we used gDNA with a DNA Integrity Number (DIN) > 8.

2.5. aCGH (Comparative Genomic Hybridization on Array)

The identification of somatic chromosomal alterations (gains and losses) was performed by aCGH, using a SurePrint G3 Cancer CGH + SNP Microarray G4869-60510 Kit, 4x180K (Cat. #G4869A, Agilent Technologies, Santa Clara, CA, USA), according to the manufacturer's instructions. After hybridization, stringency washes were performed using Agilent Oligo aCGH/ChIP-on-chip Wash Buffers 1 and 2 (Cat. #5188-5226, Agilent Technologies, Santa Clara, CA, USA), and the microarrays were scanned using an Agilent Microarray Scanner System (Cat. #G2565CA, Agilent Technologies, Santa Clara, CA, USA).

2.6. Integrative Analysis of Copy Number Alterations (CNAs)

The captured images were quantified and analyzed by Agilent CytoGenomics software (v5.4) (Agilent Technologies, Santa Clara, CA, USA) using the default analysis method (statistical algorithm ADM-2, sensitivity threshold = 6, aberration filter = 3 probes, and minimum AvgAbsLogRatio = 0.25). Furthermore, array quality was rigorously assessed using the Derivative Log Ratio Spread (DLRS) metric, excluding arrays with DLRS > 0.3 due to excessive noise. All included arrays achieved probe call rates of at least 98%, with GC correction and diploid peak centralization applied as standard preprocessing steps to enhance data accuracy. The genomic locations obtained were based on the human genome build GRCh38/hg38. For enrichment analysis, only autosomal CNAs (chromosomes 1–22) overlapping annotated genes were retained, excluding sex chromosomes and intergenic regions.

2.7. Functional Enrichment Analysis

To elucidate the biological processes associated with CNAs in our cohort, we performed an overrepresentation analysis (ORA). All analyses were conducted in R (v.4.5.1) using the clusterProfiler package (v4.16.0). To enable parallel comparisons across clinical stages (ISS I–III), we used the compareCluster function with a hypergeometric test and human genome annotations from org.Hs.eg.db (v3.21.0). Enrichment analyses included Gene Ontology (GO) (BP: biological processes; CC: cellular components; MF: molecular functions), KEGG (Kyoto Encyclopedia of Genes and Genomes), WikiPathways, and Reactome (v1.52.0). Significantly overrepresented CNAs (FDR < 0.05) were used as input, with all measured genes as the background. GO terms were filtered for semantic redundancy (cutoff = 0.7) to improve interpretability. The results were visualized as customized dot plots of $-\log10$ FDR-adjusted p-values using the ggplot2 package (v4.0.0).

3. Results

The study included a cohort of 21 patients divided into six diagnostic categories: MGUS (n = 1), SMM (n = 2), ISS-I (n = 6), ISS-II (n = 5), ISS-III (n = 6) and PCL (n = 1). The mean age at diagnosis was 60 years ($\pm$10.94), with a male predominance (13 males, 61.9%) compared with females (8 females, 38.1%). Baseline laboratory parameters were summarized based on available medical records. Hematological evaluation (available for n = 20) revealed hemoglobin levels ranging from 2.6 to 14.7 g/dL, white blood cell counts from 1000 to 14,540/µL, and platelet counts from 14,000 to 279,000/µL. Key biochemical markers showed β2-microglobulin (B2M) levels ranging from 1.49 to 37.88 mg/L (n = 19), ALB from 1.72 to 4.5 g/dL (n = 14), and lactate dehydrogenase (LDH) from 80 to 2500 U/L (n = 18).

3.1. CNA Profile of MGUS and SMM Patients

A total of 27 CNAs were identified in the pre-malignant stages, including 15 gains and 12 losses, with a mean size of 218.75 kb (ranging from 1.27 kb to 840 kb). Specifically, in

MGUS, 11 CNAs were detected (mean size: 194.86 kb, range: 1.27 kb to 818 kb), comprising seven gains confined to the p-arms of chromosomes 2, 8, 14, and 22, and four losses restricted to the q-arms of chromosomes 4, 10, 14, and 15 (Figure 1A). In contrast, in SMM, 16 CNAs were observed (mean size: 234.87 kb, range: 1.29 kb to 840 kb), which consisted of eight gains (on chromosomes 7, 8, 14, 17, 18, and 22) and eight losses (on chromosomes 2, 4, 5, 8 and 15) (Figure 1B). These data descriptively suggest a modest increase in CNA number and size from MGUS to SMM, with broader chromosomal involvement in SMM. Overall, the stage-specific CNA patterns appear consistent with the concept of progressive genomic instability during early disease evolution.

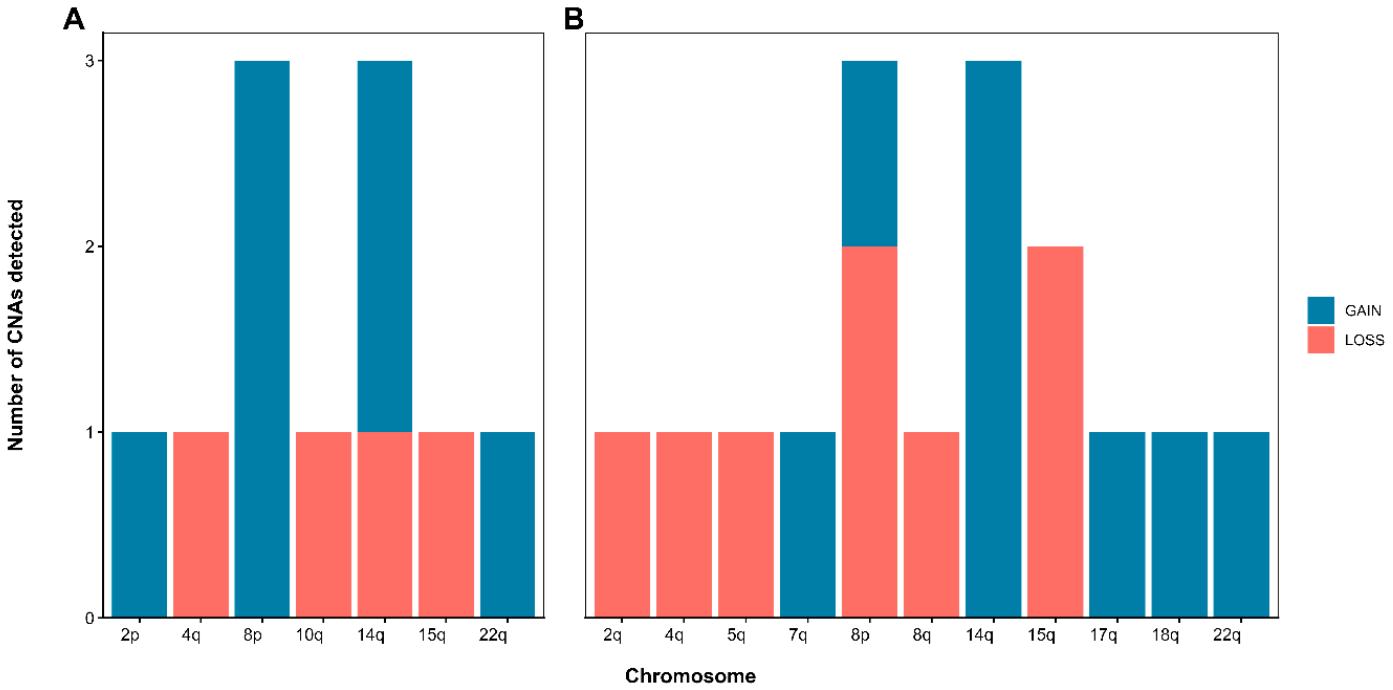


Figure 1. Distribution of copy number alterations (CNAs) across chromosomes in pre-malignant stages. The number of detected CNAs is plotted against their respective chromosomes. (**A**) CNA profile observed in Monoclonal Gammopathy of Undetermined Significance (MGUS). (**B**) CNA profile observed in Smoldering Multiple Myeloma (SMM). Red bars represent losses, and blue bars represent gains.

To explore the biological processes potentially associated with CNA-affected genes, we performed functional enrichment analysis across MGUS, SMM, MM and PCL. In MGUS, functional annotation using GO revealed significant enrichment of biological processes related to chemokine receptor and olfactory receptor activity. The cellular component was primarily limited to microvesicles, indicating a role for extracellular signaling mechanisms (Figure 2A). Pathway analysis aligned with this interpretation, showing significant enrichment of innate immune and antimicrobial pathways (Figure 2B). Notably, olfactory transduction and signaling pathways appeared in both GO and pathway analyses, reinforcing the non-canonical involvement of sensory receptor signaling in immune-related processes. These descriptive findings suggest that CNAs in MGUS affect a tightly integrated immune signaling network, characterized by chemotactic and antimicrobial effector functions, consistent with an early and signaling-focused stage of immune dysregulation.

In SMM, CNAs appeared to be associated with an expanded functional landscape that integrates immune activation, transcriptional regulation and genome maintenance. Enrichment analyses also revealed sustained innate immune responses and host–microbe interactions, along with chemokine-driven signaling. Concurrent enrichment of TFIIH and

SMN complexes and microvesicles indicated coordinated engagement of nuclear regulatory machinery and extracellular signaling (Figure 2C). At the pathway level, infection- and inflammation-related programs converged with pathways governing basal transcription and nucleotide excision repair (Figure 2D). Together, these findings indicate that CNAs in SMM disrupt a multilayered regulatory network linking immune defense, transcriptional control, and genome integrity, reflecting more advanced and multifaceted molecular perturbation compared with earlier disease stages.

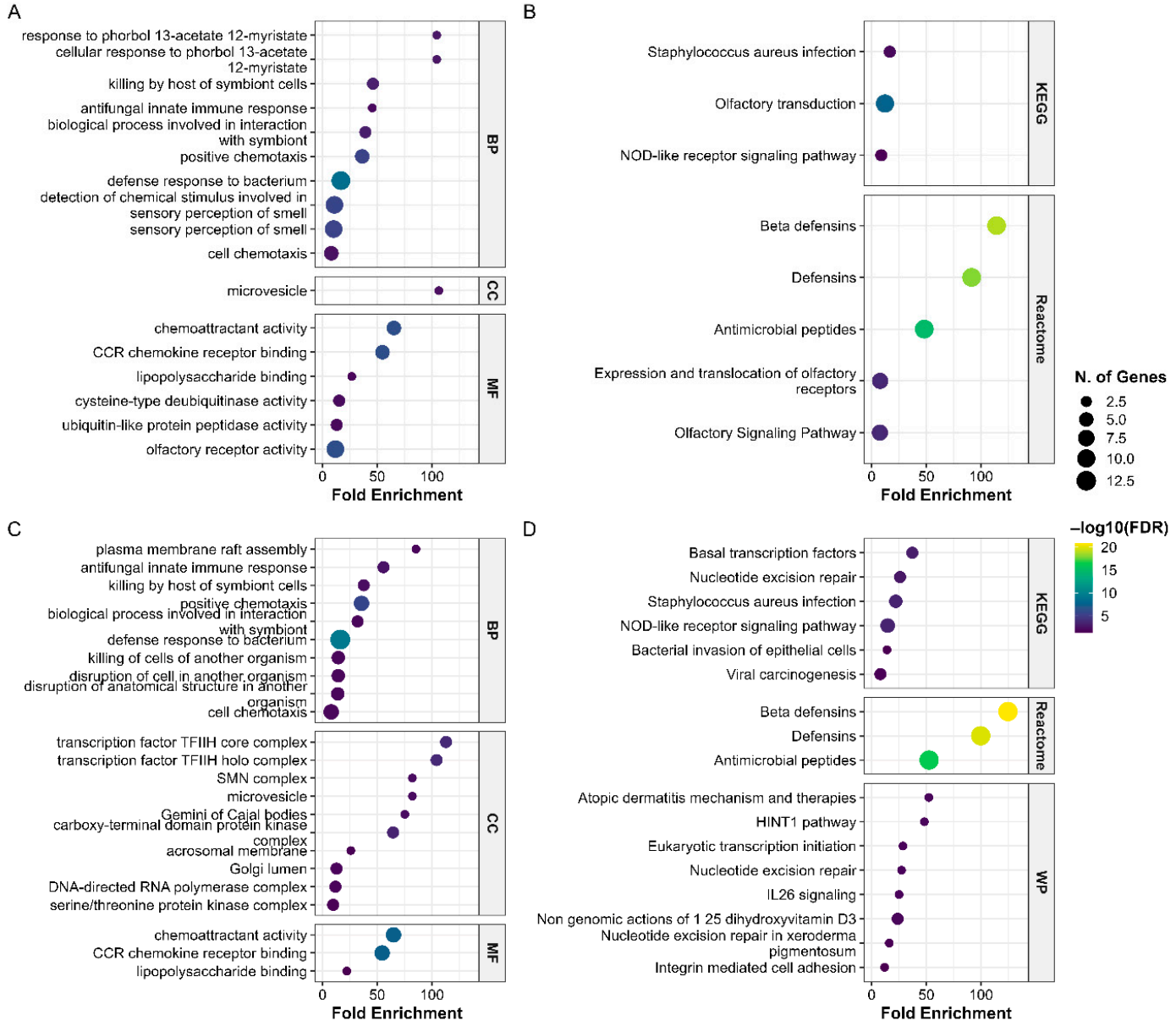


Figure 2. Functional enrichment profiles (GO and pathways) of genes affected by CNAs in Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM). (**A**,**C**) show the enrichment of Gene Ontology (GO) terms for MGUS and SMM, respectively, divided into the domains biological process (BP), cellular component (CC), and molecular function (MF). (**B**,**D**) display the results of overrepresentation analysis (ORA) of the pathways for MGUS (using KEGG and Reactome databases) and SMM (using KEGG, Reactome, and WikiPathways databases), respectively. In all panels, the degree of enrichment is shown as fold enrichment, the bubble size represents the number of associated genes, and the colors indicate the statistical significance, given by −log10(FDR). The ten most significantly enriched terms for both GO categories and pathways are displayed.

3.2. CNA Profile of MM Patients

In MM, 280 CNAs were detected, including 174 gains and 106 losses, with a mean segment size of 186.14 kb (range: 1.006 to 986 kb). Stratification by ISS showed a marked increase in CNA burden with advancing risk. The low-risk group (ISS-I) had 83 CNAs (55 gains and 28 losses; mean size: 158 kb; range: 1.063 to 984 kb), distributed across most autosomes but absent from chromosomes 12, 17, 18, and 20. The intermediate risk group (ISS-II) tumors exhibited 65 CNAs, predominantly losses (44 losses and 21 gains; mean size: 243.4 kb), affecting nearly all autosomes except chromosomes 9, 12, 19, 21, and 22. In contrast, ISS-III cases showed extensive genomic disruption, with 132 CNAs (98 gains and 34 losses; mean size: 175.6 kb) spanning all autosomes and displaying prominent arm-level recurrence, particularly on chromosomes 8 and 14 (Figure 3). These patterns demonstrate a progressive increase in both the frequency and chromosomal breadth of CNAs with increasing disease risk, consistent with escalating genomic instability in advanced MM.



Figure 3. Chromosomal distribution of CNAs across ISS risk groups in multiple myeloma. Bar plots show the number of copy number gains (blue) and losses (red) detected across autosomal chromosome arms (1p–22q), stratified by International Staging System (ISS) risk categories (ISS I-III). Each panel represents one ISS group, illustrating both the frequency and chromosomal localization of CNAs. A progressive increase in CNA burden is observed with advancing risk, with ISS-III cases showing the highest number and broadest distribution of alterations across the genome.

Subsequent GO-based overrepresentation analysis of CNA-affected genes revealed stage-specific functional programs that evolved with increasing clinical risk. In ISS-I, enrichment was largely limited to signaling and cell–cell interaction processes, including sensory perception of smell, plasma membrane-mediated adhesion, interferon receptor binding, and inhibitory MHC class I receptor activity, consistent with a restricted, receptor-centered functional profile. In ISS-II, this pattern shifted toward immune effector and proteostatic mechanisms, with prominent enrichment of defense responses to Gram-positive bacteria, proteasome-mediated ubiquitin-dependent protein catabolism, and cytolysis, along with molecular functions related to glucuronosyltransferase activity and ubiquitin-like ligase–substrate adaptor interactions. In contrast, ISS-III was characterized by enrichment of processes linked to tissue remodeling and signal transduction, including regulation of tissue remodeling, protein tyrosine kinase binding, and cytokine receptor binding, reflecting broader engagement of growth and inflammatory signaling pathways (Figure 4). Together, these ontological patterns delineate progressive reprogramming of biological functions across ISS stages, transitioning from constrained receptor-mediated signaling to immune activation and, ultimately, to complex regulatory and remodeling processes associated with advanced disease.

Next, the pathway analysis further delineated stage-specific functional programs associated with CNA-affected genes. In ISS-I, enrichment was dominated by pathways related to olfactory signaling, along with nucleotide excision repair, indicating a functional bias toward sensory receptor signaling and genome maintenance mechanisms. In ISS-II, the enrichment profile shifted toward metabolic and detoxification pathways, with prominent overrepresentation of pentose and glucuronate interconversions, glucuronidation, drug metabolism by non-cytochrome enzymes, and small-ligand GPCR signaling, consistent with enhanced metabolic adaptation and xenobiotic processing. In contrast, ISS-III displayed a distinct signaling-centric architecture, characterized by enrichment of Rap1 signaling, cytokine–cytokine receptor interactions, and PI3K-Akt signaling, reflecting activation of pathways governing cell survival, proliferation, and inflammatory communication (Figure 5). Collectively, these pathway patterns mirror the ontological findings and support stepwise functional reprogramming across disease stages, transitioning from receptor- and repair-associated processes to metabolic remodeling and, ultimately, to oncogenic and cytokine-driven signaling networks in advanced disease.

In PCL, we identified 57 CNAs, including 35 gains and 22 losses, with a mean segment size of 107.53 kb (range: 1.02–682 kb). CNAs were broadly distributed across the genome, affecting most autosomes, while chromosomes 9, 12, 17, 20, and 22 remained unaltered (Figure 6). Notably, the CNA landscape was dominated by focal gains, with a marked accumulation on chromosome 14q, consistent with a highly rearranged but size-restricted pattern of genomic disruption characteristic of advanced disease.

Overrepresentation analysis of CNA-affected genes in PCL revealed a focused functional signature centered on cell adhesion and post-transcriptional regulation. GO enrichment was dominated by homophilic cell adhesion mediated by plasma membrane adhesion molecules, along with molecular functions related to translational repression and translation regulatory activity, implicating altered control of protein synthesis. At the pathway level, enrichment of the Rap1 signaling cascade and the 5q35 copy number variation signature emerged as the most prominent features, highlighting convergence between adhesion-associated signaling and region-specific genomic alterations in advanced disease (Figure 7).

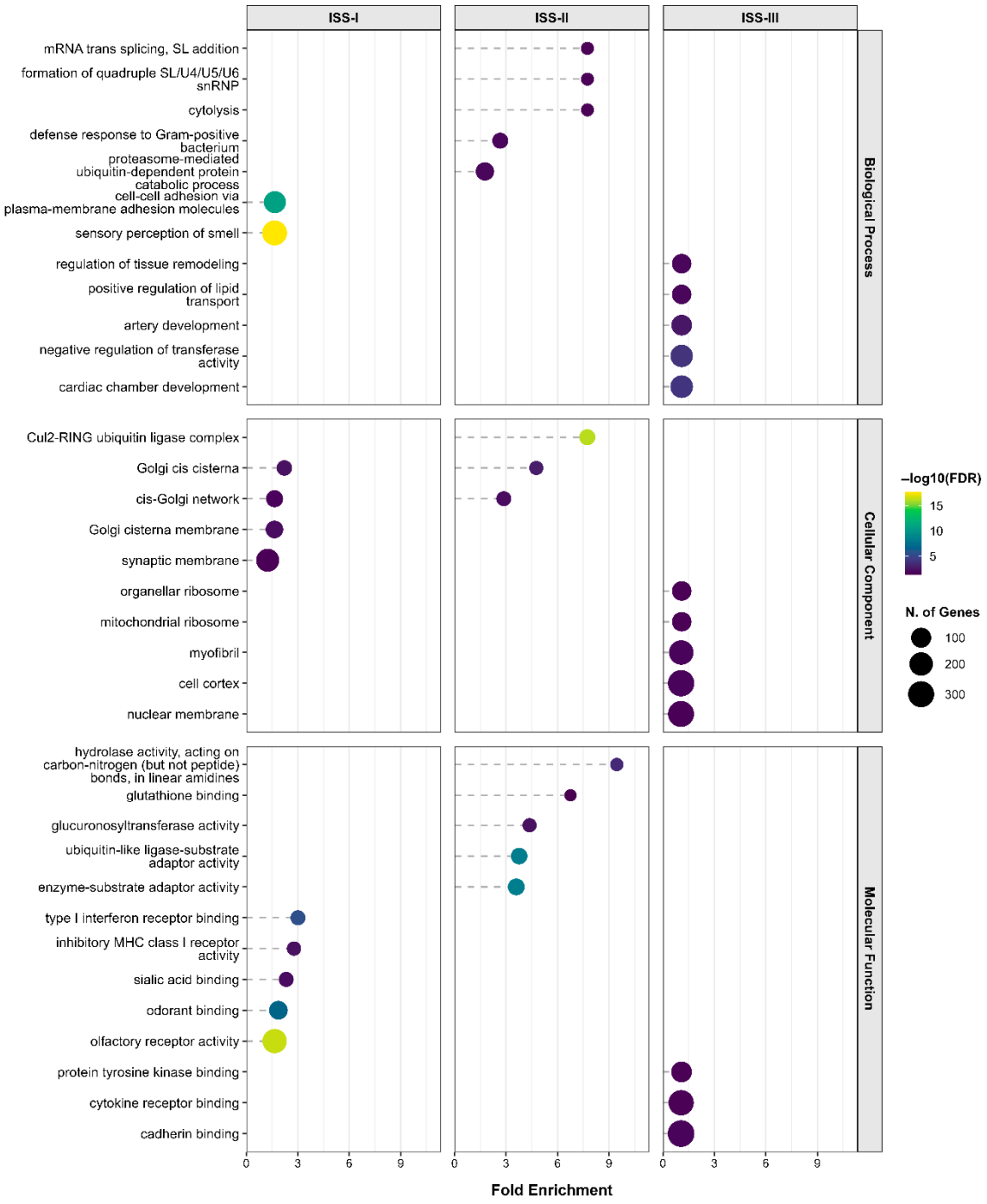


Figure 4. Stage-specific Gene Ontology enrichment profiles associated with CNAs in multiple myeloma. Bubble plots show the comparative enrichment of GO terms among International Staging System (ISS) risk groups (ISS-I, ISS-II, and ISS-III), based on overrepresentation analysis of CNA-affected genes using the compareCluster approach. Enriched terms are organized by GO domain (BP: biological process; CC: cellular component; MF: molecular function) and are displayed separately for each risk group. The x-axis indicates fold enrichment, bubble size represents the number of genes associated with each term, and color intensity reflects statistical significance (−log10 FDR). For each ISS category and GO domain, the five most significantly enriched terms are shown.

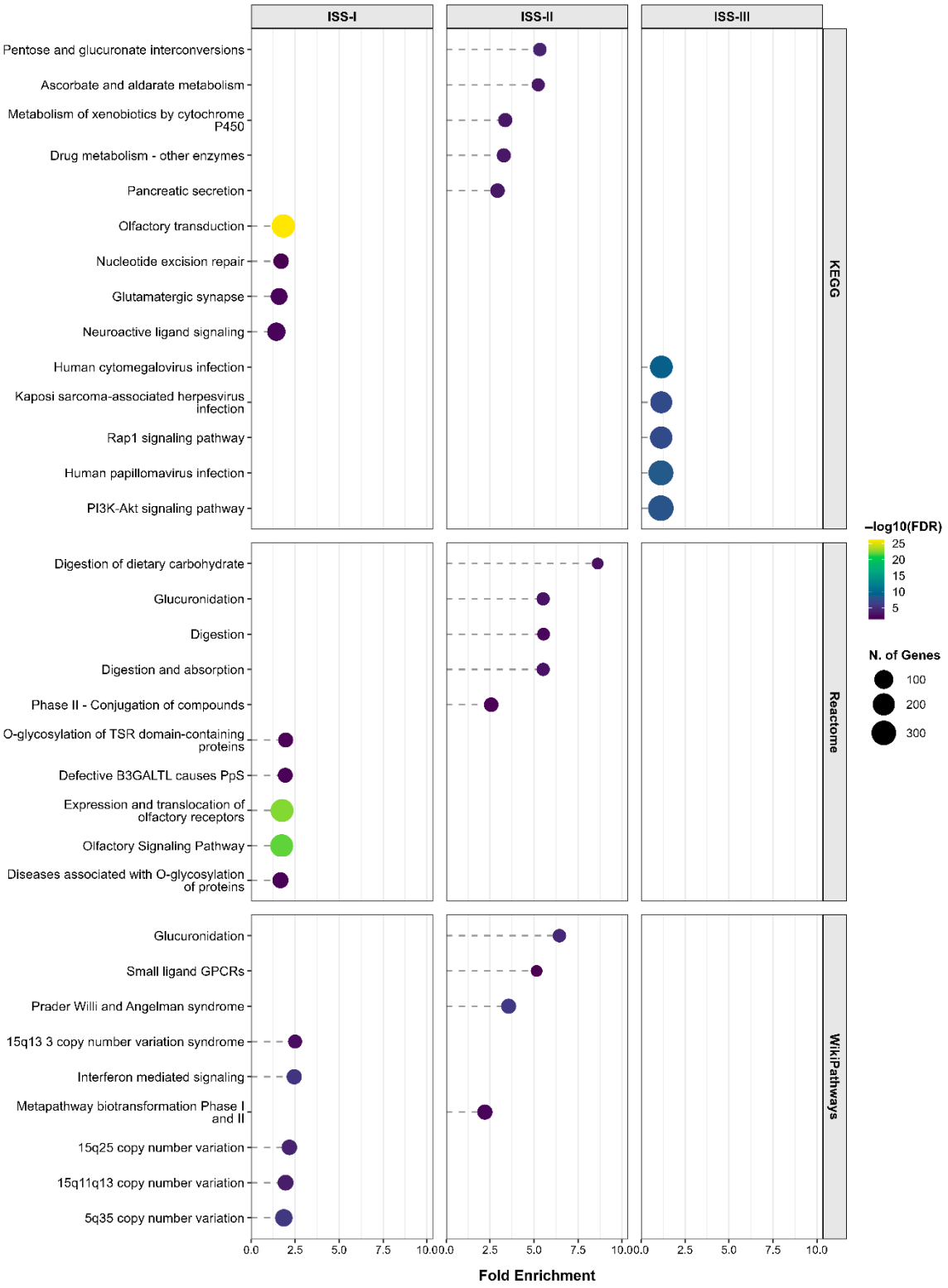


Figure 5. Stage-specific pathway enrichment is associated with CNAs in multiple myeloma. Bubble plots show the results of pathway overrepresentation analysis (ORA) performed on CNA-affected genes across International Staging System (ISS) risk groups (ISS-I, ISS-II, and ISS-III), using the KEGG, Reactome, and WikiPathways databases. For each database, enriched pathways are displayed separately by risk group, highlighting stage-dependent differences in pathway involvement. The x-axis shows fold enrichment, bubble size indicates the number of genes contributing to each pathway, and color intensity represents statistical significance (−log10 FDR). For each ISS category and database, the five most significantly enriched pathways are shown.

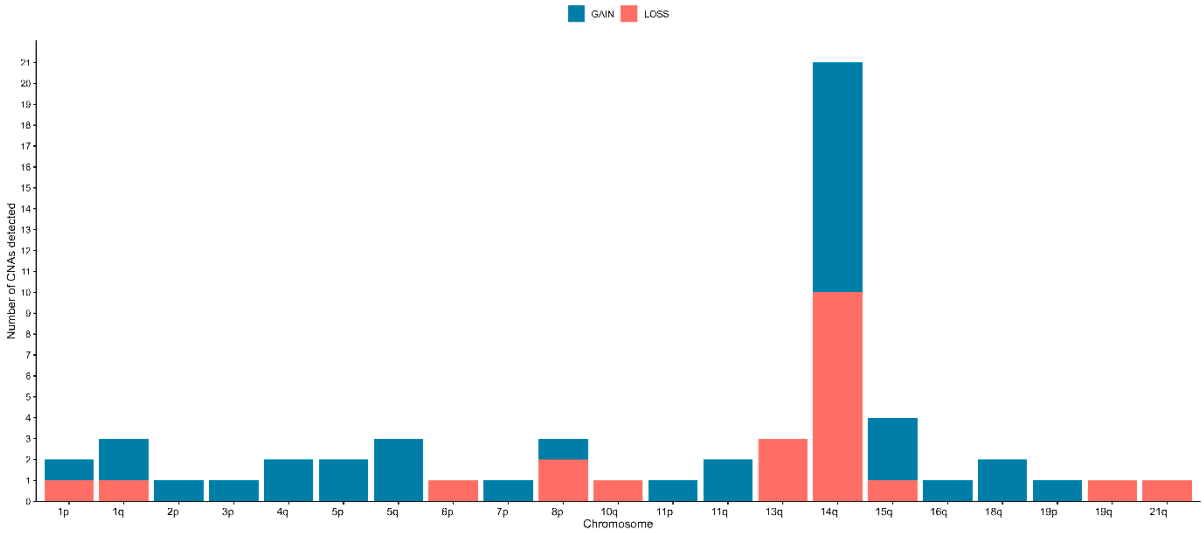


Figure 6. Chromosomal distribution of CNAs in plasma cell leukemia (PCL). Bar plots show the number of copy number gains (blue) and losses (red) detected across autosomal chromosome arms (1p–21q) in PCL. The y-axis indicates the number of CNAs per chromosome arm. CNAs are broadly distributed across the genome, with a pronounced accumulation of alterations on chromosome 14q, reflecting a gain-biased and focal pattern of chromosomal disruption characteristic of PCL.

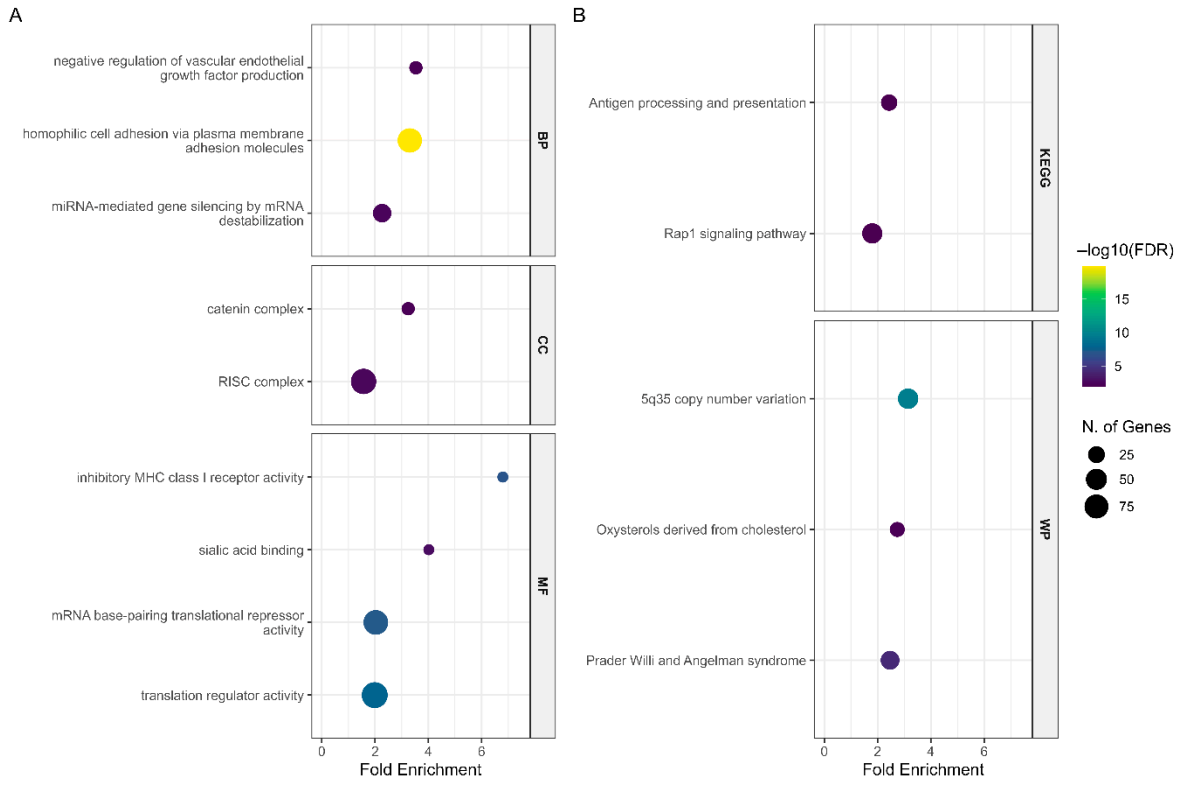


Figure 7. Functional enrichment of copy number-altered genes in plasma cell leukemia (PCL). (**A**) Bubble plots summarizing GO overrepresentation analysis of genes affected by CNAs in PCL, shown for the domains biological process (BP), cellular component (CC), and molecular function (MF). (**B**) Pathway-level overrepresentation analysis of the same gene set using the KEGG and WikiPathways (WP) databases. In both panels, the x-axis represents fold enrichment, bubble size indicates the number of genes associated with each term or pathway, and color intensity reflects statistical significance (−log10 FDR). For each category, the five most significantly enriched GO terms or pathways are shown.

4. Discussion

4.1. Genomic Instability Defines Disease Progression Across Plasma Cell Dyscrasias

The present study demonstrates a progressive accumulation of CNAs across plasma cell dyscrasias, with 27 CNAs in pre-malignant stages (MGUS and SMM), 280 CNAs in MM, and 57 CNAs in PCL. This gradual increase reflects genomic instability as a fundamental driver of malignant transformation [1,20]. Recent genomic profiling using next-generation sequencing platforms has established that CNA burden directly correlates with disease aggressiveness and clinical outcomes in MM [14,21,22]. Specifically, the identification of alterations in chr 8, 14, and 15 as the most prevalent in our cohort reflects the canonical involvement of *MYC* dysregulation and *IGH* translocations in MM pathogenesis [23,24]. Evidence from large-scale genomic studies demonstrate that copy number signatures are integral features for accurate prognostic stratification [11,25]. The transition from MGUS (11 CNAs) to SMM (16 CNAs) represents early genomic destabilization, consistent with recent findings showing that SMM exhibits intermediate mutational landscapes characterized by the accumulation of secondary genetic events [2,26]. This progressive genomic disruption underlies the clinical heterogeneity observed in MM and necessitates comprehensive molecular characterization for risk-adapted therapeutic strategies [7,8].

This progressive genomic disruption is closely tied to dynamic shifts in clonal heterogeneity across disease stages [27,28], which are phenotypically mirrored by the functional reprogramming observed in our cohort. Although the subclonal architecture and primary genetic drivers of active disease are typically established during the SMM stage, its absolute genomic complexity remains lower than in the symptomatic phase [29]. In our data, this early evolutionary stage was characterized by CNAs that disrupt a multilayered regulatory network, shifting from immune defense to genome maintenance mechanisms. This shift reflects an initial cellular response to accumulating genomic stress. Upon progression to active MM, genomic instability significantly intensifies, leading to peak intra-tumoral and spatial heterogeneity driven by branching evolution [27,30]. Conversely, the transition to PCL often reflects a phenomenon of severe clonal selection, in which a highly aberrant and dominant subclone drives systemic dissemination, resulting in a highly aggressive clinical course [28].

4.2. Functional Switch from Innate Immunity to DNA Repair in Pre-Malignant Progression

In our exploratory analysis, a notable observation was a descriptive trend suggesting a functional transition from innate immunity pathways in MGUS to DNA repair machinery in SMM, which may reflect early genomic stress preceding malignant transformation [31]. Growing evidence shows profound downregulation of antimicrobial genes (e.g., *DEFB1*) in endothelial cells and mesenchymal stromal cells from the MGUS, SMM, and MM stages, resulting in loss of immune surveillance and increased tumor permissiveness [32]. Beta-defensins play dual roles in MM pathogenesis: constitutive *DEFB1* acts as a tumor suppressor and is downregulated by chromosomal deletions or epigenetic silencing [31], while inducible defensins such as hBD-2 and hBD-3 are overexpressed in inflammatory environments and act as pro-tumoral agents by interacting with the CCR6 receptor, promoting recruitment of dysfunctional immature dendritic cells that contribute to immunosuppression and have angiogenic properties [31,33]. Alarmins, including S100A8/A9 proteins, activate TLR4 signaling, inducing cytokine production (IL-6, TNF-α) and stimulating both angiogenesis and megakaryocyte expansion in MM [34,35]. The emergence of nucleotide excision repair and TFIIH complex enrichment in SMM represents a cellular response to accumulating DNA damage and replication stress [36]. A prior study reported that DNA repair pathway alterations, particularly in homologous recombination deficiency genes (e.g., *RAD50*, *BRCA1*), define aggressive, therapy-resistant MM pheno-

types characterized by high genomic instability scores [37]. Given the limited sample size of pre-malignant stages, these stage-specific pathway differences must be interpreted as descriptive. However, this potential functional shift from immune defense to genome maintenance mechanisms generates an interesting hypothesis regarding molecular thresholds in early disease evolution, warranting validation in larger cohorts [5,6].

4.3. ISS-Dependent Stratification Reveals Distinct Molecular Programs That Drive Clinical Heterogeneity

The ISS-stratified analysis demonstrates functional divergence across risk groups, with ISS-I patients retaining cell adhesion signatures, ISS-II patients exhibiting metabolic and proteostatic reprogramming, and ISS-III patients showing extensive tissue remodeling and cytokine signaling activation [38]. In ISS-I patients, the enrichment of olfactory receptor pathways and plasma membrane adhesion signatures indicate early-stage mechanisms that maintain cellular attachment to the BM niche [39]. Recent investigations reveal that olfactory receptors (ORs), traditionally associated with odorant detection, are ectopically expressed in hematological malignancies, where they act as metabolic sensors modulating proliferation, survival, and differentiation [40,41]. Cell–cell adhesion via plasma membrane adhesion molecules is intrinsically linked to activation of pro-proliferative and pro-survival pathways, including IL-6, NF-κB, and MAPK signaling, which underpin adhesion-mediated drug resistance and clonal expansion [42,43]. The transition to ISS-II is characterized by enrichment of metabolic adaptation pathways, including pentose and glucuronate interconversions, glucuronidation, and drug metabolism, alongside proteasome-mediated ubiquitin-dependent protein catabolism [44]. This metabolic reprogramming reflects increased cellular stress, and xenobiotic processing demands characteristics of intermediate-risk disease [45]. The involvement of the Cul2-RING ubiquitin ligase complex indicates dysregulation of proteostasis pathways controlling cell cycle regulation and DNA damage responses, explaining the high clinical efficacy of proteasome inhibitors in MM treatment [36,46]. Finally, the progression to ISS-III revealed the activation of oncogenic signaling networks, particularly PI3K/AKT/mTOR, Rap1, and cytokine–cytokine receptor interaction pathways [47]. Studies have demonstrated that PI3K/AKT/mTOR pathway hyperactivation is directly associated with MM tumor development and represents a critical therapeutic target [48,49]. *AKT* regulates cellular metabolic function by maintaining glycolysis and oxidative phosphorylation while restricting FOXO activity, thereby promoting MM cell survival [50]. Pharmacological inhibition of PI3K/AKT/mTOR signaling induces apoptosis and reduces cell proliferation, migration, and invasiveness in MM cell lines [51,52]. The identification of distinct molecular programs across ISS supports development of risk-adapted precision medicine approaches targeting stage-specific vulnerabilities [12,53].

4.4. Chemokine Signaling Orchestrates Bone Marrow Microenvironment Remodeling

The enrichment of CCR chemokine receptor binding domains and chemoattractant activity pathways during disease progression highlights the central role of chemokine signaling in MM pathophysiology. The CCL3-CCR1/CCR5 axis is a critical therapeutic target, as CCL3 produced by myeloma cells promotes intense osteoclastogenesis by binding to CCR1 and CCR5 receptors, leading to bone destruction and the release of growth factors such as TGF-β and IGF-1 that support the tumor [54,55]. This chemokine axis also facilitates the egress and dissemination of neoplastic cells, contributing to disease aggressiveness [56]. Targeting the chemokine receptor CCR1 is a promising therapeutic approach, as CCR1 expression promotes plasma cell dissemination in vivo and correlates with poor clinical outcomes [55,56]. The progressive increase in chemoattractant activity from MGUS through SMM to MM reflects the transformation of the BM into a pro-tumor chemotaxis niche, where chemokines recruit myeloid-derived suppressor cells (MDSCs), tumor-associated

macrophages, and endothelial cells rather than effector immune cells [57]. This chemotactic signature promotes immunosuppression, angiogenesis, and bone remodeling, correlating with increased tumor burden and clinical aggressiveness [58]. Recent studies of the BM microenvironment in MM show that interactions between malignant plasma cells and stromal components create a permissive niche characterized by immune tolerance, angiogenic activation, and metabolic reprogramming [59,60]. Targeting chemokine-mediated microenvironmental interactions is an evolving therapeutic strategy that may overcome adhesion-mediated drug resistance and improve outcomes in high-risk patients [61,62].

4.5. PCL Shows Loss of Adhesion and Translational Dysregulation

The identification of homophilic cell adhesion deficits and alterations in translational regulation in PCL reveals the molecular basis for the aggressive circulating phenotype that distinguishes this entity from bone marrow-confined MM. The disruption of cadherin-related proteins, including CDHR2 and CDHR5, reduces cell–cell adhesion, facilitating migration and dissemination through the bloodstream [63]. Adhesion molecules play a critical role in the transition from MGUS through MM to primary PCL, with a marked deficiency of adhesion molecule expression in PCL compared to MM [3,63]. This loss of adhesion correlates with reduced dependence on BM microenvironmental signals such as IL-6 and STAT3, which normally support MM cell survival, enabling PCL cells to adopt a circulating, microenvironment-independent phenotype [64,65]. The enrichment of translational repression and translation regulatory activity domains indicates profound translational reprogramming that drives uncontrolled protein synthesis and supports survival under stress conditions [66]. Translational control mechanisms are essential for cancer cell adaptation, enabling selective synthesis of stress-response, survival, and stemness factors while globally reducing protein synthesis [67,68]. Recent studies show that highly proliferative malignancies exploit translational reprogramming through alterations in post-transcriptional regulators, including mRNA-binding proteins and modifications of the 5′ untranslated regions that govern translation efficiency [69,70]. The mTORC1-4EBP1/2 axis is a key regulatory node, as 4EBP proteins confer protection during metabolic stress by promoting NADPH homeostasis through translational repression of acetyl-CoA carboxylase 1 (ACC1), thereby mitigating oxidative stress [71]. Cancer cells, including those in PCL, exploit this regulatory mechanism to combat energetic stress and maintain tumorigenicity [72,73]. The detection of 5q35 CNA signatures in PCL patients is another critical feature, as this region harbors epigenetic regulatory genes, including NSD1, whose alterations favor transcriptional reprogramming and accelerate tumor progression [65]. The convergence of adhesion loss, translational dysregulation, and genomic instability defines the unique biology of PCL as a highly proliferative, migratory, microenvironment-independent variant characterized by accelerated clonal evolution and therapeutic resistance [74,75].

From a diagnostic and genomic profiling perspective, this extreme phenotypic shift fundamentally dictates the clinical utility of biological compartments. In pre-malignant, low-burden states such as MGUS, the malignant clone is strictly confined to the BM microenvironment, with a characteristic absence of myeloma cells in the peripheral blood. Because circulating markers such as circulating tumor DNA (ctDNA) and circulating plasma cells strongly correlate with systemic tumor burden [76], these markers may fall below the detection limits of current liquid biopsy platforms in early stages, making BM DNA and BM plasma cells indispensable for accurate genomic profiling. In contrast, the massive release of malignant plasma cells in PCL turns peripheral blood into a highly representative genomic reservoir. Therefore, despite BM DNA remaining the gold standard for mapping the genomic landscape in MGUS and active MM, peripheral blood analysis offers

a minimally invasive approach to capturing genomic complexity and disease progression in circulating variants such as PCL [77,78].

4.6. Study Limitations

While our findings delineate critical genomic transitions, this study has limitations inherent to its retrospective design. First, regarding sample size, the extremely small sample cohorts of MGUS (n = 1), SMM (n = 2), and PCL (n = 1) may limit the statistical power to capture the full spectrum of subclonal heterogeneity associated with disease evolution. Due to this significant constraint, our stage-specific observations and ORA must be interpreted as exploratory and purely descriptive. Given that MM is characterized by branching evolution and spatial heterogeneity, larger cohorts are required to validate the frequency of rare driver events in these transitional stages [79,80]. Second, regarding risk stratification, our analysis relied on the standard ISS rather than the R2-ISS. Although ISS effectively stratifies patients based on tumor burden (B2M and ALB) [12], it lacks the integration of LDH levels and high-risk cytogenetics (e.g., del(17p), t(4;14)) utilized in the R2-ISS to refine prognostic discrimination [21]. Consequently, the genomic landscape of our high-risk ISS-III group might partially overlap with intermediate-risk molecular subtypes defined by newer models. Third, regarding functional inferences: we fully acknowledge that ORA is sensitive to the size of the gene list, thresholds, and inherent biases. Since no validation was performed at the transcriptomic or proteomic level, the phenotypic consequences arising from these stage-specific CNAs should be interpreted descriptively, especially in premalignant stages and PCL. Therefore, our functional enrichment results serve as hypothesis-generating insights that still need to be validated orthogonally. Finally, regarding technical purity (CD138+), a significant limitation is the lack of CD138+ plasma cell enrichment before genomic analysis. Recent evidence shows that plasma cell sorting increases detection rates from 61% to 95.5%. Dilution by non-plasma cells may have led to underestimation of CNA frequency, especially for subclonal alterations. Fundamentally, this dilution effect introduces a bias in the comparison between different stages of the disease. Since premalignant conditions, such as MGUS and SMM, inherently exhibit much lower plasma cell infiltration in the bone marrow compared to active MM or PCL, the sensitivity of CNA detection is disproportionately reduced in these early stages, which may be reflected in lower genomic complexity in MGUS and SMM. Future studies should prioritize enrichment to achieve at least 90% purity, as recommended by the European Myeloma Network [81,82].

4.7. Conclusions, Clinical Implications, and Future Directions

The stage-specific functional programs identified across plasma cell dyscrasias underscore the need for integrated genomic classification systems that incorporate copy number signatures alongside traditional cytogenetic markers. Advanced staging systems, such as R2-ISS and consensus genomic staging, include high-risk cytogenetic features like TP53 mutations, del(17p), t(4;14), t(14;16), and 1q21 gain/amplification, achieving superior prognostic discrimination [21,38]. Recent studies have developed clonal gene signatures based on genes whose expression is driven by clonal copy number alterations, demonstrating higher performance in identifying high-risk patients compared to established signatures such as GEP70 and SKY92 [83]. Novel genomic profiling platforms, including the Unique Molecular Assay (UMA) panel, enable comprehensive detection of canonical IgH translocations, copy number alterations, and mutations in 82 genes, supporting precise risk stratification [84]. Integrating copy number signatures that reflect complex structural variants such as chromothripsis into prognostic models significantly improves accuracy, as demonstrated by the Individualized Risk Model for Myeloma (IRMMa), which achieves a

c-index value of 0.726 compared to 0.61 for ISS [11]. These functional programs align with the emerging paradigm of functional genomic classification that transcends anatomical staging to capture biological heterogeneity [85,86].

The translational implications of our findings extend directly to therapeutic decision-making. Pathway-specific alterations identified through CNA profiling can guide the rational selection of targeted agents. For instance, the functional switch from innate immunity in MGUS to DNA repair mechanisms in SMM may highlight a critical intervention window for early therapeutic approaches that may prevent progression to symptomatic MM [2,26]. Furthermore, the enrichment of defensin, chemokine receptors, and olfactory receptor pathways provides novel targets that could disrupt microenvironmental interactions driving disease progression [55]. In high-risk patients, the ISS-dependent functional divergence, particularly PI3K/AKT/mTOR hyperactivation, supports ongoing clinical trials evaluating pathway-specific kinase inhibitors in combination with standard therapies [8,45,87,88]. Similarly, for PCL, the identification of critical adhesion molecule loss and translational dysregulation suggests that targeting the translational machinery through mTOR inhibitors or 4EBP modulators may be particularly effective [41,43].

As therapeutic landscapes rapidly evolve with bispecific antibodies, CAR-T cells, and antibody–drug conjugates, comprehensive genomic characterization becomes essential for optimizing patient selection and predicting resistance mechanisms [13,84]. In this context, achieving Minimal Residual Disease (MRD) negativity has become a standard therapeutic endpoint. However, a subset of MRD-negative patients still experiences relapses, highlighting the limitations of relying solely on tumor burden quantification [89]. Therefore, CNA profiling is not intended to replace current standard MRD testing (e.g., multiparametric flow cytometry or IGH-based sequencing), but rather to synergize with it. While traditional MRD assays quantify the amount of residual disease, CNA profiling characterizes the biological quality and evolutionary potential of the surviving clones. Integrating CNA signatures with MRD monitoring allows for the identification of high-risk subclonal architectures that may persist and drive therapeutic resistance, thereby refining risk stratification and guiding preemptive interventions in the immunotherapy era [90].

Clinically, the incorporation of liquid biopsy approaches—monitoring both ctDNA and circulating myeloma cells (CMMCs) with CNA analysis—will facilitate the non-invasive tracking of clonal evolution and treatment response, which is particularly relevant for patients undergoing CAR-T Therapy [83]. Future investigations should integrate single-cell sequencing with spatial transcriptomics to dissect clonal heterogeneity and microenvironmental interactions at unprecedented resolution [13], while the application of optical genome mapping and long-read sequencing will enable comprehensive detection of complex structural variants that drive high-risk disease [86,91]. Ultimately, the convergence of comprehensive genomic profiling, functional pathway analysis, and clinical outcome data will enable true precision medicine in MM, moving beyond one-size-fits-all approaches to deliver molecularly informed, risk-adapted therapeutic strategies that improve survival while minimizing treatment-related toxicity [1,92].

Author Contributions: Conceptualization: I.V.B., G.P.d.M. and C.A.M.-N.; Data Curation: I.V.B.; Formal Analysis: G.P.d.M. and W.A.S.F.; Writing—Original Draft: I.V.B., G.P.d.M. and J.S.C.; Writing—Review and Editing: G.P.d.M., I.V.B., F.M.C.d.P.P., C.B.M., L.S.d.C., A.K.d.C.M., I.M.F., D.d.S.O., R.M.R., A.P.L.M., K.M.C.d.A., M.d.P.G., M.E.A.d.M., M.O.d.M.F., C.K.N.A., W.A.S.F., E.H.C.d.O., D.P.B. and B.M.D.N.; Project Administration: C.A.M.-N.; Supervision: C.A.M.-N. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the following Brazilian funding agencies: Coordination for the Improvement of Higher Education Personnel (CAPES; to C.B.M); the National Council of Technological and Scientific Development (CNPq) (grant number 404213/2021-9 to C.A.M.N.; grant

number 153210/2024-9 to W.A.S.F.; and Productivity in Research PQ scholarships to M.O.d.M.F., M.E.A.d.M., E.H.C.d.O and A.S.K.); the Cearense Foundation of Scientific and Technological Support (FUNCAP grant number P20-0171-00078.01.00/20 to F.M.C.d.P.P. and M.O.d.M.F. and to CAM-N); and the Evandro Chagas Institute (IEC/SVSA/MS—Brazil). We also thank PROPESP/UFPA for assisting with the publication payment.

Institutional Review Board Statement: All methods were conducted in accordance with the Declaration of Helsinki guidelines and regulations. This study received formal approval from the Research Ethics Committee (REC) of the Fortaleza General Hospital (HGF) via the national ethics platform (Plataforma Brasil), under CAAE number 010496/2022, approval date 4 May 2022.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of the data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Rajkumar, S.V. Multiple Myeloma: 2024 Update on Diagnosis, Risk-Stratification, and Management. *Am. J. Hematol.* **2024**, *99*, 1802–1824. [CrossRef]
2. Ho, M.; Patel, A.; Goh, C.Y.; Moscvin, M.; Zhang, L.; Bianchi, G. Changing Paradigms in Diagnosis and Treatment of Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM). *Leukemia* **2020**, *34*, 3111–3125. [CrossRef] [PubMed]
3. Gowin, K.; Skerget, S.; Keats, J.J.; Mikhael, J.; Cowan, A.J. Plasma Cell Leukemia: A Review of the Molecular Classification, Diagnosis, and Evidenced-Based Treatment. *Leuk. Res.* **2021**, *111*, 106687. [CrossRef]
4. Singh, S.; Peshin, S.; Wertheim, B.C.; Larsen, A.; Chineke, I.; Sborov, D.W.; Green, D.; Liedtke, M.; Okoniewski, M.; Wazir, M.; et al. Outcomes and Treatment Patterns in Primary and Secondary Plasma Cell Leukemia: Insights from a Large US Cohort Study. *Haematologica* **2025**, *110*, 2129–2138. [CrossRef]
5. Maura, F.; Rustad, E.H.; Boyle, E.M.; Morgan, G.J. Reconstructing the Evolutionary History of Multiple Myeloma. *Best Pract. Res. Clin. Haematol.* **2020**, *33*, 101145. [CrossRef]
6. Weiss, B.M.; Abadie, J.; Verma, P.; Howard, R.S.; Kuehl, W.M. A Monoclonal Gammopathy Precedes Multiple Myeloma in Most Patients. *Blood* **2009**, *113*, 5418–5422. [CrossRef]
7. Pawlyn, C.; Davies, F.E. Toward Personalized Treatment in Multiple Myeloma Based on Molecular Characteristics. *Blood* **2019**, *133*, 660–675. [CrossRef]
8. Barreto, I.V.; Machado, C.B.; Almeida, D.B.; Pessoa, F.M.C.P.; Gadelha, R.B.; Pantoja, L.C.; Oliveira, D.d.S.; Ribeiro, R.M.; Lopes, G.S.; de Moraes Filho, M.O.; et al. Kinase Inhibition in Multiple Myeloma: Current Scenario and Clinical Perspectives. *Pharmaceutics* **2022**, *14*, 1784. [CrossRef]
9. Rajkumar, S.V. Multiple Myeloma: Every Year a New Standard? *Hematol. Oncol.* **2019**, *37*, 62–65. [CrossRef]
10. Kastritis, E.; Gavriatopoulou, M.; Theodorakakou, F.; Solia, E.; Ntanasis-Stathopoulos, I.; Malandrakis, P.; Kanellias, N.; Eleutherakis Papaiakovou, E.; Migkou, M.; Spiliopoulou, V.; et al. Validation of the New Ims/IMWG Consensus Genomic Staging (CGS) of High-Risk Multiple Myeloma (HRMM) in a Contemporary Cohort of 1209 Patients. *Blood* **2025**, *146*, 923. [CrossRef]
11. Maura, F.; Rajanna, A.R.; Ziccheddu, B.; Poos, A.M.; Derkach, A.; MacLachlan, K.; Durante, M.; Diamond, B.; Papadimitriou, M.; Davies, F.; et al. Genomic Classification and Individualized Prognosis in Multiple Myeloma. *J. Clin. Oncol.* **2024**, *42*, 1229–1240. [CrossRef] [PubMed]
12. Greipp, P.R.; Miguel, J.S.; Dune, B.G.M.; Crowley, J.J.; Barlogie, B.; Bladé, J.; Boccadoro, M.; Child, J.A.; Harousseau, J.L.; Kyle, R.A.; et al. International Staging System for Multiple Myeloma. *J. Clin. Oncol.* **2005**, *23*, 3412–3420. [CrossRef]
13. Avet-Loiseau, H.; Davies, F.E.; Samur, M.K.; Corre, J.; D'Agostino, M.; Kaiser, M.F.; Raab, M.S.; Weinhold, N.; Gutierrez, N.C.; Paiva, B.; et al. International Myeloma Society/International Myeloma Working Group Consensus Recommendations on the Definition of High-Risk Multiple Myeloma. *J. Clin. Oncol.* **2025**, *43*, 2739–2751, Erratum in *J. Clin. Oncol.* **2025**, *43*, 553. https://doi.org/10.1200/JCO-24-01893.. [CrossRef]
14. Zhang, Y.; Wang, Y. Role of Cytogenetics in Multiple Myeloma: Advancing Diagnosis, Prognosis, and Treatment. *J. Cancer Res.* **2023**, *1*, 1–5.

15. Zhang, C.; Cerveira, E.; Romanovitch, M.; Zhu, Q. Array-Based Comparative Genomic Hybridization (ACGH). *Methods Mol. Biol.* **2017**, *1541*, 167–179. [CrossRef]
16. Ariceta, B.; Aguirre-Ruiz, P.; Castro, A.; Alignani, D.; Vicente, S.; Lopez, A.; Alfonso-Pierola, A.; Tamariz-Amador, L.-E.; San-Miguel, J.; Rodriguez-Otero, P.; et al. Single-Cell DNA Profiling Unveils Clonal Evolution and Identifies Mechanisms of Therapeutic Resistance and Progression in Monoclonal Gammopathies. *Blood* **2025**, *146*, 7445. [CrossRef]
17. Yoon, J.; Jeon, T.; Kwon, J.A.; Yoon, S.Y. Characterization of MYC Rearrangements in Multiple Myeloma: An Optical Genome Mapping Approach. *Blood Cancer J.* **2024**, *14*, 165. [CrossRef]
18. Hosoya, H.; Carleton, M.; Tanaka, K.; Sworder, B.; Syal, S.; Sahaf, B.; Maltos, A.M.; Silva, O.; Stehr, H.; Hovanky, V.; et al. Deciphering Response Dynamics and Treatment Resistance from Circulating Tumor DNA after CAR T-Cells in Multiple Myeloma. *Nat. Commun.* **2025**, *16*, 1824. [CrossRef]
19. Ramberger, E.; Sapozhnikova, V.; Ng, Y.L.D.; Dolnik, A.; Ziehm, M.; Popp, O.; Sträng, E.; Kull, M.; Grünschläger, F.; Krüger, J.; et al. The Proteogenomic Landscape of Multiple Myeloma Reveals Insights into Disease Biology and Therapeutic Opportunities. *Nat. Cancer* **2024**, *5*, 1267–1284. [CrossRef]
20. Cardona-Benavides, I.J.; de Ramón, C.; Gutiérrez, N.C. Genetic Abnormalities in Multiple Myeloma: Prognostic and Therapeutic Implications. *Cells* **2021**, *10*, 336. [CrossRef]
21. D'agostino, M.; Cairns, D.A.; Lahuerta, J.J.; Wester, R.; Bertsch, U.; Waage, A.; Zamagni, E.; Mateos, M.V.; Dall'olio, D.; Van De Donk, N.W.C.J.; et al. Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project. *J. Clin. Oncol.* **2022**, *40*, 3406–3418, Erratum in *J. Clin. Oncol.* **2022**, *40*, 4032. https://doi.org/10.1200/JCO.21.02614.. [CrossRef]
22. Walker, B.A.; Leone, P.E.; Chiecchio, L.; Dickens, N.J.; Jenner, M.W.; Boyd, K.D.; Johnson, D.C.; Gonzalez, D.; Dagrada, G.P.; Protheroe, R.K.M.; et al. A Compendium of Myeloma-Associated Chromosomal Copy Number Abnormalities and Their Prognostic Value. *Blood* **2010**, *116*, e56–e65. [CrossRef] [PubMed]
23. Smetana, J.; Frohlich, J.; Zaoralova, R.; Vallova, V.; Greslikova, H.; Kupska, R.; Nemec, P.; Mikulasova, A.; Almasi, M.; Pour, L.; et al. Genome-Wide Screening of Cytogenetic Abnormalities in Multiple Myeloma Patients Using Array-CGH Technique: A Czech Multicenter Experience. *BioMed Res. Int.* **2014**, *2014*, 209670. [CrossRef]
24. Barwick, B.G.; Gupta, V.A.; Vertino, P.M.; Boise, L.H. Cell of Origin and Genetic Alterations in the Pathogenesis of Multiple Myeloma. *Front. Immunol.* **2019**, *10*, 1121. [CrossRef]
25. Mohyuddin, G.R.; Rubinstein, S.M.; Kumar, S.; Rajkumar, S.V.; Fonseca, R.; Abdallah, N.H.; Calip, G.S.; Wang, X.; Parrinello, C.M.; Sborov, D. Performance of Newer Myeloma Staging Systems in a Contemporary, Large Patient Cohort. *Blood Cancer J.* **2024**, *14*, 95. [CrossRef] [PubMed]
26. Merz, M.; Hielscher, T.; Schult, D.; Mai, E.K.; Raab, M.S.; Hillengass, J.; Seckinger, A.; Hose, D.; Granzow, M.; Jauch, A.; et al. Cytogenetic Subclone Formation and Evolution in Progressive Smoldering Multiple Myeloma. *Leukemia* **2019**, *34*, 1192–1196. [CrossRef]
27. Morgan, G.J.; Walker, B.A.; Davies, F.E. The Genetic Architecture of Multiple Myeloma. *Nat. Rev. Cancer* **2012**, *12*, 335–348. [CrossRef] [PubMed]
28. Manier, S.; Salem, K.Z.; Park, J.; Landau, D.A.; Getz, G.; Ghobrial, I.M. Genomic Complexity of Multiple Myeloma and Its Clinical Implications. *Nat. Rev. Clin. Oncol.* **2017**, *14*, 100–113. [CrossRef]
29. Bolli, N.; Maura, F.; Minvielle, S.; Gloznik, D.; Szalat, R.; Fullam, A.; Martincorena, I.; Dawson, K.J.; Samur, M.K.; Zamora, J.; et al. Genomic Patterns of Progression in Smoldering Multiple Myeloma. *Nat. Commun.* **2018**, *9*, 3363. [CrossRef]
30. Rasche, L.; Chavan, S.S.; Stephens, O.W.; Patel, P.H.; Tytarenko, R.; Ashby, C.; Bauer, M.; Stein, C.; Deshpande, S.; Wardell, C.; et al. Spatial Genomic Heterogeneity in Multiple Myeloma Revealed by Multi-Region Sequencing. *Nat. Commun.* **2017**, *8*, 268. [CrossRef]
31. Winter, J.; Wenghoefer, M. Human Defensins: Potential Tools for Clinical Applications. *Polymers* **2012**, *4*, 691–709. [CrossRef]
32. Cenzano, I.; Cócera, M.; Larrayoz, M.; Campos-Dopazo, L.; Sanz, S.; Bantan, A.; Vilas-Zornoza, A.; San-Martin, P.; Aguirre-Ruiz, P.; Alignani, D.; et al. Stromal and Endothelial Transcriptional Changes during Progression from MGUS to Myeloma and after Treatment Response. *bioRxiv* **2025**. [CrossRef]
33. Yedery, R.D.; Jerse, A.E. Augmentation of Cationic Antimicrobial Peptide Production with Histone Deacetylase Inhibitors as a Novel Epigenetic Therapy for Bacterial Infections. *Antibiotics* **2015**, *4*, 44. [CrossRef]
34. De Veirman, K.; De Beule, N.; Maes, K.; Menu, E.; De Bruyne, E.; De Raeve, H.; Fostier, K.; Moreaux, J.; Kassambara, A.; Hose, D.; et al. Extracellular S100A9 Protein in Bone Marrow Supports Multiple Myeloma Survival by Stimulating Angiogenesis and Cytokine Secretion. *Cancer Immunol. Res.* **2017**, *5*, 839–846. [CrossRef]
35. Lin, C.; Garcia-Gerique, L.; Bonner, E.E.; Mastio, J.; Rosenwasser, M.; Cruz, Z.; Lawler, M.; Bernabei, L.; Muthumani, K.; Liu, Q.; et al. S100A8/S100A9 Promote Progression of Multiple Myeloma via Expansion of Megakaryocytes. *Cancer Res. Commun.* **2023**, *3*, 420–430. [CrossRef]

36. Chen, X.; Zhou, J.; Dong, X.; Xu, Y.; Chen, B. Regulatory Role of E3 Ubiquitin Ligases in Multiple Myeloma: From Molecular Mechanisms to Therapeutic Strategies. *Front. Cell Dev. Biol.* **2025**, *13*, 1620097. [CrossRef] [PubMed]
37. Banerjee, A.; Bhowmick, S.; Vasudevan, S.; Mehta, A.; Agrawal, N.; Sheth, V.; Bhurani, D.D.; Arora, N.; Raychaudhuri, J. Germline Mediated HR Deficiency, Alu Element Duplication, and Immune Pathway Alterations Define Aggressive, Drug-Resistant Multiple Myeloma. *Blood* **2025**, *146*, 7461. [CrossRef]
38. Palumbo, A.; Avet-Loiseau, H.; Oliva, S.; Lokhorst, H.M.; Goldschmidt, H.; Rosinol, L.; Richardson, P.; Caltagirone, S.; Lahuerta, J.J.; Facon, T.; et al. Revised International Staging System for Multiple Myeloma: A Report from International Myeloma Working Group. *J. Clin. Oncol.* **2015**, *33*, 2863–2869. [CrossRef] [PubMed]
39. Chung, C.; Cho, H.J.; Lee, C.E.; Koo, J.H. Odorant Receptors in Cancer. *BMB Rep.* **2022**, *55*, 72–80. [CrossRef]
40. Manteniotis, S.; Wojcik, S.; Göthert, J.R.; Dürig, J.; Dührsen, U.; Gisselmann, G.; Hatt, H. Deorphanization and Characterization of the Ectopically Expressed Olfactory Receptor OR51B5 in Myelogenous Leukemia Cells. *Cell Death Discov.* **2016**, *2*, 16010. [CrossRef]
41. Guardia, G.D.A.; Naressi, R.G.; Buzzato, V.C.; da Costa, J.B.; Zalcberg, I.; Ramires, J.; Malnic, B.; Gutiyama, L.M.; Galante, P.A.F. Acute Myeloid Leukemia Expresses a Specific Group of Olfactory Receptors. *Cancers* **2023**, *15*, 3073. [CrossRef]
42. De Raeve, H.R.; Vanderkerken, K. The Role of the Bone Marrow Microenvironment in Multiple Myeloma. *Histol. Histopathol.* **2005**, *20*, 1227–1250. [CrossRef]
43. Manier, S.; Sacco, A.; Leleu, X.; Ghobrial, I.M.; Roccaro, A.M. Bone Marrow Microenvironment in Multiple Myeloma Progression. *J. Biomed. Biotechnol.* **2012**, *2012*, 157496. [CrossRef]
44. Da Costa Machado, A.K.; Machado, C.B.; Pessoa, F.M.C.D.P.; Barreto, I.V.; Gadelha, R.B.; Oliveira, D.D.S.; Ribeiro, R.M.; Lopes, G.S.; Filho, M.O.D.M.; De Moraes, M.E.A.; et al. Development and Clinical Applications of PI3K/AKT/MTOR Pathway Inhibitors as a Therapeutic Option for Leukemias. *Cancer Diagn. Progn.* **2024**, *4*, 9–24. [CrossRef]
45. Lu, Q.; Yang, D.; Li, H.; Niu, T.; Tong, A. Multiple Myeloma: Signaling Pathways and Targeted Therapy. *Mol. Biomed.* **2024**, *5*, 25. [CrossRef]
46. Hu, S.; Xu, J.; Cui, W.; Jin, H.; Wang, X.; Maimaitiyiming, Y. Post-Translational Modifications in Multiple Myeloma: Mechanisms of Drug Resistance and Therapeutic Opportunities. *Biomolecules* **2025**, *15*, 702. [CrossRef] [PubMed]
47. Alimohammadi, M.; Rahimzadeh, P.; Khorrami, R.; Bonyadi, M.; Daneshi, S.; Nabavi, N.; Raesi, R.; Farani, M.R.; Dehkhoda, F.; Taheriazam, A.; et al. A Comprehensive Review of the PTEN/PI3K/Akt Axis in Multiple Myeloma: From Molecular Interactions to Potential Therapeutic Targets. *Pathol. Res. Pract.* **2024**, *260*, 155401. [CrossRef] [PubMed]
48. Noorolyai, S.; Shajari, N.; Baghbani, E.; Sadreddini, S.; Baradaran, B. The Relation between PI3K/AKT Signalling Pathway and Cancer. *Gene* **2019**, *698*, 120–128. [CrossRef] [PubMed]
49. Karami fath, M.; Ebrahimi, M.; Nourbakhsh, E.; Zia Hazara, A.; Mirzaei, A.; Shafieyari, S.; Salehi, A.; Hoseinzadeh, M.; Payandeh, Z.; Barati, G. PI3K/Akt/MTOR Signaling Pathway in Cancer Stem Cells. *Pathol. Res. Pract.* **2022**, *237*, 154010. [CrossRef]
50. Bloedjes, T.A.; de Wilde, G.; Khan, G.H.; Ashby, T.C.; Shaughnessy, J.D.; Zhan, F.; Houtkooper, R.H.; Bende, R.J.; van Noesel, C.J.M.; Spaargaren, M.; et al. AKT Supports the Metabolic Fitness of Multiple Myeloma Cells by Restricting FOXO Activity. *Blood Adv.* **2023**, *7*, 1697–1712. [CrossRef]
51. Zhu, F.C.; Jiang, D.M.; Zhang, M.H.; Zhao, B. 2,4-Dihydroxy-3′-Methoxy-4′-Ethoxychalcone Suppresses Cell Proliferation and Induces Apoptosis of Multiple Myeloma via the PI3K/Akt/MTOR Signaling Pathway. *Pharm. Biol.* **2019**, *57*, 641–648. [CrossRef]
52. Zhou, Y.; Hong, Z.; Jin, K.; Lin, C.; Xiang, J.; Ge, H.; Zheng, Z.; Shen, J.; Deng, S. Resibufogenin Inhibits the Malignant Characteristics of Multiple Myeloma Cells by Blocking the PI3K/Akt Signaling Pathway. *Exp. Ther. Med.* **2022**, *24*, 441. [CrossRef]
53. Garrido, D.I.; Bove, V.; Matosas, V.; Riva, E. Comparative Survival Analysis Using the International Stratification Score (ISS) in Newly-Diagnosed Multiple Myeloma in the Uruguayan Population. *Med. Pharm. Rep.* **2021**, *94*, 48–52. [CrossRef]
54. Korbecki, J.; Grochans, S.; Gutowska, I.; Barczak, K.; Baranowska-Bosiacka, I. CC Chemokines in a Tumor: A Review of Pro-Cancer and Anti-Cancer Properties of Receptors CCR5, CCR6, CCR7, CCR8, CCR9, and CCR10 Ligands. *Int. J. Mol. Sci.* **2020**, *21*, 7619. [CrossRef] [PubMed]
55. Gilchrist, A.; Echeverria, S.L. Targeting Chemokine Receptor CCR1 as a Potential Therapeutic Approach for Multiple Myeloma. *Front. Endocrinol.* **2022**, *13*, 846310. [CrossRef] [PubMed]
56. Zeissig, M.N.; Hewett, D.R.; Panagopoulos, V.; Mrozik, K.M.; To, L.B.; Croucher, P.I.; Zannettino, A.C.W.; Vandyke, K. Expression of the Chemokine Receptor CCR1 Promotes the Dissemination of Multiple Myeloma Plasma Cells In Vivo. *Haematologica* **2021**, *106*, 316–3187. [CrossRef] [PubMed]
57. Moeinabadi-Bidgoli, K.; Rezaee, M.; Rismanchi, H.; Mohammadi, M.M.; Babajani, A. Mesenchymal Stem Cell-Derived Antimicrobial Peptides as Potential Anti-Neoplastic Agents: New Insight into Anticancer Mechanisms of Stem Cells and Exosomes. *Front. Cell Dev. Biol.* **2022**, *10*, 900418. [CrossRef]
58. Albini, A.; Bruno, A.; Noonan, D.M.; Mortara, L. Contribution to Tumor Angiogenesis from Innate Immune Cells Within the Tumor Microenvironment: Implications for Immunotherapy. *Front. Immunol.* **2018**, *9*, 527. [CrossRef]

59. Lu, K.; Wang, W.; Liu, Y.; Xie, C.; Liu, J.; Xing, L. Advancements in Microenvironment-Based Therapies: Transforming the Landscape of Multiple Myeloma Treatment. *Front. Oncol.* **2024**, *14*, 1413494. [CrossRef]
60. Desantis, V.; Savino, F.D.; Scaringella, A.; Potenza, M.A.; Nacci, C.; Frassanito, M.A.; Vacca, A.; Montagnani, M. The Leading Role of the Immune Microenvironment in Multiple Myeloma: A New Target with a Great Prognostic and Clinical Value. *J. Clin. Med.* **2022**, *11*, 2513. [CrossRef]
61. Solimando, A.G.; Malerba, E.; Leone, P.; Prete, M.; Terragna, C.; Cavo, M.; Racanelli, V. Drug Resistance in Multiple Myeloma: Soldiers and Weapons in the Bone Marrow Niche. *Front. Oncol.* **2022**, *12*, 973836. [CrossRef]
62. Hervás-Salcedo, R.; Martín-Antonio, B. A Journey through the Inter-Cellular Interactions in the Bone Marrow in Multiple Myeloma: Implications for the Next Generation of Treatments. *Cancers* **2022**, *14*, 3796. [CrossRef]
63. Bou Zerdan, M.; Nasr, L.; Kassab, J.; Saba, L.; Ghossein, M.; Yaghi, M.; Dominguez, B.; Chaulagain, C.P. Adhesion Molecules in Multiple Myeloma Oncogenesis and Targeted Therapy. *Int. J. Hematol. Oncol.* **2022**, *11*, IJH39. [CrossRef] [PubMed]
64. Hov, H.; Tian, E.; Holien, T.; Holt, R.U.; Våtsveen, T.K.; Fagerli, U.M.; Waage, A.; Børset, M.; Sundan, A. C-Met Signaling Promotes IL-6-Induced Myeloma Cell Proliferation. *Eur. J. Haematol.* **2009**, *82*, 277–287. [CrossRef] [PubMed]
65. Rojas, E.A.; Gutiérrez, N.C. Genomics of Plasma Cell Leukemia. *Cancers* **2022**, *14*, 1594. [CrossRef]
66. Xu, Y.; Ruggero, D. The Role of Translation Control in Tumorigenesis and Its Therapeutic Implications. *Annu. Rev. Cancer Biol.* **2020**, *4*, 437–457. [CrossRef]
67. Kim, Y.S.; Kimball, S.R.; Piskounova, E.; Begley, T.J.; Hempel, N. Stress Response Regulation of MRNA Translation: Implications for Antioxidant Enzyme Expression in Cancer. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2317846121. [CrossRef]
68. Mahé, M.; Rios-Fuller, T.; Katsara, O.; Schneider, R.J. Non-Canonical MRNA Translation Initiation in Cell Stress and Cancer. *NAR Cancer* **2024**, *6*, zcae026. [CrossRef]
69. Watt, K.; Dauber, B.; Szkop, K.J.; Lee, L.; Jovanovic, P.; Chen, S.; Masvidal, L.; Tandoc, K.; Palia, R.; Topisirovic, I.; et al. Abstract PR002: Hypoxia-Induced Epigenetic Changes Coordinate Transcription Start Site Selection and Translational Control through Remodeling of 5'UTRs. *Mol. Cancer Ther.* **2024**, *23*, PR002. [CrossRef]
70. Cammas, A.; Desprairies, A.; Dassi, E.; Millevoi, S. The Shaping of MRNA Translation Plasticity by RNA G-Quadruplexes in Cancer Progression and Therapy Resistance. *NAR Cancer* **2024**, *6*, zcae025. [CrossRef] [PubMed]
71. Levy, T.; Voeltzke, K.; Hruby, L.; Alasad, K.; Bas, Z.; Snaebjörnsson, M.; Marciano, R.; Scharov, K.; Planque, M.; Vriens, K.; et al. MTORC1 Regulates Cell Survival under Glucose Starvation through 4EBP1/2-Mediated Translational Reprogramming of Fatty Acid Metabolism. *Nat. Commun.* **2024**, *15*, 4083. [CrossRef]
72. Robichaud, N.; Sonenberg, N.; Ruggero, D.; Schneider, R.J. Translational Control in Cancer. *Cold Spring Harb. Perspect. Biol.* **2019**, *11*, a032896. [CrossRef]
73. Truitt, M.L.; Ruggero, D. New Frontiers in Translational Control of the Cancer Genome. *Nat. Rev. Cancer* **2016**, *16*, 288–304, Erratum in *Nat. Rev. Cancer* **2017**, *17*, 332. https://doi.org/10.1038/nrc.2016.27.. [CrossRef]
74. Zatula, A.; Dikic, A.; Mulder, C.; Sharma, A.; Vågbø, C.B.; Sousa, M.M.L.; Waage, A.; Slupphaug, G. Proteome Alterations Associated with Transformation of Multiple Myeloma to Secondary Plasma Cell Leukemia. *Oncotarget* **2017**, *8*, 19427–19442. [CrossRef]
75. Gundesen, M.T.; Lund, T.; Moeller, H.E.H.; Abildgaard, N. Plasma Cell Leukemia: Definition, Presentation, and Treatment. *Curr. Oncol. Rep.* **2019**, *21*, 8. [CrossRef]
76. Manier, S.; Park, J.; Capelletti, M.; Bustoros, M.; Freeman, S.S.; Ha, G.; Rhoades, J.; Liu, C.J.; Huynh, D.; Reed, S.C.; et al. Whole-Exome Sequencing of Cell-Free DNA and Circulating Tumor Cells in Multiple Myeloma. *Nat. Commun.* **2018**, *9*, 1691. [CrossRef] [PubMed]
77. Garcés, J.J.; Bretones, G.; Burgos, L.; Valdes-Mas, R.; Puig, N.; Cedena, M.T.; Alignani, D.; Rodriguez, I.; Puente, D.Á.; Álvarez, M.G.; et al. Circulating Tumor Cells for Comprehensive and Multiregional Non-Invasive Genetic Characterization of Multiple Myeloma. *Leukemia* **2020**, *34*, 3007–3018. [CrossRef]
78. Mithraprabhu, S.; Khong, T.; Ramachandran, M.; Chow, A.; Klarica, D.; Mai, L.; Walsh, S.; Broemeling, D.; Marziali, A.; Wiggin, M.; et al. Circulating Tumour DNA Analysis Demonstrates Spatial Mutational Heterogeneity That Coincides with Disease Relapse in Myeloma. *Leukemia* **2017**, *31*, 1695–1705. [CrossRef] [PubMed]
79. Bolli, N.; Avet-Loiseau, H.; Wedge, D.C.; Van Loo, P.; Alexandrov, L.B.; Martincorena, I.; Dawson, K.J.; Iorio, F.; Nik-Zainal, S.; Bignell, G.R.; et al. Heterogeneity of Genomic Evolution and Mutational Profiles in Multiple Myeloma. *Nat. Commun.* **2014**, *5*, 2997. [CrossRef]
80. Lohr, J.G.; Stojanov, P.; Carter, S.L.; Cruz-Gordillo, P.; Lawrence, M.S.; Auclair, D.; Sougnez, C.; Knoechel, B.; Gould, J.; Saksena, G.; et al. Widespread Genetic Heterogeneity in Multiple Myeloma: Implications for Targeted Therapy. *Cancer Cell* **2014**, *25*, 91. [CrossRef]
81. Lopez Rivera, J.J.; Gomez-Lopera, N.; Moreno-Garcia, D.J.; Orduz-Rodriguez, R.; Combariza-Vallejo, J.F.; Isaza-Ruget, M. Plasma Cell Enrichment and New Genomic Approaches in Multiple Myeloma: A Scoping Review. *J. Appl. Lab. Med.* **2025**, *10*, 1292–1310. [CrossRef]

82. Ha, J.; Cho, H.; Lee, T.G.; Shin, S.; Chung, H.; Jang, J.E.; Kim, S.J.; Cheong, J.W.; Lee, S.T.; Kim, J.S.; et al. Cytogenetic Testing by Fluorescence in Situ Hybridization Is Improved by Plasma Cell Sorting in Multiple Myeloma. *Sci. Rep.* **2022**, *12*, 8287. [CrossRef]
83. Li, J.R.; Wang, C.; Cheng, C. Identifying High-Risk Multiple Myeloma Patients: A Novel Approach Using a Clonal Gene Signature. *Int. J. Cancer* **2024**, *155*, 1684–1695. [CrossRef]
84. Poletti, A.; Taurisano, B.; Mazzocchetti, G.; Lionetti, M.; Martello, M.; Vuong, V.M.; Solli, V.; Marzocchi, G.; Maeda, A.; Vigliotta, I.; et al. Unique Molecular Assay (UMA): A next-Generation Sequencing Targeted Panel for Efficient and Comprehensive Genomic Profiling and Risk Stratification of Multiple Myeloma. *Haematologica* **2025**, *110*, 2436–2450. [CrossRef] [PubMed]
85. D'Agostino, M.; Lahuerta, J.-J.; Wester, R.; Waage, A.; Bertsch, U.; Zamagni, E.; Mateos, M.-V.; Larocca, A.; Dall'Olio, D.; van de Donk, N.W.C.J.; et al. A New Risk Stratification Model (R2-ISS) in Newly Diagnosed Multiple Myeloma: Analysis of Mature Data from 7077 Patients Collected by European Myeloma Network within Harmony Big Data Platform. *Blood* **2020**, *136*, 34–37. [CrossRef]
86. Yang, P.; Zhou, F.; Dong, Y.; Gao, G.; Xue, H.; Liang, X.; Yu, S.; Xu, W.; Ma, Y.; Qin, X.; et al. The Prognostic Value of the MASS in a Multi-Center Cohort of Patients with Newly Diagnosed Multiple Myeloma. *Blood Cancer J.* **2022**, *12*, 134. [CrossRef] [PubMed]
87. Arnulf, B.; Lambert, J.; Karlin, L.; Touzeau, C.; Decaux, O.; Perrot, A.; Petillon, M.-O.; Caillot, D.; Manier, S.; Schiano De Colella, J.M.; et al. Favorable Impact of Patient's Selection on Outcome of Relapsed/Refractory Multiple Myeloma Treated with Idecabtagene Vicleucel (Ide-Cel) Chimeric Antigen Receptor (CAR) T-Cell Therapy; Experience in French Patients (Super-FENIX): An IFM Study from the Descar-T Registry. *Blood* **2025**, *146*, 4076. [CrossRef]
88. Ballesta-Alcaraz, L.; Bernal, M.; Vilchez, J.R.; Palacios, J.A.; Jiménez, P.; Garrido, P.; Gutiérrez-Bautista, J.F.; Ruiz-Cabello, F. Application of Optical Genome Mapping for the Diagnosis and Risk Stratification of Myeloid and Lymphoid Malignancies. *Int. J. Mol. Sci.* **2025**, *26*, 5763. [CrossRef]
89. Costa, L.J.; Derman, B.A.; Bal, S.; Sidana, S.; Chhabra, S.; Silbermann, R.; Ye, J.C.; Cook, G.; Cornell, R.F.; Holstein, S.A.; et al. International Harmonization in Performing and Reporting Minimal Residual Disease Assessment in Multiple Myeloma Trials. *Leukemia* **2020**, *35*, 18–30. [CrossRef]
90. Samur, M.K.; Fulciniti, M.; Aktas Samur, A.; Bazarbachi, A.H.; Tai, Y.T.; Prabhala, R.; Alonso, A.; Sperling, A.S.; Campbell, T.; Petrocca, F.; et al. Biallelic Loss of BCMA as a Resistance Mechanism to CAR T Cell Therapy in a Patient with Multiple Myeloma. *Nat. Commun.* **2021**, *12*, 868. [CrossRef]
91. Slade, M.; Fortier, J.; Fiala, M.; Dhakal, B.; Lee, H.; Kuhr, F.; Swat, W.; Tononi, P.; Manaresi, N.; Ferrarini, A.; et al. Kinetics of Circulating Multiple Myeloma Cells (CMMCs) in Patients Undergoing Standard-of-Care Anti-BCMA Chimeric Antigen Receptor T Cell Therapy for Relapsed/Refractory Multiple Myeloma. *Blood* **2025**, *146*, 5851. [CrossRef]
92. Li, S.; Li, X.; Jin, C.; Liu, W.; Zhao, Y.; Wang, J.; Wang, C.; Hou, J.; Pan, J. A Tandem Bispecific Nanobody CAR (SL1703) T Cells Targeting CD19/BCMA for Refractory or Relapsed Multiple Myeloma as Salvage Treatment after BCMA CAR-T Therapy Failure. *Blood* **2025**, *146*, 5934. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.