RESEARCH ARTICLE
ONCOLOGY

Diseases & Research

Exploring Oncogenic Factors Influence on Multiple Myeloma Progression and Patient Survival

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Backgrounds: Multiple myeloma (MM), one of the most prevalent hematological malignancies, is characterized by the proliferation of plasma cells within bone marrow and concurrent development of osteolytic lesions. The persistence of myeloma cells in the hypoxic bone marrow environment, coupled with their resistance to current therapeutic approaches, often results in relapse. Hence, there is an immediate imperative to decipher the molecular mechanisms underpinning myelomagenesis to pave the way for more efficacious treatment modalities. While prior investigations have predominantly focused on delineating the roles of individual genes in myelomagenesis, this article offers a comprehensive analysis of the current research landscape encompassing four distinct oncogenic gene signatures and their impact on patients' survival outcomes.
Methods: We utilized the most robust RNAseq datasets, GSE13591 and Compass AI8 to evaluate hypoxia, MM bone disease (MBD), dormancy and para-inflammation genes signatures. Fisher's least significant difference post hoc tests were used to determine significance between MM groups while Spearman R-value was calculated to assess regression and correlation among each gene signature. Each signature was grouped as Low and high expression based on median and survival outcomes was plotted using the Kaplan Meier.
Results: Through the collective analysis of these gene signatures, we gain invaluable insights into the intricate molecular cues that initiate and propel MM progression. Furthermore, this article sheds light on the intricate interplay among these oncogenic gene signatures, illustrating how they intersect and synergistically influence MM's pathogenesis.
Conclusion: In conclusion, this article underscores the paramount importance of a comprehensive examination of the four oncogenic gene signatures associated with myelomagenesis. By considering their collective impact on patient survival and elucidating their intricate interrelationships, we significantly augment our understanding of the complex molecular landscape governing MM.
Keywords: Multiple myeloma; Gene Signatures; Survival; Dormancy; Hypoxia.

Introduction

Multiple myeloma (MM) is characterized as a significant B cell neoplasm, distinguished by the clonal proliferation of malignant plasma cells within the bone marrow[1,2] and continues to present treatment challenges due to disease relapse and drug resistance[3]. MM is preceded by monoclonal gammopathy of undetermined significance (MGUS), with a 1.0% annual risk of MGUS progressing to MM[4]. The advanced and more aggressive form of MM is known as Plasma Cell Leukemia (PCL), characterized by an increased number of circulating plasma cells in the peripheral blood[5]. PCL and MM are often accompanied by various clinical complications such as renal insufficiency, hypercalcemia, lytic bone lesions, anemia, and thrombocytopenia[6-9].

Despite advancements in treatment options, MM continues to present significant treatment challenges, largely attributable to the development of drug resistance and the frequent relapse of myeloma cells[10-12]. Notably, myeloma cells reside in the hypoxic environment of the bone marrow, leading to heightened activity of the HIF1α signaling pathway[13-15]. HIF1α is a transcription factor that triggers the expression of genes enabling cells to adapt to hypoxic conditions[16,17]. Dormant myeloma cells, characterized by their resistance to anti-MM treatments, can evade therapeutic interventions and contribute to disease relapse[18-22].

Despite significant progress in identifying genetic markers associated with MM, there remain limitations in utilizing these markers for MM treatment. This study aims to investigate four key oncogenic factors of MM. Firstly, the presence of a high inflammatory flux is observed as myeloma cells closely interact with their microenvironment, stimulating the secretion of inflammatory cytokines by bone marrow cells, thereby supporting MM cell growth[23,24]. Secondly, severe and painful osteolytic lesions develop in MM patients, as myeloma cells not only induce osteo-

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clasts differentiation but also inhibit osteoblasts differentiation[25-27]. These oncogenic factors play a critical role in myelomagenesis and are associated with various complications. Myeloma cells secrete factors that not only enhance bone resorption through increased osteoclastogenesis, but also suppress osteoblastogenesis, resulting in the development of severe bone lesions. On the other hand, bone cells (osteoclasts/osteoblasts) secrete factors that support myeloma growth. Therefore, an elevated MBD expression profile was expected during the course of myelomagenesis, along with a strong correlation with para-inflammation. Multiple myeloma cells reside in the hub of immune cells and produce non-specific misfolded immunoglobulins that are considered to activate immune response and para-inflammation. However, an unchanged para-inflammatory expression profile during myelomagenesis might be due to sustained local immune activation in the bone marrow. We cannot exclude the possibility that several factors, including minor infections, diet, and adipocytes, may also have an activating effect on the immune system. Hypoxia and HIF1a are known to be critical for the activation and differentiation of several immune cells, including macrophages and B cells. Therefore, a strong correlation between MBD and hypoxia, along with para-inflammation, is expected.

Numerous studies have focused on unraveling the molecular mechanisms underlying these MM oncogenic factors. In this study, we provide a comprehensive overview of the gene signatures associated with these four oncogenic factors and their impact on myelomagenesis and patient survival. Additionally, we assess the interrelation between these gene signatures in MM. By elucidating the gene signatures associated with key MM oncogenic factors, this research contributes to our understanding of the molecular mechanisms driving myelomagenesis and associated complications. Furthermore, it may provide valuable insights into potential therapeutic targets for improving patient outcomes in MM.

Methods

This study utilized two datasets, GSE13591 and Compass AI8, both of which were based on CD138 + cells. GSE13591 dataset consisted of a total of 158 subjects, including 5 healthy individuals, 11 with MGUS, 133 with MM, and 9 with PCL. The Compass dataset, on the other hand, included 600 patients (newly diagnosed patients). GSE13591 was only used for to assess the level of gene signatures during MM progression and healthy donors. To construct the gene signatures, specific genes were selected for each signature. The hypoxia signature was based on previous studies[13,28], while the dormancy signature was derived from reference[29]. The para-inflammation signature genes were selected based on reference[30]. Additionally, for the MBD signature, a list of genes along with their references was provided in Supplementary Table S1. To analyze the gene expression, individual gene expressions were first normalized by calculating their median across all patients. Subsequently, the average normalized expression was calculated for each gene signature, and patients were grouped into healthy, MGUS, MM, and PCL categories accordingly. For the Kaplan Meier survival analysis, patients were divided into two groups based on their gene expression levels: low expressing (below median expression) and high expressing (above median expression) groups. Survival outcomes were then analyzed using the Kaplan Meier method. To assess the correlation between the different gene signatures, the Spearman R-value was calculated for each possible combination, providing insights into the interrelationships and potential co-regulation between these signatures.

Results and Discussion

Cancer cells have the ability to enter a quiescent state, known as dormancy, where they remain non-proliferative and non-apoptotic. Dormant myeloma cells have been found to evade therapeutic interventions and can disseminate to distant sites in the body[11,12,17,31-34]. The bone marrow microenvironment plays a crucial role in determining the fate of these dormant myeloma cells[10,23,29,35,36]. Notably, the expression of dormancy gene signatures increases with disease progression in MM, see Fig. 1. In our analysis, we observed that the level of the dormancy signature remains relatively unchanged in individuals with MGUS compared to healthy donors. However, as the disease advances to MM and PCL, a sharp elevation in the level of the dormancy signature is observed (Fig. 1A). Importantly, a high level of dormancy is associated with poor patient survival in MM. To further investigate this, MM patients were categorized into two groups based on the median expression of the dormancy signature (Fig. 1E). These findings align with the established understanding that cancer becomes more aggressive in the advanced stages of MM, frequently leading to relapse and diminishing patient survival. The increase in dormancy levels as the disease progresses provides a plausible explanation for the higher presence of circulating cancer cells, frequent relapses, and the development of drug resistance in advanced stages of MM. By shedding light on the dynamics of dormancy in MM, our analysis enhances the understanding of disease progression and its clinical implications. The observed association between elevated dormancy levels and poor patient's survival underscores the significance of targeting dormant myeloma cells to improve treatment outcomes and prevent disease relapse.

Myeloma cells predominantly reside in the hypoxic microenvironment of the bone marrow, and hypoxia is a well-known oncogenic factor that influences various aspects of tumor progression in all types of cancers, including MM[37]. Hypoxia promotes tumor growth, facilitating angiogenesis, and enhances the dissemination of tumor cells[38,39]. Analysis of the hypoxia gene signatures in MM demonstrates that the expression of hypoxia-related genes is increased not only in the pre-malignant stage (MGUS) but also in MM patients (Fig. 1C). It is widely recognized that in the early stages of MM, the hypoxic bone marrow microenvironment provides a conducive setting for the initial survival and growth of myeloma cells. However, we observed an unexpected decline in the level of the hypoxia gene signature in patients with PCL (Fig. 1C). This decline could be attributed to excessive angiogenesis in later stages of the disease, leading to a decrease in hypoxia within the bone marrow microenvironment[40]. Consistent with previous findings, we found that a high level of hypoxia gene signature is correlated with a poor prognosis in MM patients (Fig. 1G). Hypoxic tumor cells exhibit a general resistance to conventional chemotherapeutic agents and radiotherapy,

thereby promoting tumor growth and metastasis to secondary sites[41-45]. In the context of MM, the central hypoxia-inducible factor, HIF-1α, has been investigated as a potential therapeutic target. Inhibition of HIF-1α has shown promising results in suppressing tumor growth[14-16,46]. Understanding the role of hypoxia in MM progression provides valuable insights into the mechanisms underlying disease development and therapeutic resistance. Targeting hypoxia-related pathways, such as HIF-1α, may offer novel therapeutic strategies to mitigate tumor growth and improve treatment outcomes in MM.

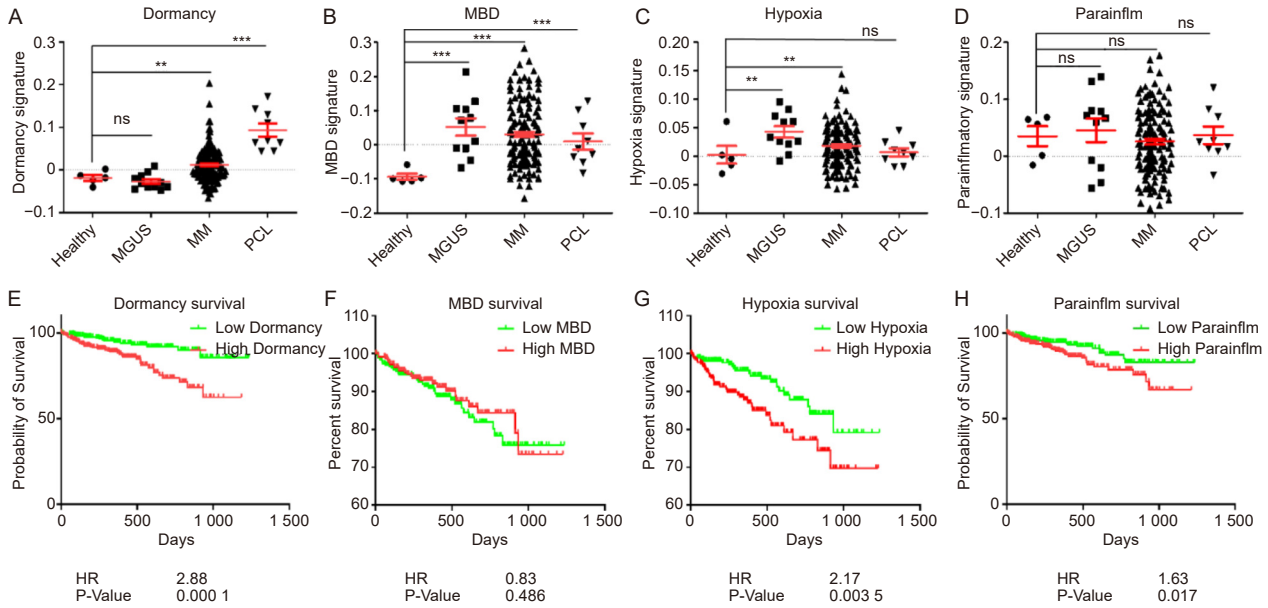

Fig. 1. Expression profile of gene signatures throughout the progression of myeloma and their impact on patient survival.
A. The expression profile of the oncogenic signatures of multiple myeloma: Dormancy.
B. The expression profile of the oncogenic signatures of multiple myeloma: MBD.
C. The expression profile of the oncogenic signatures of multiple myeloma: Hypoxia.
D. The expression profile of the oncogenic signatures of multiple myeloma: Para-inflammation.
E. The influence of these gene signatures on patient survival in the KM plot as Dormancy.
F. The influence of these gene signatures on patient survival in the KM plot as MBD.
G. The influence of these gene signatures on patient survival in the KM plot as Hypoxia.
H. The influence of these gene signatures on patient survival in the KM plot as Para-inflammation.
Statistical significance was determined using ANOVA.

In MM, a malignant plasma cell disorder, a significant majority of patients (approximately 80%) experience the development of bone lesions, which often leads to severe bone pain. These bone lesions not only have a detrimental impact on patients' quality of life but also contribute to the progression of the tumor[47-50]. The formation of bone lesions in MM is facilitated by the inhibition of osteoblastogenesis (the formation of bone-forming cells) and the acceleration of osteoclastogenesis (the formation of bone-resorbing cells)[51-55]. The characteristic MBD signature, associated with bone lesions, is elevated in all stages of MM, including the precursor of MGUS (Fig. 1B). While bone lesions are typically observed in MM patients but not in those with MGUS, several studies have also reported an increased level of bone lesion-inducing factors in MGUS[56-58]. Myeloma cells release factors that promote osteoclastogenesis, while the growth factors secreted by osteoclasts, in turn, support the growth and survival of the tumor[29,59-62]. It is plausible that this vicious cycle of bone lesion formation and tumor progression could be established in the early stages of MM. However, the development of visible bone lesions and the associated phenotype in osteoclasts require some time. Despite the significant impact of MBD on MM pathogenesis, it does not appear to affect patient survival (Fig. 1F). Tumors are complex entities influenced by various interconnected internal and external oncogenic factors that contribute to their growth and survival. One critical event in MM is the dissemination of myeloma cells, which is facilitated by hypoxia (low oxygen levels). Hypoxia has been shown to promote a process called Epithelial-Mesenchymal Transition (EMT)-like feature in myeloma cells[63,64], enabling their spread to multiple sites within the bone marrow[65-67]. In this context, it was crucial to investigate the correlation between a dormancy signature (indicative of cancer cells in a dormant state) and hypoxia. Our analysis revealed a strong correlation (Spearman R-value 4.2) between the dormancy signature and the hypoxia signature in MM patients (Fig. 1E). This finding supports previous evidence indicating that hypoxia promotes a stem cell-like phenotype in myeloma cells[68-71]. Notably, the activation of hypoxia-induced EMT-related mechanisms in multiple myeloma cells reduces the expression of E-cadherin (a protein involved in cell adhesion) and impairs the adhesion of myeloma cells to the bone marrow, thereby facilitating their dissemination from the bone marrow[67]. Myeloma cells are highly secretory and produce a substantial amount of pro-inflammatory cytokines. Interestingly, the level of pro-inflammatory genes remains relatively unchanged during the progression of MM (Fig. 1D). Furthermore, these genes do not appear to influence patient survival, as demonstrated by our meta-analysis

(Fig. 1H). These findings suggest the possibility that myeloma cells induce inflammation by stimulating a pro-inflammatory cascade in the microenvironment.

The correlation analysis in our meta-analysis revealed that the dormancy signature exhibited a weaker correlation with the MBD signature compared to hypoxia (Fig. 2A-C), regardless of the bone cells' ability to switch between dormant and active states[29,69]. While the direct link between hypoxia and osteolysis in MM has not been fully elucidated, the hypoxia signature demonstrated a strong correlation with the MBD signature (Spearman R-value 4.7) (Fig. 2D). Blocking HIF-1α, a key factor in hypoxia response, resulted in reduced bone destruction in MM, along with inhibited tumor growth. However, it remains unclear whether HIF-1α directly affects osteolysis or if the observed effects are primarily due to the decreased tumor burden[14,72]. Previous research has established a connection between the number and size of bone-resorbing osteoclasts and HIF-1[73-75]. In conclusion, both the dormancy and hypoxia signatures were found to be associated with poor prognosis in MM patients. Dormancy displayed a strong correlation with hypoxia but not with the MBD signature. Although MBD is recognized as a critical oncogenic factor in MM, it did not exhibit any association with patient survival; however, it was strongly correlated with hypoxia. Hypoxia often triggers an inflammatory response, and inflammation is known to negatively impact bone resorption. In line with current knowledge, our analysis revealed a significant correlation in hypoxia between the MBD and para-inflammatory gene signatures (Fig. 2D and Fig. 2E), as well as between para-inflammation and the MBD gene signature (Fig. 2F). These findings highlight the dynamic changes in gene signatures throughout the course of MM progression, which exert a crucial influence on patient survival.

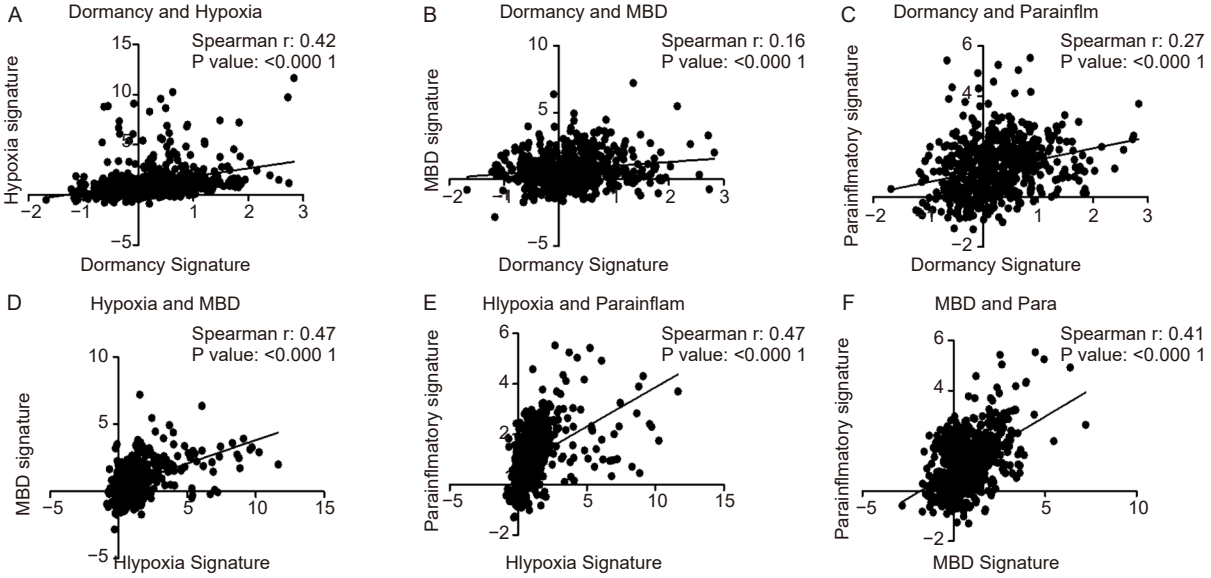

Fig. 2. The correlation between different gene signatures in MM patients. Correlation among these signatures was assessed using Spearman R test.
A. Shows a correlation between hypoxia and dormancy.
B. Represents correlation between dormancy and MBD.
C. Demonstrates correlation between dormancy and para-inflammation.
D. Shows a strong correlation between hypoxia and MBD.
E. Shows a strong correlation between hypoxia and para-inflammation.
F. Represents the relationship between MBD and para-inflammation.

Conclusion

Altogether, our study provides significant insights into the role of four oncogenic gene signatures (hypoxia, MBD, dormancy, and para-inflammation) in the progression of MM and their impact on patient survival. By integrating analyses of these gene signatures, the research enhances our comprehension of the complex molecular interplays governing MM pathogenesis. The findings underscore the importance of a multifaceted approach to studying MM, illustrating how various oncogenic factors interact and contribute to disease progression and patient outcomes. The association of specific gene signatures, such as hypoxia and dormancy, with poor prognosis highlights potential therapeutic targets and underscores the necessity of personalized medicine in treating MM.

Abbreviations

CCNB1, Cyclin B1; CD4, cluster of differentiation 4; DEPDC1B, DEP domain protein 1B; EMT, Epithelial-Mesenchymal Transition; HIF1α, Hypoxia-Inducible Factor (HIF)-1alpha; MBD, myeloma bone disease; MGUS, Monoclonal gammopathy of undetermined significance; MM, Multiple myeloma; PCL, Plasma Cell Leukemia.

Ethical approval and consent to participate

Ethical approval and consent to participate were not required for our study as we did not involve animals or humans. Instead, we utilized the reliable RNAseq datasets, GSE13591 and Compass

AI8, to evaluate gene signatures related to hypoxia, myeloma bone disease (MBD), dormancy, and para-inflammation, using existing data.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Authors' contributions

Conceived the idea and designed the study: MZ and MZK; Relevant literature search: MZ, MZK, AK, GF, PZ and IMK; Critical interpretation and Analysis: MZ, MZK, AK, GF, PZ and IMK; Wrote the manuscript: MZ and MZK; Edited: MZ, MZK, AK, GF, PZ and IMK; Project Administration: MZ; Visualization and Supervision: MZ. All the authors read and approved the final manuscript.

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