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Characterization of monoclonal gammopathy of undetermined significance progression to multiple myeloma through meta-analysis of GEO data

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ABSTRACT

The etiology of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) is still obscure as are the processes that enable the progression of MGUS to MM. Understanding the unique vs. shared transcriptomes can potentially elucidate why individuals develop one or the other. Furthermore, highlighting key pathways and genes involved in the pathogenesis of MM or the development of MGUS to MM may allow the discovery of novel drug targets and therapies.

We employed STARGEO platform to perform three separate meta-analysis to compare MGUS and MM transcriptomes. For these analyses we tagged (1) 101 MGUS patient plasma cells from bone marrow samples and 64 plasma cells from healthy controls (2) 383 MM patient CD138+ cells from bone marrow and the 101 MGUS samples in the first analysis as controls (3) 517 MM patient peripheral blood samples and 97 peripheral blood samples from healthy controls. We then utilized Ingenuity Pathway Analysis (IPA) to analyze the unique genomic signatures within and across these samples.

Our study identified genes that may have unique roles in MGUS (GADD45RA and COMMD3), but also newly identified signaling pathways (EIF2, JAK/STAT, and MYC) and gene activity (NRG3, RBFOX2, and PARP15) in MGUS that have previously been shown to be involved in MM suggesting a spectrum of molecular overlap. On the other hand, genes such as DUSP4, RN14,

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LAMP5, differentially upregulated in MM, may be seen as tipping the scales from benignity to malignancy and could serve as drug targets or novel biomarkers for risk of progression. Furthermore, our analysis of MM identified newly associated gene/pathway activity such as inhibition of Wnt-signaling and defective B cell development. Finally, IPA analysis, suggests the multifactorial, oncogenic qualities of IFNγ signaling in MM may be a unifying pathway for these diverse mechanisms and prompts the need for further studies.

1. Introduction

Multiple myeloma (MM) is a malignant blood disorder characterized by the proliferation of neoplastic plasma cells in the bone marrow (BM). The destructive nature of this proliferation along with the monoclonal antibodies that are systemically released by these cells are the principal drivers of symptoms we observe in patients [1]. However, despite accounting for nearly 20% of all deaths from hematologic malignancies, the pathogenesis of MM is still not completely understood [2]. Via oncogenic mutations in key genes, many signaling pathways have been implicated in the development of MM. These include Ras/Raf/MEK/MAPK, JAK/STAT, NF-kB, and Wnt/B-catenin [3,4]. Recent work has also focused on what is thought to be an equally significant contributor to MM development and progression: the BM microenvironment. Specifically, BM stromal cells have shown to confer MM persistence and growth via synchronous or dyssynchronous cytokine effects [5–7]. Through direct cell-to-cell interaction or paracrine action, the specific niche of the BM can increase risk of MM: whether as an initial driving force or as a promotor of disease progression [8]. For example, through release of cytokines like IL-6 and VEGF increased angiogenesis and plasma cell activation are seen in the BM [8–10]. The importance of the former mechanism is highlighted by the use of anti-angiogenic immunomodulatory drugs (like thalidomide and pomalidomide) to treat MM [4]. Recent studies have additionally proposed mechanisms where BM stroma cells release exosomes with specific miRNAs or proteins that promote MM development and even drug resistance [8,11]. This unique role of the BM microenvironment is supported by recent hypotheses that terminal plasma cell differentiation in MM is confined to the BM [12].

Regarding this immune mediated microenvironment, an area of focus of our group has been the role of TNFa and IFNy. TNFa has historically had strong associations with many hematologic and non-hematologic malignancies via various pathways [13,14]. In MM specifically, TNFa has been shown to induce pro-survival factors that provide resistance to many chemotherapeutic drugs [15]. On the other hand, use of immunomodulatory therapy, which inhibits TNF production, directly blunted this resistance [16]. The role of IFNy is not as straightforward. Previous work has shown IFNy signaling as a promoter of BCL-6 mediated pro-oncogenic states as well as an inducer of chemokine IP-10 mediated MM cell migration, growth, and survival [17,18]. Our lab's recent unpublished data has shown evidence of a reciprocal relationship of IFNy signaling between MM and immune cells that can confer immune-evasion. Yet, recent studies have also shown IFNy can limit MM via driving differentiation, promoting MM cell death, and even augmenting therapy [19,20]. Thus, in addition to understanding what differentially expressed transcriptomes predispose patients to develop MM, we are curious regarding the genetic signature that underlies TNFa and IFNy signaling in pathogenesis and which oncogenic advantages (cell survival/growth vs. shaping the immune environment) they confer.

Finally, a discussion about MM would not be complete without considering its pre-oncogenic form, monoclonal gammopathy of undetermined significance (MGUS). MGUS is characterized by plasma cell production of abnormal monoclonal protein, or M protein. While MGUS itself is asymptomatic, it generally carries a 1% per year risk to progression to multiple myeloma MM [21]. The etiology of MGUS, as well as why it progresses to MM in some cases, remains unclear; moreover, it is not known why some MGUS patients, such as Black Americans, have higher risk to progression to MM [22]. Many of the pathways and mechanisms mentioned earlier in regard to MM may indeed be initiated in the state of MGUS, which could allow for early detection and potential intervention in these patients. For example, many studies have identified various genetic mutations that may drive MGUS to MM progression like RAS, MYC, and TP53 [21]. In terms of our discussion about the importance of the BM microenvironment, VEGF mediated angiogenesis that increase BM vascularization, adipokine effects on the RANKL signaling pathway, and a decrease in SOX-2 specific T cells (important for immune surveillance) have also been suggested to play roles in the transition of MGUS to MM [4,7]. Thus, contrasting the genetic signature of MGUS and MM may better elucidate which genes are potential drivers of disease progression.

Given recent work highlighting novel mechanisms involved in the pathogenesis of MM as well as progression from MGUS, the application of a bioinformatics approach to identify genetic and pathway signatures could allow researchers to better elucidate the role of these mechanisms. Additionally, this can pave way for the of identification and further interrogation of new prognostic markers and even therapeutic targets.

2. Methods

We employed the Search Tag Analyze Resource for Gene Expression Omnibus (STARGEO) to conduct a series of meta-analyses on publicly available genetic data provided through the National Center for Biotechnology Information's (NCBI) Gene Expression Omnibus (GEO): an open database that contains biological samples from publicly funded functional genomics experiments. Our method uses the random effect model to generate meta p-values and effect sizes. The inverse-variance method was used to include the assumption that the studies included are measuring related, albeit different, intervention effects. To perform this random-effects meta-analysis, we adjust standard errors of study specific estimates to include a measure of the degree of variation among the observed intervention effects in different studies. Lastly, we scaled the fold change of each gene's effect by the significance using this formula:

−log10(*P*-value) × fold change. More information on this method can be found in our group's prior paper [23].

Our first meta-analysis was done to identify the differentially expressed MGUS transcriptome. We tagged plasma cells from the bone marrow of 101 patients with MGUS and also bone marrow plasma cells from 64 healthy subjects for our control. Samples were used from series GSE1395, GSE47552, GSE5900, GSE6477, and GSE61597. MGUS was defined using classic criteria of <10% plasma cells in the bone marrow and less than 3 g/dL of monoclonal protein in the blood [4]. The second meta-analysis sought to identify the unique MM transcriptome compared to MGUS. We tagged CD138+ cells from the BM of 383 MM patients and utilized the 101 BM plasma cell samples from patients with MGUS in the first analysis as a control. Patients were diagnosed with MM criteria which includes anemia with hemoglobin <12, elevated creatinine (>1.3 or 50% increase from baseline), hypercalcemia (serum calcium > 10.1 mg per dL), and other clinical findings such as bone pain, fatigue, or weight loss [4]. Samples were used from GSE13951, GSE2113, GSE47552, GSE5900, GSE6477. For our last meta-analysis, we similarly sought to identify the differentially expressed MM transcriptome. Thus, we tagged peripheral blood samples from 517 patients with MM and 97 samples from healthy controls. Samples were taken from series GSE13951, GSE24870, GSE27838, GSE6474, GSE39754, GSE5900, GSE6477, and GSE7116. We focused on genes with statistical significance ($p < 0.05$) and absolute experimental log ratios of at least 0.1. For all three studies, we then utilized analyzed the signatures in Ingenuity Pathway Analysis (IPA). Address comment.

3. Results

3.1. Canonical pathway, disease function, and network analysis

We conducted three meta-analyses to investigate MM and MGUS pathogenesis as well as MGUS to MM progression. For the first meta-analysis, we compared CD138+ plasma cells from MGUS patients to healthy control (MGUS-H), the second compared plasma cells from MM to MGUS patients (MGUS-MM), and the last analysis compared plasma cells from MM patients to healthy controls (MM-H). The purpose of the first two analyses was to study the processes that drive benign gammopathies to malignant ones. The last, MM-H, analysis was performed to illustrate the fundamentals of MM pathology. The results were analyzed in Ingenuity Pathway Analysis to understand the pathways, disease function, and disease networks that define the different stages of disease.

We began our analysis with identifying the top canonical pathways for the three analyses (Table 1). For the MGUS-H analysis, we found these to be EIF2 signaling, regulation of eIF4 and p70S6K signaling, JAK/Stat signaling, leukocyte extravasation signaling, and actin nucleation by ARP-WASP complex. For the MM-MGUS analysis, we identified mitochondrial dysfunction, oxidative phosphorylation, purine nucleotide de novo biosynthesis, antigen presentation, and sirtuin signaling pathway as top pathways (Table 1). Lastly, for the MM-H analysis we found interferon signaling, antigen presentation pathway, primary immunodeficiency signaling, inosine-5′-phosphate biosynthesis, and B cell development as top pathways (Table 1). These results represent the different disease processes that underpin the stages of progression from MGUS to MM.

Next, we used IPA to classify disease functions in our meta-analyses. We looked at disease functions that were predicted to be activated or inhibited and which had an absolute z-score of >2. At the MGUS-H stage, we noted activation of disease functions related to viral replication and loss of function related to the immune response. Likewise, in the MGUS-MM analysis there was activation of disease functions related to viral infection and inhibition of immune processes, but unlike the MGUS-H stage there was also activation of nucleotide synthesis and metabolism pathways likely related to cellular growth. Lastly, for our MM-H analysis, we noted activation of disease functions related to retrovirus and viral infection as in the other two analyses, in addition with disease processes more related to malignancy including inhibition of cell death and reduction in generation of reactive oxygen species (Table 2). Fig. 1 is an

Table 1
Top five canonical pathways comparing CD138+ plasma cells from MGUS, MM, and healthy patients. Degree of overlap between genes in our dataset and the gene set of the canonical pathway and p-values are shown above. Top canonical pathways were found using Ingenuity Pathway Analysis.

	Gene Overlap	*P*-Value
Top Canonical Pathways in MGUS vs Healthy Control		
EIF2 Signaling	39/225	$p < 0.0001$
Regulation of eIF4 and p70S6K Signaling	21/158	$p < 0.0001$
JAK/Stat Signaling	13/81	$p < 0.0001$
Leukocyte Extravasation Signaling	21/199	$p < 0.0001$
Actin Nucleation by ARP-WASP Complex	12/72	$p < 0.0001$
Top Canonical Pathways in Multiple Myeloma vs MGUS		
Mitochondrial Dysfunction	28/171	$p < 0.0001$
Oxidative Phosphorylation	20/109	$p < 0.0001$
Purine Nucleotides De Novo Biosynthesis II	7/11	$p < 0.0001$
Antigen Presentation Pathway	11/39	$p < 0.0001$
Sirtuin Signaling Pathway	33/292	$p < 0.0001$
Top Canonical Pathways in Multiple Myeloma vs Healthy Control		
Interferon Signaling	9/36	$p < 0.0001$
Antigen Presentation Pathway	6/39	$p < 0.0001$
Primary Immunodeficiency Signaling	6/50	$p < 0.005$
Inosine-5′-phosphate Biosynthesis II	2/3	$p < 0.005$
B Cell Development	4/36	$p < 0.05$

illustration of how one of the disease functions, "Cell Death of Cancer Cells," is inhibited.

Lastly, we further characterized pathogenesis in our three analyses using the IPA Network analysis [24]. IPA ranks networks from the Global Molecular Network based on the number of focus genes from given networks that match with our analysis. Significance is given by the p-score (p-score = -log10(*p*-value)). We identified 25 networks for the three analysis and highlighted the top five for each in Table 3. Of note, in the MGUS-H analysis we identified disease networks related to malignancy, indicating malignant changes in the MGUS stage of disease (Fig. 2).

3.2. Top up and downregulated genes and causal analysis

Next, we focus on the top upstream regulators and top up and downregulated genes in our analyses. IPA Upstream Regulator analysis identifies upstream transcription regulators that best reflect our observed genetic expression dataset [24]. The *p*-values are based on the degree of overlap of known effector targets and our gene list. The top up and downregulated genes for our analyses are detailed in Tables 4, 5 and in-text. See Supplementary Tables S1–S3 for p-values and other information.

Table 2
Top activated and inhibited disease functions, with an absolute z-score >2, associated with MGUS and MM for the meta-analyses indicated above. Activation z-scores and p-values are shown.

	Activation Z-Score	P-Value
Disease Functions in MGUS vs Healthy Control		
Replication of HIV	2.707	p<0.0001
Infection of Mammalia	2.468	p<0.0001
Replication of HIV-1	2.402	p<0.0001
Development of Genital Tumor	2.200	p<0.0001
Inflammation of Gastrointestinal Tract	2.112	p<0.0001
Immune Response of Cells	-3.566	p<0.0001
Immune Response of Leukocytes	-3.348	p<0.0001
T Cell Migration	-3.319	p<0.0001
Lymphocyte Migration	-3.226	p<0.0001
Migration of Mononuclear Leukocytes	-2.954	p<0.0001
Disease Functions in Multiple Myeloma vs MGUS		
Synthesis of Purine Nucleotide	2.765	p<0.0001
Metabolism of Nucleic Acid Component or Derivative	2.744	p<0.0001
Viral Infection	2.666	p<0.0001
Metabolism of Nucleotide	2.446	p<0.0001
Synthesis of Nucleotide	2.319	p<0.0001
Engulfment of Cells	-3.968	p<0.0001
Cell Death of Cancer Cells	-3.912	p<0.0001
Necrosis of Malignant Tumor	-3.912	p<0.0001
Binding of Blood Cells	-3.909	p<0.0001
Binding of Leukocytes	-3.902	p<0.0001
Disease Functions in Multiple Myeloma vs Healthy Control		
Infection of Retroviridae	2.703	p<0.0001
Prostatic Tumor	2.579	p<0.0001
Transactivation of RNA	2.559	p<0.0001
Transactivation	2.383	p<0.0001
Infection by RNA Virus	2.300	p<0.0001
Cell Death of Cancer Cells	-3.648	p<0.0001
Necrosis of Malignant Tumor	-3.647	p<0.0001
Cell Movement of Phagocytes	-3.632	p<0.0001
Synthesis of Reactive Oxygen Species	-3.516	p<0.0001
Production of Reaction Oxygen Species	-3.509	p<0.0001

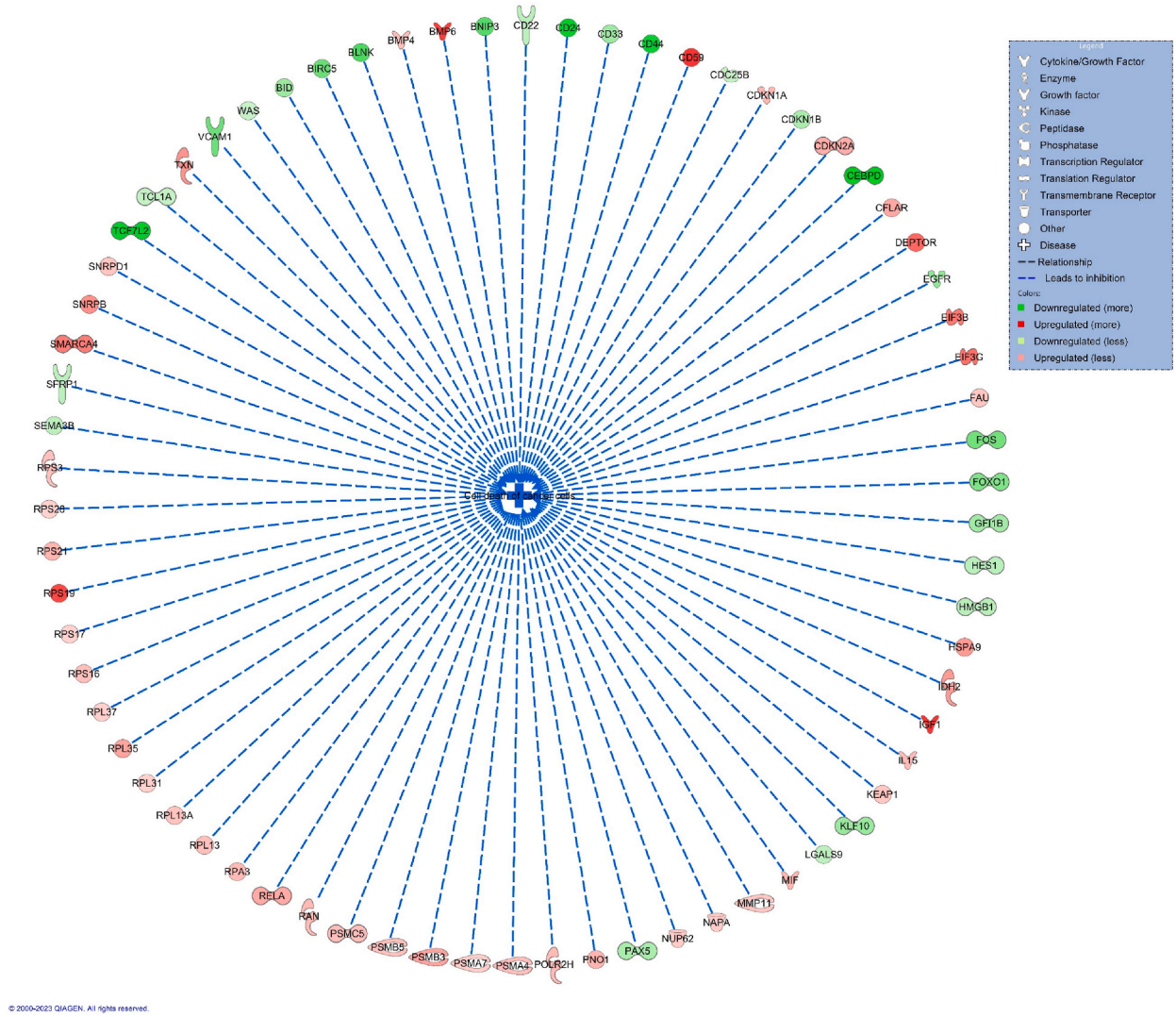

Fig. 1. Inhibition of disease function, "Cell Death of Cancer Cells," in meta-analysis comparing CD138+ plasma cells from multiple myeloma patients to healthy controls. The up and downregulation of the genes illustrated lead to inhibition of cell death (blue lines indicate inhibition of function) and depict how malignant plasma cells avoid cell death. The prediction legend illustrates the up (red) and downregulation (green) of the genes and their identity. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.3. Metanalysis 1: MGUS-H

From our first meta-analysis of MGUS, we identified TP53, TGFB1, and the proto-oncogene MYCN and MYC (with predicted activation) as top upstream regulators. The most upregulated genes included pro-oncogenes such as KIT and MLLT3, which are well-studied in acute leukemia but not yet described in MGUS [25–27]. Another top upregulated gene was NRG3, a myeloma growth factor [28]. Additionally, our analysis highlighted key genes involved in transcription and epigenetic regulation. For example, there was upregulation of RBFOX2, which is involved in alternative splicing during oncogenesis and tumor progression, and of PARP15, a transcriptional repressor with poly(ADP-ribose) polymerase activity and candidate gene for cancer development [29,30]. Also, there was upregulation of the DNA damage-inducible gene GADD45A, found to promote global DNA methylation [31]. There was also downregulation of CKAP2, which functions to maintain centrosome integrity and deletions of which have been detected in numerous malignancies including multiple myeloma [32]. Lastly, we found upregulation of COMMD3, a gene with a recently identified role in humoral activity and B cell migration.

A few genes identified above (KIT, GADD45RA) appear to be regulated by MYC signaling via multiple signaling cascades, such as JUN and NFkB. We then used IPA to identify genes of interest downstream of MYC activation in our dataset. We found upregulation of DUSP4 (overexpression has oncogenic role in MM) [33], the polycomb ringfinger oncogene BMI1 [34] genes involved in ubiquitination and described in solid tumors including UBE2T [35,36], and TXN, which expresses the anti-oxidative enzyme thioredoxin [37]

Table 3
Top five molecular networks associated with genetic differences between CD138+ plasma cells in MGUS, multiple myeloma, and healthy patients as indicated above. Significance is given by the p-score (p-score = -log10(p-value)).

	Score
Top Molecular Networks in MGUS vs Healthy Control	
Cellular Development, Cellular Growth and Proliferation, Connective Tissue Disorders	51
Cancer, Gastrointestinal Disease, Hepatic System Diseas	48
Cancer, Protein Synthesis, RNA Damage and Repair	46
Cell Morphology, Cellular Assembly and Organization, Cellular Function and Maintenance	43
Gene Expression, Protein Synthesis, RNA Damage and Repair	41
Top Molecular Networks in Multiple Myeloma vs MGUS	
Cancer, Gene Expression, Protein Synthesis	52
Infectious Diseases, Inflammatory Disease, Organismal Injury and Abnormalities	52
Cell Death and Survival, Hereditary Disorder, Organismal Injury and Abnormalities	44
Dermatological Diseases and Conditions, DNA Replication, Recombination, and Repair, RNA Post-Transcriptional Modification	42
Cellular Assembly and Organization, Post-Translational Modification, Protein Folding	39
Top Molecular Networks in Multiple Myeloma vs Healthy Control	
Amino Acid Metabolism, Developmental Disorder, Small Molecule Biochemistry	40
Gene Expression, Infectious Diseases, Protein Synthesis	40
Developmental Disorder, Hereditary Disorder, Metabolic Disease	37
Developmental Disorder, Hereditary Disorder, Neurological Disease	37
Hereditary Disorder, Neurological Disease, Organismal Injury and Abnormalities	37

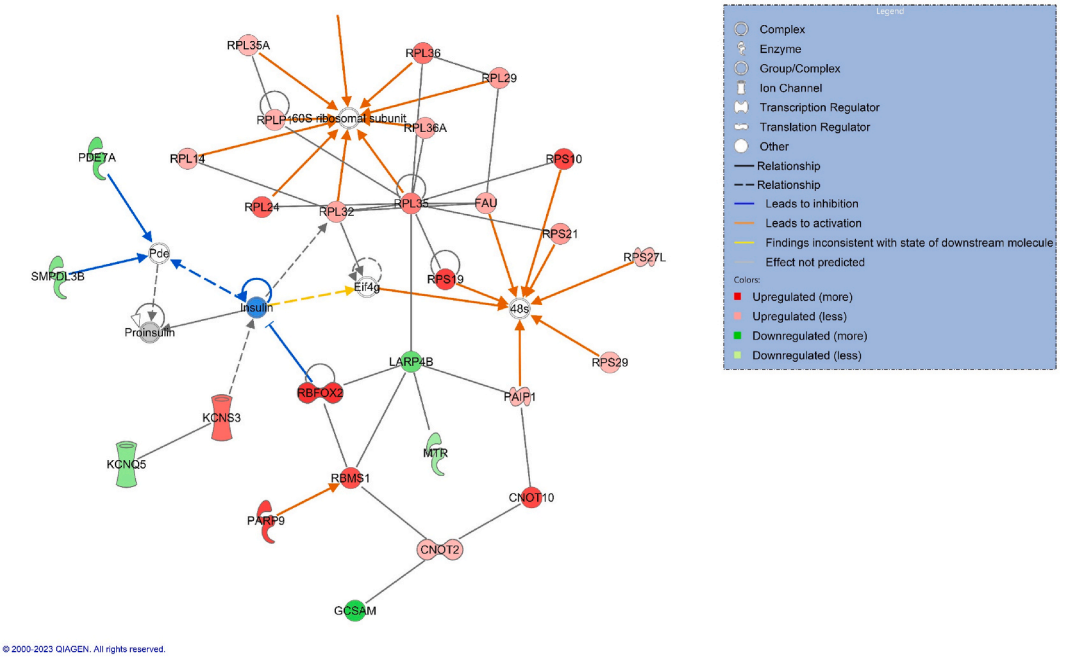

Fig. 2. One of the top disease networks (Cancer, Protein Synthesis, RNA Damage and Repair) in MGUS vs healthy control meta-analysis identified by IPA. Legend indicated up and downregulation of genes and gene function. Solid lines indicate direct relationships and dashed lines indicated indirect relationships.

(Fig. 3).

3.4. Metanalysis 2: MGUS-MM

From our second meta-analysis comparing MM and MGUS, like our first analysis, TP53 (with predicted inhibition), TGFB1, and MYC (with predicted activation) were top upstream regulators. The most upregulated gene was NUP62, a nucleoporin and novel regulator of cell proliferation and inducer of MYC activity [38,39]. MYCBP, MYC binding protein, which enhances c-MYC activity was also upregulated [40]. Our analysis also illustrated pro-oncogenic signaling pathways such as the Wnt pathway through upregulation of the ubiquitin ligase RNF14 and serine/threonine kinase through upregulation of SRPK2 [41,42]. Moreover, we found upregulation of the super-enhancer DUSP4, a phosphatase whose over-activity may drive MM severity [33]. Other up regulated genes included, THHAP1, a regulator of endothelial cell proliferation, NUDT3, part of a family of proteins that are homeostatic checkpoints of

Table 4
Summary of the list genes that are the most up-regulated and down-regulated in our meta-analysis of CD138+ plasma cells between MGUS, multiple myeloma (MM), and healthy patients as indicated. Experimental log ratios are shown.

Top Up-Regulated Genes				Top Downregulated Genes			
MGUS vs Healthy		MGUS vs MM		MGUS vs Healthy		MGUS vs MM	
NDNF	0.573	NUP62	0.858	IGLC1	−2.229	IGLV1-44	−2.280
KIT	0.558	DUSP4	0.547	IGLV4-60	−1.753	IGH	−1.972
HVCN1	0.537	DCLRE1A	0.527	IGLV1-44	−1.673	IGHV3-73	−1.771
COMMD3	0.479	SRPK2	0.527	IGK	−1.187	IGLC1	−1.602
MLLT3	0.466	LAMP5	0.478	IGKV1OR2	−0.841	IGLJ3	−1.478
NRG3	0.446	NUDT3	0.473	IGKC	−0.754	IGLV4-60	−1.471
RBFOX2	0.428	THAP1	0.460	IGKV1-17	−0.731	IGKV1-17	−1.446
UBALD2	0.420	MYCBP	0.448	CKAP2	−0.592	IGK	−1.391
PARP15	0.395	RNF14	0.411	CD81	−0.557	IGKV1OR	−1.381
GADD45A	0.379	KCNN3	0.407	CTSH	−0.528	HLA-DR4	−1.325

Table 5
Summary of the list genes that are the most up-regulated and down-regulated in our meta-analysis of CD138+ plasma cells between multiple myeloma and healthy patients. Experimental log ratios are shown.

Top Up-Regulated Genes		Top Downregulated Genes	
Multiple Myeloma vs Healthy		Multiple Myeloma vs Healthy	
NDNF	0.953	IGHD	−1.756
HGF	0.902	IGLV3-19	−1.413
DKK1	0.894	IGHM	−1.370
CHSY3	0.894	IGKV4-1	−1.305
CPEB4	0.840	IGLV2-23	−1.264
PARP14	0.814	IGHV3-23	−1.232
FRZB	0.803	IGLV1-40	−1.210
MSANTD4	0.803	IGL	−1.177
HIST1H1C	0.734	IGLV1-36	−1.149
PARP9	0.714	IGLL1/IGLL	−1.144

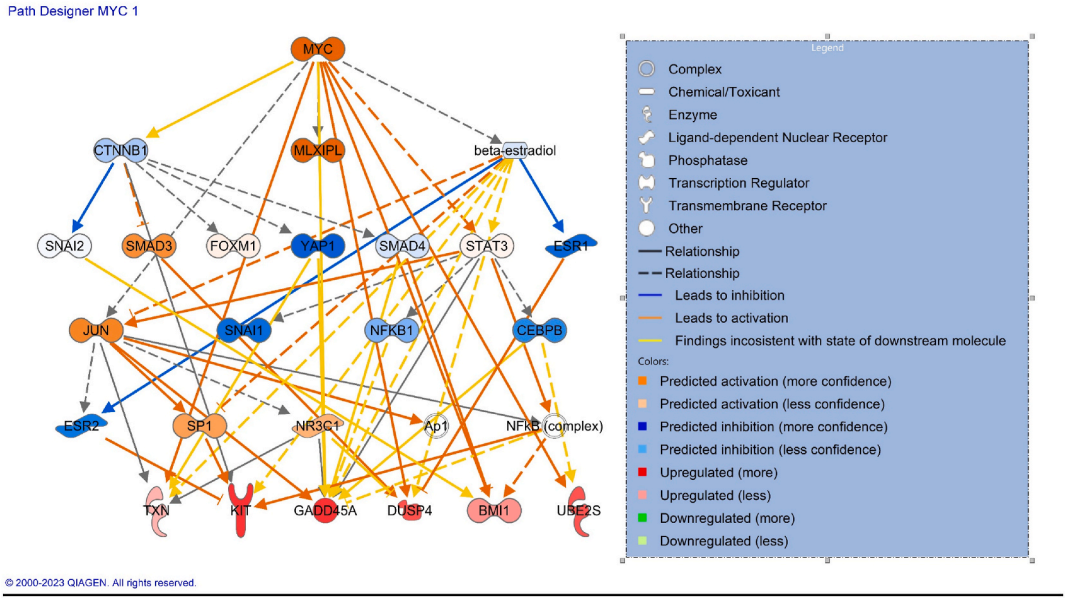

Fig. 3. Role of MYC signaling in MGUS. Results generated from MGUS vs healthy meta-analysis and genes above play various roles in malignancy, suggesting changes in the MGUS stage of disease that predispose patients to developing multiple myeloma. See legend for relationship between genes.

nucleoside metabolism and also modulate cell migration, and lysosomal associated membrane protein LAMP5, which was recently identified in single-cell RNA sequencing of MM patients and may play a significant role in disease [43–45]. Lastly, we found upregulation of KCNN3, an ion channel, which has previously been shown to impart drug resistance in ovarian cancer, but is only recently being identified as differentially expressed in MM [46,47].

3.5. Metanalysis 3: MM-H

Lastly, we describe the regulators and changes in gene expression from our MM vs healthy meta-analysis. Top regulators included IFNγ, TNF, the oncogenic transcription regulator SMARC4, and CNOT7 (with predicted inhibition). We found inhibition of Wnt-signaling through stark upregulation of DKK1 (correlated with osteolytic lesions in MM) and the Wnt-binding protein antagonist FRZB [48,49]. We also noted increased B cell survival through upregulation of the ADP-ribonyltransferase and B cell survival regulator PAPR14 and CPEB4, a gene required for cell cycle progression [50,51]. Additionally, apoptotic signaling was diminished through downregulation of CNOT7 (limits cell proliferation) [52], genes involved in lysosomal disruption during apoptosis such as cathepsin H and lysozymes, the apoptotic Bcl-2 family protein BNIP3 [53], and the pattern recognition receptor NOD2 (involved in autophagy) [54]. B cell development was impaired through downregulation of essential genes such as BLNK, a linker protein involved in B cell receptor signaling [55]. Epigenetic changes were reflected by upregulation of the histone genes such as histone 1 genes HIST1H1C/1H2BD. Among histone 1's related pathways are E2F-mediated DNA replication and hypoxia-independent gene expression [56]. Additionally, we found upregulation of tumorigenic genes such as neuron derived neurotrophic factor, NDNF [57], and hepatocyte growth factor, HGF, which has yet to be described in MM [58]. Interestingly, pathway analysis demonstrated that this diverse set of disease processes are downstream of IFN-γ signaling. Several genes identified described above (PARP14, NOD2, DKK1, FRZB, and CREB4) appear to be regulated by INF-γ signaling via multiple signaling cascades, such as STAT, MYC and NFkB. INF-γ signaling seems to be implicated in B cell development, increased cell survival and proliferation, antigen presentation, and autophagy (Fig. 4).

4. Discussion

There remains much to be learned about the pathogenesis of MGUS and Multiple Myeloma. Here, we use meta-analysis of public data using the STARGEO platform to search for deeper insights into disease pathogenesis and to identify potential therapeutic drug targets. We conducted three meta-analyses comparing MGUS plasma cells to healthy controls, Multiple Myeloma plasma cells to healthy controls, and Multiple Myeloma plasma cells to MGUS plasma cells.

In our first analysis comparing MGUS plasma cells to healthy controls, we identified EIF2/EIF4/p70S6K signaling and JAK/STAT signaling as top canonical pathways. EIF2, EIF4, and p70S6K, signaling have previously been described as three canonical pathways that play a role in translational regulation that are differentially expressed in the spectrum of disease spanning MGUS and Multiple Myeloma. EIF2 in particular catalyzes the first step of protein synthesis initiation and has been shown in multiple meta-analyses to be significantly deregulated in Multiple Myeloma pathogenesis [59]. Prior research has shown that JAK/STAT pathway is aberrantly and constitutively active in MM. Recent studies have found that inhibition of JAK/STAT suppressor genes may be the cause of this aberrant activation and may offer potential use as a predictive factor in the transformation of MGUS to MM [60]. We noticed that viral replication was among the top disease functions in our MGUS analysis. EBV has been shown in the past to be more clinically prevalent in transplant patients with MGUS when compared to healthy controls [61], perhaps suggesting a viral component to MGUS pathogenesis.

Among the top upstream regulators included TP53, TGFB1, and proto-oncogenes MYC and MYCN. TP53 is a tumor-suppressor gene that is commonly mutated in many cancers. In MGUS and MM, it has been shown that TP53 alterations increase across disease progression [62]. Since MGUS is a precancerous precursor of MM, it is no surprise that many of the top upstream regulators in our analysis were pro-tumorigenic. TGFB1 is a cytokine whose inhibition has been shown to cause suppression of MM cell growth [63]. Furthermore, MYC signaling has been shown to be differentially expressed in MM when compared to MGUS [64]. These pro-tumorigenic markers can be used to track the progression of malignant transition of MGUS.

Indeed, most of the top upregulated genes in this analysis themselves were involved in cancer progression. KIT is a hematopoetic growth factor with tyrosine kinase activity that has been shown to be expressed in MGUS and is putatively a specific oncogenic pathway in MM [65]. MLLT3 is a proto-oncogene that is enriched in HSCs and that governs their self-renewal [66]. RBFOX2 is a splicing factor which plays a role in oncogenesis through alternative splicing [67]. PARP15 is a candidate gene for cancer development and has recently been shown to be a potential therapeutic target for patients with acute myeloid leukemia [68]. NRG3 is encodes for tyrosine kinase receptors and is a myeloma growth factor that is overexpressed in myeloma plasma cells when compared to normal controls [69]. Taken together, these results indicate that MGUS is a precancerous state in which multiple oncogenetic factors are upregulated, many of which can potentially be used to track evolution into MM.

Our second analysis compared MM samples directly with MGUS samples in a head to head analysis. We identified mitochondrial dysfunction, oxidative phosphorylation, purine nucleotides de novo biosynthesis, and sirtuin signaling as top canonical pathways. These pathways provide insight into the malignant transformation of MM from MGUS. Dysregulated mitochondrial biogenesis has previously been shown to play a major role in myeloma progression, perhaps due to increased cytosolic iron burden, which promotes oxidative damage [70]. The increased reliance of MM on oxidative phosphorylation has further been elucidated with novel anti-oxidative phosphorylation drugs that have shown antimyeloma activity [71]. Additionally, sirtuins are a class of histone deacetylases that are differentially expressed in many cancers and play an active role in regulating tumor processes [72]. Recent research has shown that sirtuin signaling is an important mechanism of drug resistance in myeloma, perhaps indicating the importance

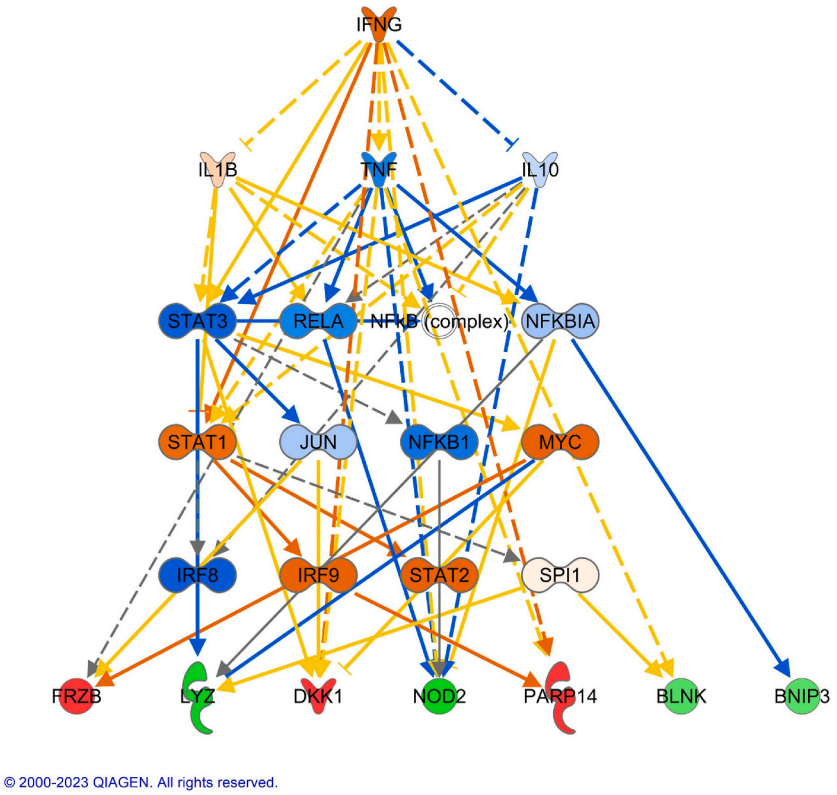

Fig. 4. Role if interferon-y in MM pathogenesis. IFNy signaling is linked to several disease processes such as Wnt signaling, inhibition of cell death, epigenetic regulation, and others through influence of downstream genes discussed. See prediction legend from Fig. 3.

of developing sirtuin inhibitors for future myeloma treatments [73].

Among the top upregulated genes in our head-to-head analysis were NUP62, DUSP4, DCLRE1A, SRPK2, LAMP5, NUDT3, THAP1, RNF14, and KCNN3. Many of these genes have been shown to play some active role in cancer progression. NUP62 is a nucleoporin that regulates nuclear trafficking and has been linked to regulation of cell proliferation in squamous cell carcinoma [74]. Interestingly enough, it is the same nuclear transporter for MUC1-C which has been shown to induce MYC transcription in MM [75,76]. DUSP4 is a phosphatase that has been shown to be upregulated in MM and functions as a super-enhancer [77]. DCLRE1A is a DNA cross-link repair protein that is overexpressed in plasmactyomas, including myeloma [78]. SRPK2 is a serine protein kinase that is upregulated in multiple cancers and promotes growth and migration specifically in colon cancer [79]. LAMP5 is a lysosome membrane associated protein that is overexpressed in multiple myeloma as seen through single cell RNA sequencing [80]. Furthermore, LAMP5 expression is associated with poorer prognosis in patients with gastric cancer [81]. NUDT3 is a Nudix protein that possesses mRNA decapping activity in cells and modulates cell migration in breast cancer, but has not yet been shown to have significant expression in MM [82]. THAP1 is human nuclear factor that is a regulator of endothelial cell proliferation through modulation of the pRB/E2F cell cycle genes [83]. RNF14 is an E3 ubiquitin ligase that modulates Wnt pathway activity and has recently been shown to activate oncogenes via protein stabilization, thus being an essential gene for cancer cell survival [84]. Lastly, KCNN3 is an ion channel that is upregulated by over 16 fold in bortezomib-resistant myeloma cells and offers potential utility as a marker of drug resistance in MM [85]. Our head to head analysis offers insight into the malignant transformation of MGUS to MM. The majority of upregulated genes are pro-oncogenic targets, while a few of them have not yet shown much association with MM. These results mark an attempt to discover new targets to determine prognosis and therapy for MM.

Our last analysis compared MM samples to healthy controls. We identified IFNγ signaling, primary immunodeficiency signaling, B cell development, and antigen presentation as the top canonical pathways. The role of IFNγ in MM remains mixed and unclear. IFNγ has been shown to limit MM and even drive differentiation. Moreover, IFNγ may promote MM cell death and augment therapy [86]. In contrast, IFNγ signaling promotes B cell-intrinsic induction of the pro-oncogene BCL-6 [87]. IFNγ can also work synergistically with other activation signals, such as CD40, to increase BCL-6 expression. These studies have led to interest in targeting BLC-6 in MM. Furthermore, IFNγ can induce expression of the chemokine IP-10 that can bind CXCR3 in plasma cells and MM cells to control migration to the bone marrow and regulate growth and survival of MM cells [88]. Lastly, our unpublished data at the Benson Lab suggests IFNγ can even mediate immune-evasion in MM. More remains to be understood of how IFNγ contributes to MM and how to modulate it for therapy. B-cell development and antigen presentation were other canonical pathways. B-cell development is controlled by a coordination of transcription factors, including X-box binding protein 1 and PAX5. These genes are involved in the pathogenesis of

MM, and studies with transgenic mice have shown that their overexpression yields a myeloma-like phenotype [89]. Although the upregulation of antigen presentation may seem antithetical to MM progression, recent evidence illustrates increased antigen presentation to T-regulatory cells, leading to immune tolerance [90].

Top upregulated genes in our analysis included FOXP2, NDNF, HGF, DKK1, PARP14, and HISTH1C. FOXP2 is a neuronal transcription factor which is known to cause speech defects, but more relevantly, whose overexpression is significantly seen in both MGUS and MM [91]. NDNF is a neuron derived neurotrophic factor that bind to MM cell receptors to initiate a signaling cascade that is critical to the interaction of MM with bone and stoma, thereby allowing for MM tumor progression [92]. HGF is a hepatocyte growth factor that plays a critical role in the plasma cell microenvironment and is thought to promote angiogenesis and bony lesion formation [93]. DKK1 is an inhibitor of Wnt signaling pathway and is widely expressed in myeloma. It plays a critical role in bone physiology and activates osteoclasts, leading to the classical bone lesions seen in MM [94]. Inhibition of DKK1 offers promise in stemming myeloma bone disease. PARP14 is a polyADP-ribose polymerase that is a key regulator of B-cell survival. It is highly expressed in myeloma plasma cells and its overexpression rescues myeloma cells from apoptosis by binding and inhibiting Jun N-terminal kinase (JNK) signaling [95]. HIST1H1C is a part of the histone linker protein family and is frequently mutated at diagnosis of MM, suggesting an epigenetic component to pathogenesis [96].

Our meta-analysis contributes to a more inclusive understanding of the pathogenesis of MGUS and its transition to MM, illustrating the gene activity that control disease progression and offering multiple possible targets for therapeutic intervention. However, this study is not without its limitations. Firstly, considering that the data utilized is from a large public source and compiled from multiple independent studies, information on patient characteristics/demographics is not readily available. Thus, limitations to data analysis and external application of results due to lack of information on heterogeneity of the patient samples and potential confounders should be taken into account. However, genomic and proteomic data, while robust and offering a global view of disease function and patterns, only paints a correlative picture and cannot make causative claims without more direct experimentation follow up. Additionally, significant differences in how samples are collected, processed, and analyzed amongst the studies utilized can also introduce errors in transcriptomics meta-analysis. The purpose of this study is to identify potential genes and pathways that may not have previously been recognized to play a role in disease function and begets the need for follow up studies to specifically investigate these in a more robust manner. Thus, our results offer a launching pad for future studies to further elucidate the pathogenies of MGUS and MM as well as the progression of MGUS to MM.

Author contributions

Jihad Aljabban; Sharjeel Syed; Saad Syed; Michael Rohr: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Mohamed Mukhtar; Hisham Aljabban; Fracesca Cottini; Mohammed Mohammed: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Tiffany Hughes; Taylor Gonzalez: Performed the experiments.

Maryam Panahiazar; Dexter Hadley; Don Benson: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17298.

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