# Understanding the multiple biological aspects leading to myeloma

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Cancer should be considered in the context of its normal cellular counterpart, and in the case of myeloma, this is a normal plasma cell which exists to produce functional antibody. In this respect, myeloma arises as a consequence of the deranged biological behavior of a plasma cell that has undergone a complex development process. This plasma cell differentiation process has been shaped by evolution and the need to resist infection by the production of effective antibodies.[1,2] The description of the "Molecular Hallmarks" of cancer provides an excellent framework against which to consider the ways in which a normal plasma cell can become cancerous.[3] While the mechanisms underlying this transformation process generally involve the acquisition of DNA mutations over time, it is becoming increasingly recognized that epigenetic changes play an equally important function.[4,5]

This mechanistic approach to treatment is one of the key tenets of modern medicine, where the overall aim is to understand the pathological basis of the disease such that it can be manipulated therapeutically. If this is the case, then the problem of curing myeloma can be viewed simply as an issue of understanding what is underlying the normal behavior of the normal plasma cell which has become deregulated to give rise to myeloma. Here we provide a structure, based on relevant publications, that may be helpful to devise future research strategies. Many of the aspects concerning the generation of myeloma have come from a limited number of clinical and laboratory systems which have been extensively investigated. Despite this, the application of novel technologies to these systems can continue to yield important new evidence.

## Aspect 1. The clinical behavior of cases with myeloma

One of the key insights into myeloma comes from an understanding of the clinical behavior of the disease. A number of distinct clinical phases of myeloma can be recognized, including monoclonal gammopathy of undetermined significance (MGUS) and asymptomatic or smoldering multiple myeloma (SMM).[6] A recent study has suggested that all cases of myeloma pass through a MGUS phase, but it is often unrecognized or subclinical.[7] While both these disease phases lack the clinical features of myeloma, they do share some of the genetic features of symptomatic myeloma.[8] In contrast, symptomatic multiple myeloma (MM) is defined by clinical symptoms and evidence of end organ damage.

A characteristic feature of myeloma cells is the requirement for an intimate relationship with the bone marrow microenvironment where plasma cells are nurtured in specialized niches that maintain their survival long term and protect them from drug-induced apoptosis.[9] However, with disease progression, clonal cells tend to develop the ability to proliferate at sites outside of the bone marrow, manifesting as extra-medullary myeloma (EMM) and plasma cell leukemia (PCL).[10,11] These cells constitute the end stages in the multistep transformation process from normal to malignant plasma cells.

This multistep progression system provides us with a system to understand how acquired genetic and epigenetic changes contribute to disease progression. The basic hypothesis being that progression events collaborate with etiological events to push a clonally-damaged cell through a series of transformation steps eventually leading to PCL. What is now realized is that there is intraclonal heterogeneity within the pre-dominant myeloma clone, and that subtle variation in biological behavior associated with these variants, combined with Darwinian natural selection, mediates disease progression and the development of treatment resistance.[12]

## Aspect 2. Environmental and inherited contribution

Epidemiological studies have shown risk factors for the development of MM including increasing age, male gender, familial background and a past history of MGUS.[13] MGUS is a common pre-malignant disorder found in 3.2% of Caucasians aged 50 years or older.[14] It is associated with an annual actuarial risk of progression to MM of 1%.[7,15] Environmental risk factors have also been implicated in increasing MM risk, including obesity,[16,17] immune dysfunction (including auto-immune disease, HIV and transplantation),[18–20] and agricultural or industrial exposure to chemicals, pesticides or radiation.[21,22] A key hypothesis that has been addressed in numerous studies is that genetic variation governing individual response to environmental exposures may mediate some of the familial aggregation seen in MM. The descriptions of families with more than one case of MM support the suggestion that there is an underlying genetic predisposition with an increased relative risk of developing MM for first degree relatives (increased risk of developing MM (RR=2.1; 95%CI: 1.6-2.9) and of developing MGUS (RR=2.1; 95%CI: 1.5-3.1)).[23] There is reportedly a racial contribution to the risk of developing MM,[24] with a greater prevalence of MGUS and MM in African Americans.[24,25] However, it is likely that other factors influence this risk, such as inequalities in access to care and/or confounding effects due to environment and behavioral factors.[26–28] Molecular epidemiological approaches have been used to gain insights into the earliest genetic factors leading to the development of myeloma. An increased risk of developing myeloma is associated with 7 genetic loci located at 2p, 3p, 3q, 6p, 7p, 17p and 22q. Such inherited variation accounts for approximately 13% of the familial risk of myeloma. Further studies are required to gain insight into the functional consequences of alterations at these loci. Potential genes include *DNMT3A* or *CBX7* as they are already implicated in other cancers.[29,30] Given the sample size and the submaximal linkage disequilibrium in these GWAS studies, it is probable that many other genetic loci remain unidentified.[29,30]

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### Aspect 3. Normal plasma cell development

Understanding the behavior and developmental processes giving rise to a normal plasma cell is crucial if we are to understand how these processes are deregulated to give rise to a malignant plasma cell. Humans have evolved in the context of a constant requirement to resist infections, and antibodies are key effectors of this process. A reductionist approach to the description of a plasma cell is that it is simply a specialized antibody-producing cell. Such a cell, however, has a number of important behavioral features to which it must conform if it is not to become malignant. One of these key characteristics is that once formed in response to an infection, it should undergo apoptosis when it is no longer required. It should also be able to survive long term to produce long-term immunological memory for the infection against which it was generated.[2] Understanding the mechanisms underlying the deregulation of these key biological features is likely to give insights into the process of myelomagenesis.

We know that the derangement of developmental processes often underlie the process of carcinogenesis and the same is true in myeloma. Following the rearrangement of their immunoglobulin genes to generate a functional B-cell receptor, B cells leave the bone marrow as naive B cells. After an encounter with their cognate antigens, activated B cells migrate to the germinal center. Within the germinal center, B cells that express a functional B-cell receptor undergo affinity maturation in response to antigen presented on antigen-presenting cells. This process requires that the DNA encoding the hypervariable regions of the immunoglobulin heavy chain (IgH) gene undergoes somatic hypermutation (SHM) to produce highly specific and avid antibodies.[1]

The functionality of these antibodies is increased by class switch recombination (CSR), which produces antibodies of different immunoglobulin (Ig) isotypes. CSR is a region-specific deletional recombination reaction which replaces one switch region with another.[31] Mechanistically, both SHM and CSR require the expression of activation-induced deaminase (AID)[32] and are mediated by the generation of double-strand DNA breaks (DSB) in the Ig loci. Although AID-induced DSBs are mostly repaired locally, they can be joined to DSBs occurring elsewhere in the genome leading to aberrant chromosomal translocations, one of the central molecular hallmarks of myeloma.[1]

Another of the key developmental challenges for a normal plasma cell is the effective generation of antibodies. Central to this process is an ability to differentiate from an immature B cell, located within a germinal center, to a mature antibody-secreting plasma cell located in the bone marrow. This differentiation process requires cessation of cell cycle, compaction of chromatin, and silencing of cellular functions unnecessary for antibody production, at the same time as switching on key programs required to make and secrete antibodies. Checkpoints in development have been identified as key features of these biological systems where cells that fail quality control can be deleted *via* apoptosis.[31] For example, one effective developmental checkpoint is the ability to make and correctly fold nascent antibody.[33]

Normal plasma cell differentiation is controlled by the coordinated regulation of transcription factors. Interferon regulatory factor 4 (IRF4) down-regulates BCL6, resulting in the upregulation of B-lymphocyte-induced maturation protein 1 (BLIMP1, also known as PRDM1), leading to the downregulation of paired box gene 5 (PAX5) and upregulation of X box binding protein 1 (XBP1). The expression of IRF4, BLIMP1 and XBP1 are necessary for the ongoing survival of plasma cells.[31] XBP1 is the transcription factor that is key in mediating the final stages of plasma cell development.[34] It is regulated by inositol-requiring enzyme 1α (IRE1α), a key sensor of unfolded protein and cellular stress in the endoplasmic reticulum.[33] IRE1α mediates the splicing of XBP1 to XBP1s, its active transcriptional state, which provides key growth and survival signals, as well as stimulating the production of genes necessary for Ig production and the unfolded protein response (UPR).[35–38] These genes are involved in the pathogenesis of myeloma, and transgenic mice over-expressing XBP1s develop a syndrome that recapitulates some of the features of myeloma.[36]

### Aspect 4. The cell biology of myeloma and the role of the bone marrow niche

Having exited the germinal center, normal plasma cells migrate to the bone marrow where they either relatively rapidly undergo apoptosis after cessation of the immune response, or they migrate to specialized niches where they can survive for many years as long-lived plasma cells providing serological memory. Competition for access to this bone marrow niche seems to be[38,39] important in maintaining the immune response long term, as well as immortalizing abnormal plasma cells.[39,40] Understanding how myeloma plasma cells interact with and come to dominate access to such a niche is important in understanding how the process of myeloma is initiated and subsequently progresses.

A series of cell biological studies have established our key understandings of how a myeloma cell survives in relation to its local environment. These investigations have established the importance of several cytokines (including IL-6, TNFα, BAFF, IGF and HGF), adhesion molecular networks (including VLA4, VCAM1, Syndecan-1), and the cellular compartment (including stroma cells, osteoblasts, osteoclasts, T and natural killer (NK) cells).[41,42] Interactions with the bone marrow stromal cells, chiefly via adhesion molecules, lead to the activation of complex signaling pathways that govern cell survival and tumor progression.[42,43] Myeloma cells also interact with endothelial cells inducing neoangiogenesis and, therefore, progression.[44] Interactions with osteoclasts and osteoblasts, especially the increase in osteoclast activity and osteoblast inhibition are responsible for the bone lesions that are accountable for a large proportion of myeloma morbidity.[45,46] The important biological factors influencing this process include RANKL, OPG, and members of the Wnt pathway (including DKK1).[47] Finally, the immune microenvironment imparts immune changes leading to immune evasion and disease persistence.[48–54] Loss of interaction with the bone marrow microenvironment, caused by reduced expression on MM cells of adhesion molecules (CD56, LFA-1) and chemokine receptors such as CXCR4, leads to impaired retention of malignant cells in the bone marrow and immune evasion leading to extra medullary spread, plasmocytoma and PCL.[10,11]

### Aspect 5. Chromosomal changes associated with myeloma

The cytogenetic study of myeloma cell lines has been hugely informative in developing our understandings of the biology of myeloma. At the cytogenetic level, the myeloma genome is recognized as being complex and more reminiscent of epithelial cancers rather than the simpler leukemias.[55] The key genetic lesion identified using metaphase analysis was the presence of balanced translocations at the IgH region on chromosome 14q32 which provided a major key to understanding the genetic makeup and etiology of myeloma. Once it was realized that the translocations consistently involved the IgH regions it was possible to use positional cloning to understand the site of breaks in the Ig regions, as well as to identify and clone recurrently deregulated genes.

In myeloma, most translocations, such as the t(4:14), occur through class switch recombination (CSR) in mature B cells. Nevertheless, a recent study suggests that, in some cases, translocations are generated through $D_H$-$J_H$ recombination, suggesting that they may arise in an earlier B-cell precursor (pro-B cell stage). From an etiological perspective, this may suggest that myeloma initiation can occur early on in the B-cell development.[56] As mentioned previously, the other necessary actors in the translocation and mutation process are receptor revision and somatic hypermutation. In the context of a normal immune system, IgH rearrangements and somatic hypermutation confer a benefit by increasing the quality of the immune response. The consequence of this process being that, despite being highly regulated, abnormal events do occur which can lead to the development of malignant transformation. These abnormal events and the malignant transformation are tolerated in an evolutionary sense as they are rare.[57] It seems, therefore, that the price of an effective immune system protecting from infections throughout life is a background rate of B-cell tumors and myeloma, particularly later in life. In this respect, it is perhaps not surprising that in populations over the age of 50 there is evidence of a clonal expansion of plasma cells in the form of MGUS in more than 3.2% of individuals.[14]

The study of chromosomal translocations, generated by either aberrant CSR or VDJ rearrangement, shows that a number of oncogenes (cyclin D1 (CCND1), CCND3, fibroblast growth factor receptor 3 (FGFR3), multiple myeloma SET domain (MMSET; also known as WHSC1), MAF and MAFB) are placed under the control of the strong enhancers of the Ig loci, leading to their deregulation independently from the mechanism of IgH rearrangement.[58] Deregulation of the G1/S transition is a key early molecular abnormality in myeloma. The consistent deregulation of the D group cyclin was first noted as a consequence of studying the CSR driven t(11;14) and t(6;14) translocations, which directly deregulate cyclin D1 and cyclin D3, respectively.[58,59] The t(4;14)(p16.3;q32.3) is found in 15% of presenting cases and is associated with a significantly worse prognosis than other biological subgroups. As a consequence of the translocation, two genes are aberrantly expressed: the fibroblast growth factor receptor 3 (FGFR3) and a multiple myeloma SET domain containing protein, MMSET (WHSC1/NSD2), both of which have potential oncogenic activity.[60] Importantly, FGFR3 shows only weak transforming activity and is eventually lost in 30% of patients,[61] suggesting that it is not the main oncogenic factor. In contrast, MMSET gene overexpression is universal in t(4;14) cases. MMSET is known to have histone methyl transferase activity[62] and is deregulated early on in myeloma genesis. Overexpression of MMSET leads to global changes in histone methylation that promotes cell survival, progression and DNA repair,[63–65] confirming it is central to the pathogenesis of this subtype of MM.

Other IgH translocations are seen in myeloma and tend to occur later in the disease process.[66,67] The gene typically deregulated by such events is *MYC*, the deregulation of which may lead to a more aggressive disease phase[68] but such events still occur in 21% of myelomas at presentation and involve the sequestration of active enhancer elements, resulting in increased expression of MYC (BA Walker *et al.* submitted manuscript, 2014). Interestingly, transgenic mice engineered to over-express MYC in late B cells also develop myeloma.[69]

The other major set of recurrent genetic abnormalities seen in myeloma is hyperdiploidy, associated with the gain of the odd numbered chromosomes including 3, 5, 7, 9, 11, 15, 19 and 21. The mechanism underlying hyperdiploidy is much less tractable than translocations and so the mode of its generation remains uncertain. However, one hypothesis, based on what has been suggested in hyperdiploid acute lymphoblastic leukemia (ALL), is that the gain of whole chromosomes occurs during a single catastrophic mitosis rather than via the serial gain of chromosomes over time.[70]

### Aspect 6. The mutation profile of myeloma

The frequency and recurrent nature of interstitial loss of copy number and loss of heterozygosity (LOH) suggests that the minimally deleted regions may contain tumor suppressor genes. Deregulation of these genes may be seen as driver events leading to the development and progression of myeloma.[71–73]

*Tumor suppressor and cell cycle deregulations:* most tumor suppressor genes require inactivation of both alleles and have either been identified by the study of homozygous deletions or through the integration of mutational analysis with copy number status.[74] Examples of potential relevant tumor suppressor genes include *FAM46C*, *DIS3*, *CYLD*, Baculoviral IAP repeat containing protein 2 (*BIRC2*; also known as cIAP1), *BIRC3*, and tumor necrosis factor receptor associated factor 3 (*TRAF3*).[72,75] Deregulation of the G1/S transition is also a key early molecular abnormality in myeloma, with loss of negative cell cycle regulators being important. In addition to down regulation of CDKN2C by loss of chromosome 1p32[76] and inactivation of CDKN2A by methylation are important,[77,78] inactivation of RB1 also affects this checkpoint and may occur as a result of loss of chromosome 13, present in 58% of cases.[73] The loss of the *TP53* gene, encoding for a tumor suppressor protein (p53) has been implicated in a variety of human cancers.[79] In myeloma, its loss is associated with a significantly more aggressive disease phenotype[80,81] and disease progression.[82] Mutations occurring at a low frequency have also been described.[74,83]

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*NFKB alterations:* other important regions of interest include 11q, the site of the *BIRC2* and *BIRC3* genes, 16q the site of *CYLD* and 14q32 the site of *TRAF3*.[56,71,72,84,85] All of these genes are involved in the NF-κB pathway, indicating that upregulation of NF-κB signaling is important in myeloma.

Whole genome- and whole exome-based sequencing strategies have shown that there are approximately 35 non-synonymous mutations per sample in myeloma, which is in between the numbers present in those of the genetically simpler acute leukemia (8 non-synonymous mutations)[86] and those present in the more complex epithelial tumors, such as lung cancer (540 non-synonymous mutations).[87] There are few recurrently mutated genes in myeloma, a feature consistent with other hematologic malignancies, such as acute myeloid leukemia, and this is in stark contrast to hairy cell leukemia and chronic myelogeneous leukemia (CML) where single unifying mutations are seen (*BRAFV600E* and BCR-ABL, respectively).[88,89] However, there are a number of recurrent pathways which are deregulated, e.g. the high frequency of mutations in the ERK pathway (*NRAS* in 24%, *KRAS* in 27% and *BRAF* in 4% of cases) indicates that the ERK pathway is crucial for myeloma development and points to a treatment strategy that has so far not been harnessed.[73] Deregulation of the PI3K pathway is also important in myeloma, but in contrast to the RAS pathway, the PI3K pathway is not frequently mutated. However, phosphorylated AKT, which is indicative of PI3K activity, is detected in 50% of cases.[90] In addition, DEP domain-containing MTOR-interacting protein (DEPTOR), a positive regulator of the pathway, is frequently up-regulated, especially in cases with MAF translocations.[91] A further and potentially relevant gene that is very frequently deregulated is *MYC*, which if over-expressed in germinal center cells in a mouse model can give rise to myeloma.[92]

### Aspect 7. Epigenetic changes

Genetic modifications have been considered essential in myeloma, but another type of alteration, the epigenetic event, also contributes to the oncogenic transformation of normal plasma cells by altering gene expression. The methylation of DNA and histones is one of the main physiological processes to induce silencing of gene expression and has been implicated in cancer progression.

The most important epigenetic change relevant to the pathogenesis of myeloma is global hypomethylation and gene-specific hypermethylation during the transformation of MGUS to myeloma. The most pronounced DNA methylation changes are seen in the 15% of patients with the t(4;14) translocation, where the 4p16 break point occurs telomeric to the 5' intron of *MMSET*, resulting in an MMSET overexpression.[58] This translocation leads to a gene-specific hypermethylation signature compared to other cytogenetic sub-groups.[5,93] Other histone modifiers deregulated in myeloma include KDM6A (UTX), a histone demethylase, MLL, KDM6B and HOXA9.[94] Chromatin regulators have the potential to be attractive targets in cancer therapy. Super enhancers (clusters of transcriptional enhancers that drive expression of genes usually defining cellular identity) are found at the position of key oncogenic drivers. Targeting super enhancers such as BRD4 preferentially affects oncogenes such as Myc, which is implicated in more aggressive disease.[95]

### Aspect 8. Stem cell and biology of myeloma evolution

If the biological process of myeloma is to be deciphered, we need to have a framework against which to test ideas generated from cell biological and genetic analyses. Simply describing the molecular genetics of myeloma, while informative, does not help us to understand how myeloma develops. There is clearly a myeloma stem cell, but its biology is difficult to understand. For example, a key concept in stem cell biology is plasticity, where an equilibrium exists between a cell with a stem cell phenotype and a mature terminally differentiated plasma cell.

The other important concept is that cancer stem cells are heterogeneous. This heterogeneity is an essential requirement for cancer development and progression through the various disease stages associated with increasing clinical aggressiveness. The understanding of cancer evolution that has come from the study of the simple cancer system of pediatric acute lymphoblastic leukemia (ALL) has significantly improved our concepts of how myeloma develops and how we could computer model such systems.[96–98] Intraclonal heterogeneity is present in myeloma and this is the essential molecular substrate for cancer evolution.[12,98] It is interesting that even for a dominantly acting oncogene, such as NRAS or KRAS, it is possible to identify variation in the size of the clone carrying the mutation, pointing to the presence of intraclonal heterogeneity and to potential difficulties in the use of targeted treatment strategies. In addition, the degree of intraclonal heterogeneity in myeloma has been highlighted recently by following patients through their treatment. Genetic studies demonstrate a number of clones present with the frequency of the clones changing with disease stage and therapy.[99]

### Aspect 9. Understanding the mechanism of action of drugs that are active in myeloma

In recent years, two new classes of drug which are active in myeloma have been identified and introduced into the clinic. Understanding the mode of action of these drugs and how they kill myeloma cells can inform us of clinically useful pathways crucial to myeloma biology.

*Proteasome inhibition:* targets a number of important biological pathways relevant to myeloma, such as the ubiquitin proteasome system, NF-κB activationm,[100,101] Bcl-2-induced apoptosis[102] and the unfolded protein response[103] emphasizing the importance of these pathways. The ubiquitin proteasome system, by promoting the timely degradation of short-lived protein, is a key factor of homeostasis. A better understanding of toxicity profiles has focused the attention on the upstream enzymes (E3-ubiquitin ligases and their regulators) as potential targets. Resistance to proteasome inhibitors include a number of mechanisms such as mutations (e.g. PSMB5 mutations or mutations in proteosome subunits),[104] overexpression of PSMB5,[105] alterations in the Bcl2/Mcl1 ratio,[106,107] and suppression of the Ire1-Xbp1 pathway. Conflicting data regarding the suppression of the Ire1-Xbp1 pathway suggests that it could promote either resistance[108] or sensitivity to proteasome inhibition.[109]

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*Thalidomide and its derivatives* kill myeloma plasma cells at a number of biological levels, and understanding how this occurs at a molecular level can provide major insights into the biology of malignant plasma cells. The recent description of cereblon as a thalidomide-binding protein and its downstream impact on IRF4 is a significant step forward in understanding the mechanisms of action of immunomodulatory drugs (IMIDs) and in identifying possible biomarkers.[110] Although early *in vitro* data on cell lines suggest the lack of correlation between Cereblon levels (both at the protein and RNA level) and response to IMIDs,[111] these will be improved with the ability to accurately measure the level of cereblon protein in the cell.

## Implication for myeloma patients

Both clinically and biologically, myeloma is not a single disease but a collection of diseases with different clinical behaviors. Understanding this heterogeneity will enable us to move forward from a standardized approach to precision medicine where clinical decisions are based on molecular subtypes. The first step towards precision medicine is to apply a risk stratification approach based on fluorescence *in situ* hybridization (FISH) abnormalities and gene expression profiling. FISH has identified prognostically important lesions such as gain 1q, del 17p and t(4:14) that when combined with other markers, such as ISS (albumin and beta2microglobulin), can be used as a prognostic marker.[80,81] Gene expression profiling (GEP) can also define independent signatures that could also predict outcome.[112–115] Identifying these groups and designing clinical trials for them will refine our current management strategies, avoiding over or under treating specific subgroups. Some clinical trials have already been designed in this respect.[116]

The second step forward is to develop a targeted treatment approach for specific molecular subtypes. Although there is probably not an "imatinib" for myeloma that would control all subtypes, selected molecular subtypes may respond to specific therapies. Based on our knowledge of epigenetic mechanisms, demethylation agents could be investigated in a subset of myeloma patients over-expressing MMSET. Currently, BRAF inhibitors show some promising responses in the small subset of patients with a *BRAF*V600E mutation. Ongoing studies will aim to target the RAS pathway that is mutated in approximately 50% of myelomas. But if we fail to integrate the notions of tumor heterogeneity and clonal evolution into this targeted treatment approach it is destined to fail. Combined treatment approaches based on both targeted and current agents are likely to be required to help us address these issues and build towards a cure for myeloma.

## Conclusion

The analysis of the currently available data has helped us understand the causes and consequences of the abnormalities occurring in normal B cells that lead to myeloma. It has also made clear that beyond the complexity of genetic and epigenetic events leading to myeloma progression, an additional complexity is given by the degree of both inter- and intraclonal heterogeneity. The methodical application of these aspects to myeloma has provided us with the tools to translate these data into valuable keys that can be taken forward to the clinic. Importantly, these advances underline the constant need for a collaborative effort between the clinic and the laboratory in developing novel approaches for myeloma. However, given the nature and the complexity of the disease outlined here, even with these advances, challenges will still remain in the years to come in the search for a cure for myeloma.

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*We appreciate that we have only referenced a small number of papers; we are very conscious that many others have contributed to the field and apologize that we cannot cite them all.*

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