MGUS to myeloma: a mysterious gammopathy of underexplored significance

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All cases of multiple myeloma (MM) are preceded by precursor states termed monoclonal gammopathy of undetermined significance (MGUS) or smoldering myeloma (SMM). Genetic analyses of MGUS cells have provided evidence that it is a genetically advanced lesion, wherein tumor cells carry many of the genetic changes found in MM cells. Intracranial heterogeneity is also established early during the MGUS phase. Although the genetic features of MGUS or SMM cells at baseline may predict disease risk, transition to MM involves altered growth of preexisting clones. Recent advances in mouse modeling of MGUS suggest that the clinical dormancy of the clone may be regulated in part by growth controls extrinsic to the tumor cells. Interactions of MGUS cells with immune cells, bone cells, and others in the bone marrow niche may be key regulators of malignant transformation. These interactions involve a bidirectional crosstalk leading to both growth-supporting and inhibitory signals. Because MGUS is already a genetically complex lesion, application of new tools for earlier detection should allow delineation of earlier stages, which we term as pre-MGUS. Analyses of populations at increased risk of MGUS also suggest the possible existence of a polyclonal phase preceding the development of MGUS. Monoclonal gammopathy in several patients may have potential clinical significance in spite of low risk of malignancy. Understanding the entire spectrum of these disorders may have broader implications beyond prevention of clinical malignancy. (Blood. 2016; 128(23):2599-2606)

Historical context and definitions

The quote above from Winston Churchill’s famous radio broadcast was meant to discuss his inability to precisely predict Russia’s actions during World War II, but may as well apply to monoclonal gammopathies. Monoclonal gammopathies were first described as a clinical entity termed essential hypergammaglobulinemia by the late Jan Gosta Waldenström in 1960.1 In 1978, seminal studies by Kyle and colleagues introduced the term monoclonal gammopathy of undetermined significance (MGUS) to illustrate the potential of some of these lesions to progress to clinical malignancy such as multiple myeloma or related disorders.2 The term smoldering myeloma (SMM) was then coined in 1980 to describe patients with continued clinical stability in the face of bone marrow plasmacytosis, similar to myeloma requiring therapy.3 With the introduction of the serum-free light-chain assay, light-chain gammopathy was described as a precursor to light-chain myeloma.4 Although the diagnostic criteria (in terms of cutoffs) for SMM differed in early reports, and many patients with MGUS in the initial studies did not undergo diagnostic bone marrow biopsies, the current definition of these disorders is well validated and based on the presence of a clonal plasma cell disorder in the absence of myeloma-related organ dysfunction or amyloidosis, and a cutoff of serum M spike ≥3 g/dL or bone marrow plasmacytosis of ≥10% for distinguishing asymptomatic multiple myeloma (AMM) vs MGUS.5 It is notable that in models evaluating disease risks, these cutoffs do not represent discrete risk inflection points,6 and quantifying percent marrow plasmacytosis can be challenging because of multifocal involvement. Nonetheless, these criteria have served the field well to harmonize clinical research, and they identify cohorts with distinct risks of progression to myeloma requiring therapy (1% per year for MGUS and 10% per year for AMM).7,8 Measures of tumor bulk (level of M spike, free light chains), nature of IgH type (IgG vs IgA), proportion of clonal plasma cells, and immune paresis have been used to create risk models.9,10 These models are again useful to guide clinical research, in spite of suboptimal concordance between them.11 Prospective and mature data sets with uniformly staged patients at baseline (such as the recently reported SWOG trial)9 are currently limited. More recently, marked elevation of serum-free light-chain ratio >100, presence of ≥2 focal lesions on magnetic resonance imaging, and extreme bone marrow plasmacytosis (≥60%) were proposed as criteria for initiation of therapy.5 Long-term impact of early therapy of these lesions remains to be determined. In spite of major advances, our understanding of the pathogenesis of MGUS and MM remains incomplete. Several aspects of clinical diagnosis and management of these precursor lesions have been a subject of excellent reviews and updated guidelines.12,13 In this perspective, I will emphasize the emerging insights in the biology of these preneoplastic lesions and their transition to clinical malignancy.
All myeloma clones are preceded by corresponding precursor states but do they all take the same road?

Most human cancers are preceded by a precursor state that is more common than the cancer itself, and myeloma is no exception. It is now well appreciated that nearly all cases of MM are preceded by an asymptomatic precursor state such as MGUS or SMM. Landgren et al analyzed subjects from a large screening trial to demonstrate that MGUS could be consistently documented in the samples collected before the diagnosis of myeloma.14 Another study by Weiss et al documented the presence of preceding monoclonal gammopathy in 27 of 30 myeloma patients, using sera collected before the diagnosis of clinical MM.15 The concept of MGUS as a precursor state bears a striking resemblance to precursors for other hematologic malignancies characterized in recent years.16,17 MGUS/MM is an important model to study basic aspects of early human carcinogenesis, because the precursor state is not resectable and can be sampled repeatedly; both tumor cells and nonmalignant cells from the bone marrow can be readily isolated; tumor cells secrete a highly tumor-specific biomarker in the form of clonal immunoglobulin; patients with preneoplasia lack cytopenia requiring transfusions or other therapeutic interventions. Myeloma is not a single disease and can be classified into several broad genetic subtypes.18,19 Tumor in each individual patient has a unique profile of genetic and epigenetic changes and clonal architecture.18,20-22 How and whether the individual subclones compete or cooperate with each other are areas of active investigation in diverse cancers. In hematologic malignancies such as MM, tumor cells are “disseminated” even at earlier stages. At a simplistic level, the process of malignant transformation in MM could be viewed as a change in the net clonal mass, which in turn depends on the balance of birth and death rates of individual subclones, affected by the crosstalk with host factors.22-24 It will be important to test whether the mechanisms underlying malignant transformation differ between individual subtypes or even individual patients. Factors regulating tumor progression could be classified as tumor cell autonomous (or intrinsic) or microenvironment-dependent/ extrinsic factors, and as we discuss later, may well differ between individual subclones. Importantly, these interactions between evolution of tumor subclones and host response are likely to be bidirectional and depend on each other.

MGUS as a genetically advanced lesion

Introduction of cytogenetics and gene-expression profiling has led to the surprising finding that the majority of cytogenetic changes detected in MM cells can also be detected in MGUS cells.18,25-30 Gene-expression profiling of purified MGUS cells revealed that purified plasma cells from MGUS are much closer to MM cells than normal plasma cells.31 Cytogenetically, the presence of specific chromosome abnormalities such as del(17p), t(4:14), 1q gains, and hyperdiploidy seem to correlate with increased risk of disease progression in SMM.32-34 All of the GEP-based subsets of MM can also be identified in the precursor cohorts, although none of these GEP-based subsets (which do correlate with some of the cytogenetic subsets) have a dramatically altered risk of progression.6 Notably, the musculoaponeurotic fibrosarcoma subset, which typically associates with high-risk MM, does not portend similar high risk when identified in the MGUS/AMM setting.6 Interestingly, the presence of a 70-gene gene-expression profiling signature (which correlates in part with chromosome 1 abnormalities and identifies high-risk MM) as well as a 4-gene signature,35 were found to be strong predictors of risk of progression to clinical MM requiring therapy. Progression to clinical MM has also been linked to the activation of c-myc21,36,37 and other signaling pathways,38 and reduced capacity for Ig secretion.39 Other important tumor-cell intrinsic regulators of malignant transformation could be changes in noncoding RNAs40 or epigenetic changes41 in tumor cells. Together these data suggest that genetic and genomic properties of MGUS cells could be strong predictors of eventual risk of malignant transformation.

Comparison of plasma cells from MGUS vs MM cohorts revealed increasing proportion of clonal plasma cells with genetic abnormalities, overall consistent with the expansion of preexisting clones at the transition of MGUS to MM.28 Genome sequencing studies have mostly focused on MM and revealed complex patterns of clonal evolution with about 4 to 5 major subclones within MM genomes.22,42 These studies are also consistent with patterns of divergent evolution possibly involving a less differentiated clonal progenitor in some cases.43 To date, only 2 small studies have described genome sequencing in paired, prospectively collected samples of precursor states compared with progression to clinical MM in the same patient.44,45 Both of these studies have shown that genomic complexity and intraclonal heterogeneity of tumor cells is established early in evolution of tumors. In these studies, progression to clinical MM in most patients did not involve new/recurrent somatic mutations, although there was some subclonal selection with progression. Besides small sample size, the studies are also limited by short time to progression in the patients studied. Interestingly, the baseline mutational spectrum in progressive lesions demonstrated greater overlap with known changes in the genomes of clinical MM than in nonprogressor lesions.45 These data (albeit preliminary particularly because of the small sample sizes) again suggest that the many of the genetic changes observed in MM are already present before clinical malignancy, and that the baseline pattern of genetic changes may correlate with the ultimate risk of malignant transformation. Larger studies to prospectively evaluate evolution of precursor states, and including modern single-cell technologies, should shed further light on this issue. Genomic analysis of MGUS in particular needs to account for the contamination of normal plasma cells in CD138-selected cells. Analysis of genomic diversity, however, needs functional validation of growth potential of the subclones, and one of the challenges in the field has been the inability to reliably grow human preneoplastic gammopathies in vivo. Recent development of humanized mouse models is permitting successful growth of MGUS lesions or their subclones in vivo in preliminary studies and may provide novel insights into the biology of these lesions.46 Initial studies from these models also illustrate the genomic complexity in MGUS, as well as the presence of minor subclones that may carry malignancies (such as chromosome 1 changes) typically associated with high-risk disease.46 The realization that MGUS is a genomically complex lesion carrying many of the mutations seen in MM without clear evidence for recurrent new lesions at transition to MM raises several questions: What keeps MGUS lesions/subclones stable? Why do minor subclones with potentially higher-risk lesions not become dominant already at the MGUS stage? How is this complexity generated?
Is it all about the soil? The role of tumor microenvironment

The concept that most MGUS lesions exhibit clinical stability in spite of advanced genomic complexity and intraclonal evolution of the tumor clone suggests the possibility that changes in growth rate and therefore malignant transformation may depend in part on interactions of tumor cells with the tumor microenvironment (TME) (Figure 1). Recent studies have shown that MGUS cells mediate progressive growth upon xenotransplantation in humanized mice.46 In this model, genetic humanization of mice is achieved by the expression of several human genes in mice that are essential for the growth of human cells and humanization of mice is achieved by the expression of several human genes in mice that are essential for the growth of human cells and mediate species-specific effects.46,47 This observation provides direct support to the concept that the observed clinical stability of MGUS lesions may indeed depend predominantly on tumor-extrinsic growth controls. In other words, the process of “malignant transformation” may depend more on how the tumor cells modify the host-mediated growth control. MGUS or MM cells grow primarily in the bone marrow and interact with several cells in this complex microenvironment, including immune cells, bone cells, endothelial cells, stromal cells, and non-cellular matrix.48 Because MGUS is a disorder of an immune cell infiltrating the bone marrow, I will particularly focus on the immune and bone component of the TME. Simplistically, tumor-TME interactions can be classified as those permissive or antagonistic to tumor growth. In many instances, it is the loss of normal microenvironment that creates conditions permissive for tumor growth.

Immune cells

Interaction of tumor with immune cells can mediate both pro- and antitumor effects. Several studies have shown that MM tumors are infiltrated with dendritic cells (DCs) and macrophages.48 Interactions of MM cells with both myeloid or plasmacytoid DCs can promote tumor growth.49-52 Tumor-DC interactions may also promote cell fusion and formation of osteoclasts,53,54 as well as genetic instability by inducing the expression of cytidine deaminases.55 The importance of T-follicular helper (TFH) cells in the generation of long-lived plasma cells is well established.56 Although less studied directly in the context of MM, interactions with TFH cells may also promote malignant B-cell differentiation.57 Several studies have demonstrated the capacity of innate and adaptive immune cells to recognize MM/MGUS cells and potentially mediate growth control.58 Tumor-specific CD4 and CD8+ T cells can be identified in the bone marrow of MGUS patients.59 Much of this response is specific to individual tumors.59 However, search for shared antigens has identified distinct targets of immunity in MGUS, such as SOX2 embryonal stem cell antigen.60 In a recent prospective study, the presence of SOX2-specific T cells and the expression of PD-L1 on tumor cells and T cells at baseline correlated with risk of progression to clinical MM requiring therapy.61 Progression to clinical MM is associated with a loss of effector function in several immune effectors including T, natural killer (NK), and NKT cells.62,63 However even in the setting of clinical MM, the bone marrow contains antimyeloma T cells that may be harnessed for immune therapy.53,64 Several mechanisms have been proposed to help explain the loss of tumor immunity with malignant progression. These include shedding of suppressive factors such as NKG2D ligands,65 immune suppressive cytokines, as well as suppression mediated by regulatory T cells,66,67 or myeloid-derived suppressor cells.68-70 It is notable that clinical MM is associated with a switch to IL17-producing Th17 cells, which correlate with MM bone disease.71-73 Several recent studies have demonstrated the expression of inhibitory immune checkpoints such as PD-L1 on tumor cells,61,74 although a role for other checkpoints such as CD22675 and induction of T-cell senescence76 has also been implicated. In addition to conventional T cells, other subsets of innate immune cells may also play a role in immune surveillance. In particular, importance of NK cells in MM control has been demonstrated in mouse models,75,77 and human NK
cells can kill MM targets. Mechanisms underlying altered immune surveillance by NK and other innate immune cells may therefore also regulate myelomagenesis. Another common feature of evolution to MM appears to be in biochemical features of chronic inflammation including bioactive lipids. Recent studies have identified subsets of human CD1d-restricted type II NKT cells against these lipids that are enriched in human MM and promote plasma cell differentiation. Altered balance of type I vs type II NKT cells may therefore also be an important immune-regulatory axis in evolution of MM and is further supported by loss of CD1d expression with disease progression of MM. Together these studies paint a complex picture, with a potential role for several immune cells and likely create redundancy that may affect immune-mediated growth control. They also suggest that combination approaches may be desirable for immune-based prevention or therapy of MM.

Role of bone marrow niche

An important aspect of both MGUS and MM is that the growth of tumor cells is largely restricted to the bone marrow. The tumor cells may therefore share niche with hematopoietic stem cells and/or normal long-lived plasma cells also thought to reside in the bone marrow. The nature and availability of the niche, the nature of niche-derived signals, and the competition or cooperation between subclones of tumor cells and their normal counterparts may all play a role in regulating the behavior of tumor cells in vivo.

Bone cells

Development of lytic bone disease is a characteristic feature of MM. However alteration in bone homeostasis occurs early, and patients with MGUS can have alterations in skeletal architecture with an increased risk of fractures. Increased bone turnover is an early feature of gammopathy, and progression to clinical MM has been associated with an uncoupling of bone turnover with a decline in osteoblast function.

Increased osteoclastogenesis in MM is thought to be the result of several factors including altered ratio of RANKL and OPG, as well as expression of chemokines such as macrophage inflammatory protein (MIP)1α/β, IL6, and metalloproteinases. Osteoclasts and MM cells are involved in a positive feedback loop, wherein MM cells promote osteoclast differentiation/activity, and osteoclasts in turn support MM cell growth and survival. The mechanisms underlying loss of osteoblast differentiation/function in MM is an area of active investigation, but a role for IL3, wt inhibitor Dickkopf1, and altered Notch signaling has been implicated. In a recent study, interaction with osteoblasts was implicated in inducing a dormancy signature, which was reversed by osteoclasts in a murine MM model. Therefore the balance of osteoclast/osteoblast interactions with tumor cells could play a direct role in regulating growth kinetics or tumor cells and thus malignant transformation. Accordingly, careful analyses of mediators or regulators of bone turnover or MM bone disease may provide important biomarkers of risk of malignancy in MGUS.

Other stromal elements

Bone marrow stromal cells (BMSCs) from MM patients promote tumor growth both in a cell-contact mediated fashion, as well as via the secretion of soluble factors. Secretion of growth differentiation factor 15 by BMSCs enhanced self-renewal of MM cells. BMSC-derived exosomes have been implicated in regulating MM cell growth through transfer of miRNAs. Another feature of MM marrow is increased angiogenesis, which has been postulated because of loss of an angiogenesis inhibitor. Recruitment of endothelial progenitors to the bone marrow niche was shown to regulate the growth of murine MM and may also play a similar role in human disease.

Taken together, it appears that there are several candidate players both in terms of growth-permissive and restrictive signals from the tumor microenvironment. It is likely that these signals co-evolve with the tumor. The balance of these factors is likely a key determinant of growth control of early tumors and malignant transformation.

How did we get here? The case for pre-MGUS and polyclonal phase: new insights from high-risk populations

The finding that MGUS lesions carry most of the genomic complexity found in MM suggests the need to explore the mechanisms underlying these genetic changes. Much of the genomic instability in MGUS is thought to originate in the germinal center. At least some of the genetic changes such as IgH translocations involve cytidine deaminases such as activation-induced cytidine deaminase, which can be induced by crosstalk between tumor cells and DCs. Analysis of mutational signatures also suggest the involvement of APOBECs in some MM lesions. Some of the genetic changes such as IgH translocations appear to be early events in myelomagenesis. However, the mechanisms that regulate the evolution of these early preclinical lesions are not known. Recent studies with deep sequencing of the Ig locus suggest ongoing somatic hypermutation in tumors from at least a subset of patients, which is also consistent with germinal center origin of the clone and is an area of active investigation. The absence of major genetic sweeps in most cases is also consistent with a “big bang” model for early origins, with clonal evolution subsequently shaping the overall architecture. As we diagnose these early lesions, it will be equally important to ascertain whether the mechanisms driving genomic instability are still active and how they could be arrested.

Current diagnosis of MGUS is based largely on the detection of clonal immunoglobulin by relatively insensitive assays such as serum protein electrophoresis and immunofixation. However, the introduction of new mass spectrometry–based and other techniques may permit the detection of clonal immunoglobulin at earlier stages. We refer to these earlier plasma cell clones (ie, clonal plasma cells or Igs that do not meet the current criteria for MGUS) as pre-MGUS, and suggest that understanding the biology of these lesions will be important to understand the earliest events in the evolution of these tumors. As discussed earlier, recent availability of new mouse models that allow growth of precursor states will greatly facilitate these insights.

Analysis of populations at higher risk for developing MM provides another important opportunity to gain insights into the early events in myelomagenesis, which in turn could translate into effective prevention. Gaucher disease (GD) is an inherited metabolic disorder characterized by marked accumulation of glucosphingolipids, particularly lyso-glucosylceramide (Lyso-GL1). GD cohorts exhibit >30-fold risk of developing MM compared with age-matched controls. Lyso-GL1 is recognized by a distinct set of type II NKT cells that provide help to B cells and promote plasma cell differentiation. Lipid-mediated immune activation may therefore promote the development of gammopathy in GD mice and patients. Consistent with this hypothesis, reduction of antigenic substrates leads to reduction in gammopathy in GD mouse models. Risk reduction was most impressive when the reduction of antigenic substrates was initiated earlier in the course of the gammopathy. Race is an important risk
factor for the development of gammopathies, which then translates to higher risk of MM in blacks. Notably, both GD and African cohorts (in Ghana) also have an increased incidence of polyclonal gammopathy. 

This biology bears resemblance to B-cell tumors such as Epstein-Barr virus–driven lymphoproliferative disorders. In the setting of GD, both the polyclonal as well as monoclonal phases may be lipid-driven. However, the presence of polyclonal plasma cells or Igs of the same antigenic specificity as the clonal PCs/immunoglobulins found in MGUS remains to be shown. Two other cohorts carry an increased risk of gammopathy/MM and could also be very instructive in exploring novel approaches to prevention. Risk of gammopathy is increased in obesity and in cohorts of patients with a history of exposure to certain toxins such as Agent Orange. Obesity also creates a permissive environment for the growth of tumor cells in mice. These considerations impel the need to directly test whether lifestyle modifications targeting obesity will alter the natural history of gammopathy in these cohorts.

Are we underexploring the significance of MGUS?

To date, nearly all of the attention in terms of clinical care of patients with MGUS relates to the risk of development of MM. MGUS cohorts have a lower life expectancy compared with age- and sex-matched population controls, which is not entirely explained by the risk of malignant transformation. MGUS patients are also at an increased risk of morbidity related to several conditions such as skeletal morbidity, infections, other malignancies, neuropathies, thrombosis, and renal disease. If we were to apply emerging technologies to diagnose gammopathies earlier, we are likely to further increase the estimated prevalence of these disorders. The great majority of these early lesions would likely have low malignant potential but could still carry important clinical implications in terms of a defined morbidity.

One example of such a concept is the recent appreciation of monoclonal gammopathy of renal significance. Further studies are therefore needed to understand the potential implication of the diagnosis of an expanded plasma cell clone in selected clinical settings wherein they might similarly affect pathogenesis and, ultimately, management. Some examples of such states may include acute osteoporosis, clinical suspicion of amyloid syndromes, neuropathies, and refractory autoimmunity (Table 1). Studying the biology of the clonal plasma cells and properties of immunoglobulins in these settings may allow us to develop simple approaches to diagnose and intervene early and eventually modify the risk of these morbidities. Early diagnosis in appropriate clinical settings may also help us identify clones that are genetically less advanced than those currently diagnosed as MGUS, and perhaps more amenable to eradation. Although we have made great strides in the management of MM in the last decade, our best bet to eradicate this malignancy may lie in preventing it in the first place. Fully exploring the biology of MGUS may have broader implications for human health beyond MM.

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