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Vitae

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Abstract

The standard model of multiple myeloma (MM) oncogenesis from monoclonal gammopathy of undetermined significance (MGUS) relies on genetic instability in the normal counterparts of MM cells. However, the importance of both MGUS-associated and MM-induced bone changes has been recently re-appraised, emphasizing the bone microenvironment (BME) as a tissue of significance. In this review, we propose that early BME alterations (bone senescence and inflammation, i.e. bone inflamm'aging) at the pre-MGUS stage could be causal, and not simply permissive, and creative of phenotypic instability and genetic alterations thanks to the concept of tissue disruption-induced cell stochasticity (TiDiS). This article offers a bone scenario challenging the chromosome-and-gene-centric standard model of MM oncogenesis. The high incidence of both MGUS and MM in Gaucher disease supports such a scenario.

Key Words

Multiple myeloma, monoclonal gammopathy of undetermined significance, tissue disruption-induced cellular stochasticity (TiDiS), bone inflamm'aging, bone marrow microenvironment, endosteal niche, mesenchymal-stromal to osteoblast transition (MS-to-ObT), Gaucher disease

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Abbreviations

BME: Bone Micro-Environment

GD : Gaucher Disease

LBL: Lytic Bone Lesion

MGUS: Monoclonal Gammopathy of Undetermined Significance

MS-to-ObT: Mesenchymal-Stromal to Osteoblast Transition

MM: Multiple Myeloma

TiDiS: tissue disruption-induced cellular stochasticity

I - The current standard, then permissive views of cancer and the TiDiS concept

Cancer is not considered anymore as the simple accumulation of genetic mutations into targeted cells (standard view) but rather as an ecological and evolutionary process, by analogy with the mechanisms involved in the evolution of species (permissive view) [1]. In such an ecological context (of cancer evolution), the host environment turns out to play a critical role through its selective interactions with the phenotype (and not directly the genotype) and the extended phenotype of the (pre)-cancer cells [2,3]. Only cells with the best capacity to adjust to the remodeling environment will be selected and will replicate. This capacity of adjustment represents a survival and proliferating advantage. According to this scheme, the (environmental) niches and their disruption appear to play a pivotal role in the emergence of cancers, especially in hematological malignancies [4]. More precisely, the niche represents the relevant and selective environment of reference for a dedicated cancer, and its disruption appears to be a critical event for the emergence of this cancer, through its effects on genetic and epigenetic instability. This perspective is well-supported by the concept of tissue disruption-induced cellular stochasticity (TiDiS), stochasticity being defined as random epigenetic and genetic instability. This concept is able to reconcile genetics and environment in the origin of cancer, and gives to the remodeled environment a causal role [5-9].

Viewing cancer mainly as a developmental and differentiation disease linked to aberrant gene expression patterns resulting from tissue disruption is not a new idea (see for instance [10,11]). However, this view can now be envisaged through a new molecular perspective. Indeed, the acquisition of differentiated states associated with epigenetic and phenotypic stability appears to be achieved through the reduction of gene expression variability (noise) by the establishment of direct or long-range cellular interactions [12]. Thus, any disruption of the tissue equilibrium would produce an increase in phenotypic variation leading to a loss of coordination in cellular functions. Aging and oncogenesis could find a common origin in such

a TiDiS [8]. More precisely, senescence, including bone senescence, immune deficiency and associated-inflammatory states could represent a shared origin for many processes of oncogenesis because they induce a disruption between the micro-environment and the pre-cancerous cells.

II - The current standard, then permissive views of MM

During the last 25 years, a lot of works has been devoted to the biology of multiple myeloma (MM), including genetics, genomics, epigenetics and the mechanisms of lytic bone lesions (LBL), hallmark of the disease. These works led to the standard 'chromosomes and genes centric' model of MM oncogenesis. However, the limitations of this model were underlined because it does not integrate bone diseases, except as end damages [7,9]. Indeed, MM bone disease is constant at the histological level and specific of MM. This specificity suggests that the mechanisms of bone disease could be close to those of MM oncogenesis and that the bone microenvironment (BME) could be involved as a causal factor in this disease.

However, the standard view is currently evolving towards a more permissive one. Many recent studies on the natural history of MM, from the normal counterparts of MM cells residing inside the bone marrow, support the BME as an environment of significance. Especially, its precursor stages (monoclonal gammopathy of undetermined significance, MGUS, and pre-MGUS) are associated with recurrent bone changes. Recent expertise and re-appraisals of both MGUS-associated and MM-induced bone changes offer a new point of view on the role of BME in MM oncogenesis. It integrates BME as a tissue of significance for MGUS and as a permissive environment for MM. Indeed, there is a shared background in MGUS (and pre-MGUS) and MM represented by a bone fragility and a generalized bone loss, linked to a disruption of the mesenchymal-stromal to osteoblast transition (MS-to-ObT) responsible of prolonged osteoblast suppression.

In MGUS, the frequent associated bone changes (with increased fracture risk and excess of circulating bone factors) are enough to present MGUS as a monoclonal gammopathy of skeletal significance [13]. In MM, the importance and specificity of this osteoblast suppression in the occurrence of LBL is becoming increasingly evident since their first description [14]. Careful evaluation of the precursor bone cells reveals that their abnormal senescent profile in the context of inflammatory processes (concept of inflamm'aging) could contribute to this specific prolonged osteoblast suppression, through a late disruption of the MS-to-ObT [15]. This contribution occurs in addition to the direct MM-induced uncoupling between bone resorption (increased) and bone formation (suppressed) taking place through the soluble factors directly or indirectly produced by the MM cells. This prolonged osteoblasts suppression not only facilitates the occurrence of LBL, but also increases the generalized bone loss of MM patients which is first observed in MGUS. This represents a bone continuum between MGUS and MM, and leads to the view that the altered BME (as soil) behaves as a permissive environment in MGUS and MM which is able to contribute equally with the genetic alterations of MM cells and their precursors (as seeds) to the development of the disease.

However, this point of view has some limitations: many experimental and clinical cancer models show that the quality of soil is more important than the number of seeds. Furthermore, this permissive view does not integrate the possibility of a potential causal role of the BME alterations which could lead the genetic alterations themselves. Thanks to the TiDiS concept, such a relation could be explained, and the BME could be viewed as permissive but also as causal factor. Finally, this causal view unravels the direct link existing between the mechanisms of bone disease, especially osteoblast suppression, and those of MM oncogenesis.

III - The TiDiS concept in MM: towards a 'bone paradigm' challenging the standard and permissive models of MM oncogenesis.

The TiDiS concept integrates the idea that the disruption of the MS-to-ObT increases the stochasticity of MM cells and of their precursors from their normal counterparts inside the normal endosteal niche [7,9]. This disruption leads to partial dedifferentiation through a destabilization of the normal phenotypic features, to increased epigenomic and genomic instability, and ultimately to overt MM.

In MGUS, this disruption of the MS-to-ObT leads to the disruption of the endosteal niche, as first described in 1996 [16]. It is characterized by a shift from an osteoblastic to an osteoclastic profile. Osteoblast senescence (aging) in the context of inflammation (inflamm'aging) favors such disruptions. In MM, such an 'inflammatory' component exists, is totally dependent on IL6, and is of strong prognostic value (as strong as genetics) [17]. Thus, one can consider that this inflammatory component is already at work in the early stages of MM. Animal experiments demonstrated an excess of IL6 production into the disrupted/osteoclastic endosteal niches [18].

Based on the major role of the disrupted BME, the TiDiS theory allows to formulate a 'bone scenario' at the origin of MGUS and MM. The proposed bone paradigm challenges the 'chromosome-and-gene-centric' standard and permissive models with the following critical events:

a) accelerated bone senescence and inflammatory processes (excess of IL6): bone inflamm'aging;

b) early disruption of the MS-to-ObT in pre-MGUS and MGUS leading to the disruption of the endosteal niche. This disrupted endosteal niche becomes more attractive, acidic, hypoxic, immunosuppressive, clastogenic, and selective [19];

c) selection of the most disrupting clones with increased cellular stochasticity and altered morphotype (lack of complete differentiation, then residual proliferation) to reach overt MM. The other characteristics of the MM cells subsequently appears: genetic and epigenetic modifications, altered phenotypes (activation of ancillary survival pathways conferring survival phenotypes) and extended phenotypes (osteoblast suppression, LBL).

Thus, the TiDiS concept is based on initial bone tissue disruption causing differentiation and subsequent genetic problems. It bypasses the classic concept of MM bone diseases as end damages. It also goes further than the concept of permissive environment facilitating MM cell growth. Even more radically, this bone challenging could explain the occurrence of MM in the absence of chromosomal alterations [20].

IV - Gaucher disease as proof of concept.

A significant excess of hypergammaglobulinemia, MGUS and MM is now well-documented in the Gaucher disease (GD) [21]. It is thus possible to conclude that the GD recapitulates the oncogenesis of MM according to a multistep transformation process from the polyclonal activation of B cells (polyclonal immunopoiesis) to the malignant transformation of plasmacytopoiesis (MM), through clonal immunopoiesis (MGUS). A recent and major critical achievement to this scheme has been the demonstration that GD MGUS specifically recognizes glucosylsphingosine, the specific lysolipid which accumulates in the macrophages of GD patients due to an enzyme deficiency [22]. This observation explains that a long-term polyclonal then monoclonal immune activation of B cells exists in the GD [23,24]. Furthermore, the observations made in GD patients receiving an oral inhibitor of glucosyl ceramide synthase, and those made in murine and humanized xenograft models of GD, show that there is a clear antigen-mediated regulation of MGUS and MM in GD [23,24]. Moreover, a significant percentage of sporadic MGUS also recognizes the same antigen [22]. Thus, this antigenic specificity is not an exception restricted to the GD. It suggests that MGUS and MM

monoclonal immunoglobulins have a restricted repertoire to some particular antigens. To our knowledge, there is no current explanation to such a restriction. Regardless the future explanation, a major pending question remains to explain why progression to MM is accelerated in so many GD MGUS. In this context, the explanation could come from the TiDiS theory. Indeed, the GD also presents as a bone disease, under the form of an osteoclasts-osteoblasts uncoupling, that is a disruption of the BME [25]. As detailed in our current work, such disruption could increase the genetic and epigenetic instability of the GD MGUS clones. To summarize, in this model of GD, the oncogenesis of MM could be supported by two major independent components: an immune one and a bone one.

V - Perspectives and conclusion

Several mechanistic and clinical perspectives can be drawn in the light of this proposal. As the murine model of GD is the sole to recapitulate the MM pathogeny, it should allow to manipulate the BME so as to evaluate its impact on the appearance of MGUS and MM. More specifically, Decorins were previously identified as potential important interaction proteins in the endosteal niche involving osteoblasts and plasma cells [7,9]. Thus, dysregulating Decorins expression or targeting osteoblasts in this model should be informative on the ability of the altered BME to modify MGUS and MM frequencies.

From a therapeutical point of view, reacquiring epigenetic and phenotypic stability should be the key to stop proliferation. Epigenetic drugs are proposed to allow such normalization of cell phenotypes but they are not as efficient as hoped. Re-expressing key repressed genes indeed appears to be crucial to achieve such normalization of cell phenotypes. But phenotypic stabilization, then normalization, should be viewed as the achievement of an equilibrium between the random cellular biochemical reactions and the multiscale constraints produced by the dynamical organization of the biological system, especially at the tissue level [12]. This highlights the need for a second step to get such cell stabilization. Together with

the re-expression of key interaction proteins, bringing in the BME some elements that are able to interact with the re-expressed proteins should trigger cell signaling and epigenetic stabilization of the re-expressed genome [26]. Again, the models of GD should also allow to test the coupling of epigenetic drugs with soluble peptides mimicking Decorins domains and/or the stimulation of osteoblast proliferation/survival.

The hypothesis that a disrupted BME could increase the genetic and epigenetic instability of the MM precursor cells (pre-MGUS and MGUS cells), and thus have a causal role in the emergence of their full malignant transformation, could be tested by looking at the effects of some 'BME-modulating' drugs on the evolution of MM from its precursors. In the context of TiDiS, modulating the disrupted niche could be proposed as a 'niche therapy'. It is already known that the beneficial effects of the two major drugs used in the treatment of MM, i.e. proteasome inhibitors and thalidomide derivatives, result in part from the effects of these drugs on the BME. Conversely, some bone specific agents like Zoledronate could improve the overall survival of MM patients [27]. Thus, it would be of interest to test the beneficial effects of some 'BME-modulating' drugs on the MM precursor cells, especially those able to stimulate bone formation (rather than those able to inhibit bone resorption). For example, this could be done, without ethical damages, in patients with both osteoporosis and MGUS. The follow-up of large cohorts of such osteoporotic patients could give interesting information on the maintenance or evolution of their MGUS into overt MM. Such cohorts are particularly interesting because they are close to the status of GD with MGUS, and because some of these patients already receive either Zoledronate or anti-RankL monoclonal antibody (denosumab). Overall, animal and humanized models could be helpful.

Whereas the standard model of MM oncogenesis considers LBL only as end-damages, a recent reassessment of the bone changes in MGUS and MM suggests that alterations of the BME intervene equally with genetics by creating a permissive environment in the early

stages, and not only in disease progression. In line with this perspective, we go further than previous proposals on the role of the BME [13] by considering that it is causal and not only permissive (in particular creative of genetic alterations) thanks to the TiDiS concept. An early disruption of the BME at the pre-MGUS stage could lead to a cascade of events opening the way to permanent MGUS and overt MM by favoring genetic instability inside precursors of MM cells. Bone senescence (especially of osteocytes and osteoblasts) and inflamm'aging could be at the origin of this early disruption. It is now well-documented that some acute myeloid leukemia emerge from pre-existing pre-leukemic states, characterized by chromosomal abnormalities as clonal markers (clonal hematopoiesis), in the context of bone progenitors dysfunction [28,29]. Thus, the oncogenesis of MM, which results from the malignant transformation of the process of plasmacytopoiesis, could mimic this scenario. MGUS could be viewed as a pre-MM state characterized by clonal chromosomal markers (clonal immunopoiesis) in the context of bone progenitors dysfunction.

VI - References

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