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ORIGINAL ARTICLE

The multiple myeloma bone eco-system and its relation to oncogenesis

L'écosystème osseux du myélome et ses relations avec l'oncogenèse

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KEYWORDS
Multiple myeloma;
Bone disease;
Bone formation;
Bone resorption

Summary Pure lytic bone lesions are the hallmark of myeloma (MM). MM is the only hematological malignancy associated with lytic bone lesions and the mechanisms of bone destruction are well documented both at the cellular and molecular levels. An uncoupling bone process characterizes MM, with stimulation of bone resorption and inhibition of bone formation. The capacity of MM cells to directly or indirectly inhibit bone formation is specific of MM, although many carcinomas have the capacity to stimulate bone resorption, directly or indirectly in a similar way to MM. Few MM do not develop bone lesions, while true sclerotic MM remain exceptional. Inhibition of bone formation is the major event explaining the transition from MGUS to overt MM. It is now well documented that bone cells regulate MM cell growth, osteoclast stimulating MM cell growth and osteoblasts inhibiting it. Progression of MM from MGUS is characterized by the selection of MM clones able to inhibit osteoblasts, favoring tumor growth. These data underline the interest of new treatments able to regenerate bone.

MOTS CLÉS
Myélome multiple ;
Maladie osseuse ;
Formation osseuse ;
Résorption osseuse

Résumé Les lésions ostéolytiques pures sont une caractéristique du myélome (MM). Le MM est le seul cancer hématologique associé à des lésions ostéolytiques et les mécanismes de la destruction osseuse sont bien décrits tant en ce qui concerne les aspects cellulaires que moléculaires. Un processus de découplage des activités cellulaires osseuses caractérise le MM avec une stimulation de la résorption et une inhibition de la formation osseuse. La capacité des cellules myélomateuses d'inhiber directement ou indirectement la formation osseuse est spécifique au MM. De rares MM ne développent pas de lésions osseuses et les myélomes condensant restent exceptionnels. L'inhibition de la formation est l'évènement majeur expliquant la transition MGUS à myélome avéré. Il est maintenant bien établi que les cellules osseuses régulent la croissance des cellules myélomateuses : les ostéoclastes stimulent la croissance des

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plasmocytes myélomateux alors que les ostéoblastes l'inhibent. La transformation d'une MGUS en MM est caractérisée par la sélection de clones capables d'inhiber les ostéoblastes, ce qui favorise la croissance tumorale. Ces données soulignent l'intérêt de nouveaux traitements capables de régénérer le tissu osseux.

Introduction

Multiple myeloma (MM) is a monoclonal plasma cell malignancy characterized by the accumulation of malignant plasma cells within the bone marrow [1]. Accumulation of MM cells occurs at the expense of surrounding bone trabeculae, which are completely destroyed (Fig. 1). The specific capacity of MM cells to destroy bone trabeculae represents their specific ''extended phenotype'', which is explained by special interactions of MM cells with their cellular microenvironment: MM bone eco-system [2,3]. Of major importance, most MM cases emerge from a premalignant state termed either monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM (SMM) according to the extent of bone marrow involvement and serum Ig monoclonal component levels [4]. The purpose of this review is to summarize the mechanisms of bone disease in MM and to show that MM bone disease results from a selection of aggressive extended phenotypes (to bone disease) of MM cells during the transition from MGUS/SMM to overt disease and subsequently. The knowledge of the cellular events involved into this transition through the selection of aggressive phenotypes for the microenvironment, especially bones, is critical to find out new therapeutic avenues, since overt MM remains a lethal disease despite recent advances related to the use of thalidomide derivatives and proteasome inhibitors. Our review is also an effort to emphasize the importance within the MM bone eco-system of the reactive stromal microenvironment at the origin of bone changes and of selection pressures ensuring the progression of MGUS to overt MM.

Pure lytic bone lesions are the hallmark of MM

MM associated with lytic bone lesions

MM is the only hematological malignancy associated with lytic bone lesions (LBL), and the mechanisms of bone destruction are well documented both at the cellular and molecular levels. Within hematological malignancies, LBL are the hallmark of MM. Almost all MM patients will develop LBL during the evolution of their disease. Bone trabeculae rather than cortical bones are the target of the MM process. Actually, MM patients present with more or less LBL (bone heterogeneity) in relation to the other characteristics of their tumors, especially genetic instability (aneuploidy). For example, hyperdiploid MM are more osteolytic that those with 14q32 translocations. It is now well established that a MM-induced uncoupling process, which is an increased bone resorption with a decreased bone formation is at the origin of LBL [5]. This uncoupling is only observed in the close vicinity of MM cells (Fig. 2). The mechanisms of LBL have been extensively and recently reviewed, including by ourselves [6—8].

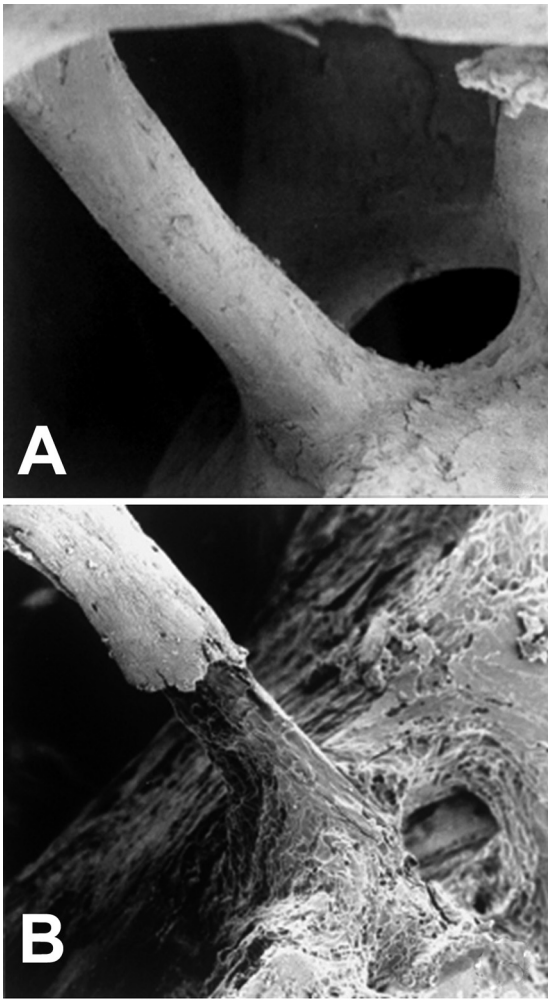

Figure 1 Normal (A) and myeloma-destroyed (B) bone trabeculae in scanning electron microscopy.
Aspect en microscopie électronique à balayage d'une travée osseuse normale (A) et profondément érodée au cours d'un myélome (B).

Briefly, MM cells: directly produce osteoclast activating factors, such as MIP-1 alpha, IL3, IL7...; produce and/or induce RankL, the most potent activator of osteoclasts on stromal cells, through VLA4/VCAM1 interactions (Fig. 3). This is the proof of the existence of a reactive stroma in MM, as in carcinomas. No direct contact