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GENERAL REVIEW

The use of animal models in multiple myeloma

L'utilisation des modèles animaux dans le myélome multiple

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5T33MM;
5TGM1;
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Xenograft;
Pristane

Summary In myeloma, the understanding of the tissular, cellular and molecular mechanisms of the interactions between tumor plasma cells and bone cells have progressed from *in vitro* and *in vivo* studies. However none of the known animal models of myeloma reproduce exactly the human form of the disease. There are currently three types of animal models: (1) injection of pristane oil in BALB/c mice leads to intraperitoneal plasmacytomas but without bone marrow colonization and osteolysis; (2) injection of malignant plasma cell lines in immunodeficient mice SCID or NOD/SCID; the use of the SCID-hu or SCID-rab model allows the use of fresh plasma cells obtained from MM patients; (3) injection of allogeneic malignant plasma cells (5T2MM, 5T33) in the C57BL/KalwRij mouse induces bone marrow proliferation and osteolytic lesions. These cells did not grow *in vitro* and can be propagated by injection of plasma cells isolated from bone marrow of a mouse at end stage of the disease into young recipient mice. The 5TGM1 is a subclone of 5T33MM cells and can grow *in vitro*. Among the different models, the 5TMM models and SCID-hu/SCID-rab models were extensively used to test pathophysiological hypotheses and to assess anti-osteoclastic, anti-osteoblastic or anti-tumor therapies in myeloma. In the present review, we report the different types of animal models of MM and describe their interests and limitations.

MOTS CLÉS
Modèle murin de myélome ;
Ostéolyse ;
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SCID ;

Résumé Dans le myélome, la compréhension des mécanismes tissulaires, cellulaires et moléculaires des interactions entre les plasmocytes tumoraux et les cellules osseuses a progressé à partir des études in vitro et in vivo. Cependant, aucun des modèles animaux de myélome ne reproduit exactement le myélome humain. Il existe actuellement trois types de modèles animaux : (1) l'injection d'huile pristane chez des souris BALB/c conduit à des plasmacytomes intrapéritonéaux mais sans qu'il y'ait colonisation de la moelle osseuse et développement d'une ostéolyse ; (2) l'injection de lignées de plasmocytes malins chez des souris immunodéficientes

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SCID-hu ;
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Pristane

SCID ou NOD/SCID ; l'utilisation du modèle de souris SCID-hu ou SCID-rab permet d'injecter des plasmocytes tumoraux frais obtenus à partir de patients atteints de myélome ; (3) l'injection de cellules plasmocytaires allogéniques (5T2MM, 5T33) chez la souris C57BL/KalwRij induit une prolifération tumorale dans la moelle osseuse et des lésions ostéolytiques. Ces cellules ne se cultivent pas in vitro et peuvent être propagées par injection de plasmocytes isolés, à partir de moelle osseuse de souris au stade terminal de la maladie, dans des souris receveuses jeunes. La lignée 5TGM1 est un sous-clone des cellules 5T33MM et peut se développer in vitro. Parmi les différents modèles de myélome, les modèles 5TMM et les modèles SCID-hu/SCID-rab ont été largement utilisés pour tester des hypothèses physiopathologiques et évaluer l'effet de thérapies anti-ostéoclastiques, de thérapies anti-ostéoblastiques ou des thérapies anti-tumorales du myélome. Cette revue de la littérature décrit les différents types de modèles existants avec leurs intérêts et leurs limitations.

Introduction

Myeloma (MM) is a hematological malignancy whose prevalence is 1 in 10,000 people; the median survival is approximately three years. MM is due to the proliferation of malignant plasma cells (PC) in the bone marrow. The overt disease is clinically characterized by bone pain and asthenia. Biologically, a monoclonal protein (M-protein) is found in blood and/or urine in 98% of cases. Skeletal abnormalities characterized by osteolytic foci and diffuse osteolysis is observed on radiographs in 90% of patients during the time course of the disease. Osteolysis is due to an increased osteoclastogenesis induced by the tumor and not to the malignant PCs, which do not have the cytologic machinery for resorbing the calcified bone matrix. Hypercalcemia, which reflects bone lysis, is often associated. Osteolysis causes serious clinical problems (fractures, spinal cord compression, bone pain...). Pathophysiology and etiology of osteolysis in myeloma are still imperfectly known. It was shown that the destruction of the bone tissue was not associated with tumor PCs themselves, but by the stimulation of osteoclast activity which occurs in the vicinity of tumor nodules.

Osteolytic cavities are generated in response to a variety of local factors produced by the malignant PCs and by the bone marrow microenvironment. These factors favoring osteolysis include tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), macrophage inflammatory protein-1-alpha and beta (MIP-1α and MIP-1β) and ligand for receptor activator of nuclear transcription factor-κB (RANKL) [1]. However, none of these factors appears to be solely responsible for bone destruction. In addition, the implication of several of these factors (IL-6, IL-1, TNF-α) in osteolysis has been shown *in vitro* but their implication *in vivo* is uncertain [2]. In MM, interaction with bone marrow microenvironment is essential for MM progression. The interaction of stromal cells with tumor PCs through the adhesion molecules VCAM-1/α4-ß1 increases osteoclastogenesis and resorption activity [3]. The VCAM-1/α4-ß1 interaction is also involved in RANK-L/OPG and IL-6 released by stromal cells [4,5]. IL-6 association with its soluble receptor promotes the proliferation and survival of tumor cells. Additional growth factors are also released by the microenvironment that can promote the tumor growth such as IGF-1 [6].

In overt MM, a decrease in bone formation is also associated, leading to an uncoupling in bone remodeling. Inhibition of osteoblastogenesis is due to inhibitors released by PCs and depressing the Wnt-signaling pathway: DKK1 (Dickkopf-1) and Sfrp2 (secreted frizzled-related protein 2) [7,8] or acting on the osteoblastic precursors: hepatocyte growth factor (HGF), IL-3 and IL-7 [9—11].

In MM, there is a vicious circle in which tumor PCs stimulate bone cells which in turn stimulate the tumor growth. Understanding of the tissular, cellular and molecular mechanisms of interactions between tumor PCs and bone cells suffers from the low number of available animal models. Models are interesting:

- to evaluate pathophysiology of the disease and its effect on bone remodeling;
- to test the effect of therapeutic with an anti-osteoblastic, anti-osteoblastic or anti-tumor activity.

At present, only mouse models are available and reflect more or less perfectly the human disease. In the present review, we report the different types of animal models of MM and describe their interests and limitations.

Induction of plasmacytomas in BALB/c mice with pristine oil

The injection of the mineral oil pristane into the peritoneum of BALB/c mice induces plasmacytomas with a high frequency [12]. This model has been discovered in 1969 and has constituted at that time the first one to study MM. Pristane oil induces a chronic inflammatory tissue where plasmacytomas develop with a 60% frequency after 16 weeks [12]. Plasmacytomas can then be transferred to other mice pretreated with pristane. Plasmacytomas predominantly secrete a monoclonal IgA in 60% of cases. This is a limitation of the model because IgG MM is the most frequent form in humans [13]. The main disadvantages of the model are that PCs are restrictively localized in the peritoneum and do not extend to the bone marrow; so bone lesions are not observed. This model does not faithfully reproduce human

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