GENERAL REVIEW

The use of animal models in multiple myeloma

L’utilisation des modèles animaux dans le myélome multiple

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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.

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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 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 5TG1 est un sous-clone des cellules 5T33MA 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 antitumorales du myélome. Cette revue de la littérature décrit les différents types de modèles existants avec leurs intérêts et leurs limitations. © 2015 Elsevier Masson SAS. Tous droits réservés.

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 anemia. 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/α4β1 increases osteoclastogenesis and resorption activity [3]. The VCAM-1/α4β1 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-ostéoblastic, anti-ostéoblastic 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
MM and thus cannot be used to study the pathophysiology of MM-induced bone lesions. However, it is well adapted to study the gene expression profile in PCs during tumor progression [14,15]. Another interest of the pristane model is the possibility to study of the oncogenic rearrangements of c-myc [16,17]. Beside to cytogenetic studies, the role of IL-6 has also been investigated in this model. IL-6 is now well known to be involved in survival and proliferation of PCs in MM [18]. It has been shown that BALB/c mice deficient for the IL-6 gene failed to develop plasmacytoma after pristane injection [19,20].

Experimental therapies on the plasmacytoma model have been tested but they were focused only on the effect of tumor growth [12]. One interesting study was the use of zoledronic acid (ZOL, the most potent bisphosphonate of the 3rd generation) currently used to prevent bone lesions in human MM. It is well known that ZOL is effective in reducing and delaying skeletal events in MM patients [21]. The direct effect of ZOL on PCs was less evident in vivo. A reduction of plasmacytoma development and an increase in survival have been observed in BALB/c mice, which have received ZOL on the 1st day after pristane injection [22].

**Immuno-deficient mice: the SCID model**

It consists in the injection of human PCs in severe combined immunodeficiency (SCID) mice, so it represents a xenograft model. However, the choice of the plasma human tumor line appears critical because of they can be of myeloma-toous or lymphoblastoid origin and their Epstein-Barr virus status may differ (EBV- or EBV+). The malignant human cells colonize the bone marrow microenvironment and develop in the marrow cavities. Osteolytic lesions occur and are similar to those described in humans; in addition, a M-protein is secreted and can be dosed in the serum [23–27].

Some of these myeloma lines, as the KPMM2, are well characterized [28]. KPMM2 is EBV- originated from a MM patient. These cells are strongly dependent to IL-6 as in human MM. In addition, their proliferation is induced by IL-6 via an autocrine mechanism. Intravenous injection of the cells in SCID mice induces a major development within the hematopoietic bone marrow and lymph nodes [27]. Osteolytic lesions are observed 30–40 days after inoculation and mice exhibit hind limb paralysis at the end course of the disease. In the KPMM2 model, injection of anti-human IL-6 receptor significantly reduces the development of the disease. Other studies have been done with human PCs from a leukemia line transformed by the Epstein-Barr virus (ARH77) [23]. SCID mice develop paralysis of the lower limbs 28 to 35 days after inoculation of ARH77 cells. Hypercalcemia is observed within 5 days after the onset of paralysis. Histological examination of various organs shows a PC infiltration of the liver, spleen, spine and long bones. A significant increase is observed in MIP-1α level in the bone marrow environment. In contrast, serum or medullar level of local factors such as IL-6, IL-1, TNF TGF-α, TNF-α, lymphotxin and PTHrp were not significantly increased, although ARH77 are able to produced IL-6 in vitro. Cell lines JNJ3 or KPMM2 have not been often used as an animal model for MM. In contrast, ARH77, despite the disadvantage of the EBV status, remained the most widely used cell line in the SCID model. Several types of treatment were tested in the ARH77 model like ibandronate, an antisense construct against MIP-1α and the recombinant RANK antagonist molecule RANK-Fc [29–31].

The route of inoculation has also an influence on the tumor development in the SCID model [32]. The intravenous route is preferred and is associated with typical osteolytic lesions. Intraperitoneal injection is accompanied by localizations in the pancreas, spleen, liver, intestine, kidney but bone marrow is rarely invaded. The intra-cardiac or intra-osseous combines injection direct intramedullary tumor growth associated with osteolytic lesions but also extramedullary proliferations.

Most of the SCID models which were described in the literature used MM cell lines. The transplant of fresh primary cells induced growth in SCID mice and production of monoclonal immunoglobulin but without colonization into the bone marrow [33,34]. Because of the difficulty to generate bone marrow colonization of fresh primary human MM cells using conventional SCID mice, xenografts of fresh MM cells were tested in a highly immunodeficient mouse; the non-obese diabetic SCID mice (NOD SCID). These mice are characterized by the absence of NK cells. Therefore, the majority of injection studies with xenogeneic PCs is performed in NOD SCID mice since year 2000 [26]. Injection of PCs from blood of MM patients using the intracardiac or intra-osseous route, leads to colonization into bone marrow and osteolytic lesions [26]. The time development to observe symptoms was fluctuant between one to five months depending of the PCs origin. Bones lesions are observed in different skeletal sites: long bones, vertebrae and also the skull.

The SCID model can be refined by grafting fragments of living human fetal long bone in the recipient animals, where they constitute a “micro-environnement” favoring the development of transplanted human PCs. This model (referred as SCID-hu) is associated with a homing of the human PCs within the fetal bone graft. Primary human MM cells can also be directly injected into the grafted bone [35]. Osteolytic activity develops only in the xenogeneic bony graft. Several studies on this model were focused on MM therapy such as anti-angiogenic drug thalidomide, inhibitor of DKK1 and the use of RANK-FC [36–38]. All treatments decrease osteolysis and MM progression. However, this model is cumbersome to implement and may raise ethical problems. The authors have also developed a similar model in which SCID mice are grafted with a piece of rabbit fetal bone (referred as SCID-rab) grafted similarly [39].

**The 5TMM model in the C57BL/KalwRij mouse**

The C57BL/KalwRij mouse was described by Radl et al. in 1978. With age, mice of this strain develop several monoclonal B-cell proliferative disorders with a frequency of 80% [40]. When mice are older than two years, 0.5% develops a typical MM or a Waldenström’s disease. Several spontaneous MM have been isolated and are called the 5TMM series. Different 5TMM lines were obtained after transplantation of bone marrow cells into syngeneic young mice by the intravenous route (Fig. 1). Eight 5TMM were isolated and most of them were characterized in detail: isotype of the M-protein, bone marrow involvement, presence of osteolytic
growth and osteolytic lesions. In addition and in contrast to the human disease, osteolysis represents the unique consequence of the inoculation of 5T2MM cells because of the absence of renal lesions due to light chain deposition [42]. On the other hand, the 5T33MM is a very aggressive line with a rapid tumor growth and involvement of other organs (non-hematopoietic), a condition, which is rarely observed in humans. Kinetic developments of these two models are strongly different: 5T2MM cells can be detected at nine weeks after inoculation whereas 5T33 can be observed as early as two weeks after inoculation [43]. In the 5T2MM model, osteolytic lesions can be observed from the 11th week and the end-stage occurs at 16-week post-injection of the PCs. In the 5T33MM model, the terminal stage of the disease is obtained 4–5 weeks after inoculation. A subclone of 5T33MA cells, which can grow in vitro, has been established and named the 5TGM1 cells [41,44]. When it is inoculated intravenously to young syngeneic mice, it reproduces the same pathological characteristics than those observed in the 5T33MA. More recently, both 5TGM1 and 5T33MM cell were used to generate fluorescent cells allowing visualization and localization of MM cells in whole body by fluorescence imaging [45,46]. Since the discovery of the 5TGM1subclone, the 5T33MM has been used less frequently. Moreover, despite the capacity of 5TGM1 to grow in vitro, the 5TGM1 model did not replace the 5T2MM model, which is remaining extensively used to study pathophysiology of MM and to evaluate new therapeutics.

Several studies have shown that 5T2MM and 5T33MM models have similar pathophysiological characteristics to those of human MM: the cytokine network involved and the adhesion molecules are the same. 5T2MM and 5T33MM express the following adhesion molecules: CD44, α4/β1 and α5/β1 [43,47,48]. Moreover in in vitro experiments, 5TGM1 cells establish direct contacts with stromal cells via the interaction of α4/β1 and VCAM-1. This finding is particularly interesting as interaction of PCs with stromal cells is essential for the tumor growth [2].

Osteolytic lesions have been well characterized in the 5T2MM mice [43,49,50]. X-ray assessment of bone lesions revealed that lesions are preferentially localized in long bones (proximal tibia, distal femur and humerus). In the mouse, these zones have physiologically a high bone turnover, this leads to a preferential localization of the tumor and secondarily promotes the tumor growth as several cytokines are mitogenic factors for PCs. The development of osteolytic lesions is well-studied using digital X-ray or mammography films [49,50]. Bone lesions appear as numerous small and round cavities that develop from the endosteal envelope. Lesions are preferentially localized in the metaphyses and also systematically observed at the tibial crest (Fig. 2). Lesions can be observed in the acetabulum and in the iliac crest when using an aggressive subclone of 5T2MM cells characterized by a faster development rate [51]. Bone lesions in the 5T2MM are therefore similar to those observed in human with one exception: the absence of bone lesions in the skull. However, the tibial crest of the mouse has a bony architecture, which mimics the human bones of the skull where the diploë (a kind of cancellous bone with large trabeculae) is limited by two thick cortices.

Histological examination of invaded bone shows that the marrow is replaced by tumor nodules at the terminal lesions and growth pattern [41]. Seven cell lines produce an IgG immunoglobulin with a light chain. The circulating monoclonal M-protein reflects the extent of the tumor load and can be easily monitored by electrophoresis of the serum (Fig. 1). Two lines have been particularly studied: the 5T2MM and 5T33MM. The 5T2MM represents a model situation of the most common forms of the human MM with a moderate
stage of the disease. Around the tumor nodules, there is a considerable increase in the number of osteoclasts. They are responsible for the resorption of trabecular as well as cortical bone. At the end stage of the disease, trabecular bone has completely disappeared and cortical perforations are evidenced (Fig. 3). Scanning electron microscopy was used to visualize and quantify the endosteal resorption on long bones. Eroded surface occupied almost the whole bone surface (Fig. 4). It has been shown that eroded surfaces occupy 76.2 ± 17.1% in ST2MM mice cells vs. 19.2 ± 7.1% in control mice [49]. X-ray microcomputed tomography (microCT) with 3D reconstruction can accurately visualize bone resorption, it confirms radiological findings, allows quantitative analysis of trabecular and cortical bone, and histological analysis is possible because the technique is non-destructive for the samples (Fig. 5).

Figure 2 X-ray image of the pelvis and hind legs of a C57BL/KalwRij mouse injected with ST2MM cells at end stage of the disease. Note the existence of numerous osteolytic lesions on both distal femur and proximal tibia.

Figure 3 Goldner trichrome stained section of the femur from ST2MM mice at early stage (A) and end stage (B) of the disease. At early stage, cortical bone and trabecular bone are preserved whereas at the end stage, trabecular bone has almost disappeared and several cortical perforations were observed (arrow). Note the existence of extramedullary extension of the tumor under the periosteum.

Figure 4 Scanning electron microscopy micrographs of the endosteal surface from vertebral body of a ST2MM mouse. The whole surface is eroded. Note the typical appearance of eroded surfaces formed of valleys and pits. Image de microscopie électronique à balayage de la surface endostée d’un corps vertébral chez une souris ST2MM. Toute la surface est érodée. Noter l’aspect typique des surfaces érodées (aspect de « coups de dents » ostéoclastiques).
The three models 5T2MM, 5T33MM and STGM1 have provided very useful data on key actors in the pathogenesis in MM and on the testing of new drugs. In MM, osteolysis is the consequence of both an increase in osteoclastic resorption and a decrease in osteoblastic formation. Alteration of the bone turnover is due to the release of local factors secreted by PCs directly or indirectly via normal cells of the bone microenvironment. Identification of these factors (termed osteoclast activating factors [OAF] by Mundy et al. [52]) came first from in vitro studies but their roles in vivo were confirmed by using the 5TMM models. The key role of the RANK/RANKL/OPG system in osteolysis has been shown in 5T2MM mice treated with a recombinant osteoprotegerin protein. Administration of OPG prevents osteolysis and preserves trabecular bone [53]. More recently it has been shown an increase of soluble RANKL in the serum of 5T2MM mice as seen in MM patients [54,55]. The increased level of soluble RANKL is associated with dramatic bone destruction strongly suggesting a key role for soluble RANKL in the pathogenesis of osteolysis [54]. In addition soluble RANKL is not detected in 5T33MM mice, thus confirming that 5T2MM model is more closely related to the human disease. Increased resorption in MM is also due to macrophage inflammatory protein-1α (MIP-1α) produced and released by PCs. In the STGM1 model, the increase in MIP-1α stimulates osteoclastic resorption; this increase is, in part, dependent from RANKL pathway [56]. Inhibition of MIP-1α in vivo has an effect both on osteolysis and on the tumor burden leading to an increase in the survival of mice.

Another specific aspect of MM concerns the molecular mechanisms leading to a reduced bone formation. Several factors have been identified: DKK1, sFRP-2, IL-3, Runx2 and TGF-β [2].

Most factors implicated in the pathogenesis of MM are produced and secreted in the bone marrow microenvironment, which is essential for the growth of PCs. In addition to local factors, physical interaction of PCs with various cells of the bone marrow (stromal cells, osteoclasts, endothelial cells) is required. Several studies have suggested that PCs modify bone marrow at the cellular and molecular level to promote growth and survival. A recent study has shown an increase in stromal cell number and a mirror decrease in osteoblasts number in MM patients [57]. This has been confirmed in the STGM1 model where an increase in stromal cells associated with a decrease of osteoblast number correlates with the tumor burden [57].

Another way to show the key role played by the microenvironment in MM progression is to modify the bone remodeling prior to the inoculation of PCs. Indeed, it has been shown that a high bone remodeling level (as induced by ovariectomy in mice) accelerates PC growth in the 5T2MM murine model and considerably increases the number of osteolytic foci (Fig. 6) [58]. Moreover, a subline of 5T2MM (the 5THL cells) has been selected by the altered microenvironment resulting in a more aggressive cell line with preservation of the original clone phenotype [51]. 5THL mice are characterized by a M-protein detectable 6 weeks after cells injection and osteolytic lesions start to appear at eight weeks; end stage of the disease being obtained at 10 weeks. Another method for increasing bone remodeling is to feed animals with a low calcium diet. This induces a secondary hyperparathyroidism and animals grafted with 5THL PCs have a considerable increase in the extend of osteolytic foci together with a more severe disease associated with frequent paraplegia due to invasion of the spinal canal by PCs (Fig. 7) [59]. The microenvironment is also enriched in microparticles (fragments of PC membrane covered with CD138) released by the malignant cells but the role of these cellular debris remains unknown [60]. Up to recently, no study on the 5TMM model was conducted to evaluate the
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existence of gene alterations. Recent data have identified deletion in the SAMS1 tumor gene suppressor in the 5TM1 model, which is correlated with human findings [61]. These data open the way for possible investigations in the pathogenesis of MM using the 5TM1 model.

As the 5TM1 model constitutes a good model to evaluate pathophysiological aspects of MM, it is also well adapted to evaluate various therapeutic strategies in MM. The effect of treatment combining interferon-α and melphalan was tested in ST33MM mice [62]. This combination significantly reduces tumor growth and leads to an increased animal survival. The use of antibodies against the IgG2ακ M-protein reduces tumor growth in most animals [63]. Bisphosphonates are currently the standard way to prevent and treat osteolytic disease in MM. These compounds have anti-osteoclastic properties by inducing apoptosis of these cells. Several types of bisphosphonates have been tested in the 5TM1 models. Initially, oral pamidronate (APD) was used in the 5TM1 [64]. Treated animals showed preservation of bone mass and partial restoration of osteolytic lesions. However, APD has no effect on the tumor mass itself [58,64]. The amino-bisphosphonate, ibandronate has also been tested in both models ST2MM and ST33MM [65]. It induces a significant reduction in the occurrence of osteolytic lesions; however, it has no effect on tumor growth or animal survival. It should be noted that in these models, the doses of bisphosphonates used are generally 100 times higher than those required in other animal models of bone hyper-resorption (such as the ovariectomized mice). New generations of bisphosphonates such as ZOL or apomine were tested in the 5TM1 model and showed interesting results as they act on several aspect of MM disease: osteolysis, tumor growth, survival and angiogenesis [66,67]. In these studies, treatment was started at early stage of the disease when the M-protein is detectable in the serum. ZOL and apomine have different modes of action: ZOL decreases osteoclastogenesis whereas apomine does not, suggesting a direct effect of apomine on PCs in vivo. This direct effect is not observed for all the other bisphosphonates in vivo but has been shown in vitro when PCs are cultured in presence of ZOL added to the medium [68]. A comparison between ZOL and APD was recently done in the 5THL model. Previous studies have shown that APD preserved the trabecular bone mass but had no effect on the amount of cortical perforations. A microCT
analysis evidenced that ZOL was superior to APD and considerably reduced the number and size of cortical perforations [69].

Because of advances in the comprehension of MM pathophysiology, novel therapeutic approaches have emerged and some were tested in the ST2MM model. The proteasome, which constitutes the physiological way to degrade proteins in eucaryotic systems, was found to play a key role in MM. It is involved in the regulation of the RANK/RANKL system and proteasome inhibitors (such as bortezomid) are currently used in the treatment of human MM [70]. Proteasome inhibitors have also been shown to promote osteoblast differentiation and bone formation [71]. Treatment of ST2MM mice with bortezomid reduces the incidence of bone lesions, tumor growth and angiogenesis [72]. The effect of proteasome inhibitors in vivo is mediated by PTH receptors [73]. In parallel to these treatments, radioimmunotherapy targeting syndecan (CD138 antigen) were conducted in ST3MM mice and it has been suggested to use in combined therapies [74–76].

Because MM always induced a marked reduction in bone formation, several trial have been done with drugs known to stimulate osteoblasts by acting on the Wnt pathway:

- fluoride was used in clinical practice but induced fluorosis without healing of MM lesions [77,78] however, the drug was never evaluated in the mouse;
- parathyroid hormone was successfully tested in the SCID-hu and SCID-rab model and promoted bone formation [79], however, clinical data are contradictory [80];
- stimulation of the Wnt pathway by lithium chloride protects STG1 mice against osteolysis and decreases tumor growth [81].

The use of anti-DKK1 antibodies in the ST2MM mice induces similar effects [82].

Conclusion

As usual with animal models, the development of such systems is very interesting since they offer the possibility to evaluate new hypothesis and therapeutics strategies. However, they do not represent exactly the human disease and differences are noted when trying to predict human response to drugs. Animal models are interesting to test hypothesis and understand the pathophysiological mechanisms of the disease and exploring new genetic or pathways hypotheses.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

References

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