The Bone Niche of Chondrosarcoma: A Sanctuary for Drug Resistance, Tumour Growth and also a Source of New Therapeutic Targets.

Emmanuelle David, Frédéric Blanchard, Marie-Françoise Heymann, Gonzague de Pinieux, François Gouin, Françoise Rédini, Dominique Heymann

To cite this version:
Emmanuelle David, Frédéric Blanchard, Marie-Françoise Heymann, Gonzague de Pinieux, François Gouin, et al.. The Bone Niche of Chondrosarcoma: A Sanctuary for Drug Resistance, Tumour Growth and also a Source of New Therapeutic Targets.. Sarcoma, Hindawi Publishing Corporation, 2011, 2011, pp.932451. 10.1155/2011/932451. inserm-00667904

HAL Id: inserm-00667904
https://www.hal.inserm.fr/inserm-00667904

Submitted on 8 Feb 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
The Bone Niche of Chondrosarcoma: A Sanctuary for Drug Resistance, Tumour Growth and also a Source of New Therapeutic Targets

E. David, F. Blanchard, M. F. Heymann, G. De Pinieux, F. Gouin, F. Rédinì and D. Heymann

1 INSERM, UMR 957, Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses primitives, Faculté de Médecine, 1 rue Gaston Veil, 44035 Nantes Cedex 1, 44035 Nantes, France
2 Université de Nantes, Nantes Atlantique Universités, Laboratoire de Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses primitives, 44035 Nantes, France
3 University Hospital, Hôpital Dieu, CHU de Nantes, 44035 Nantes, France
4 EA3855, University Hospital, 2 bd Tonnelle, 37044 Tours Cedex, France
5 University Hospital, Hôpital Trousseau, CHRU de Tours, 37042 Tours Cedex, France

Correspondence should be addressed to D. Heymann, dominique.heymann@univ-nantes.fr

Received 25 November 2010; Revised 28 January 2011; Accepted 10 February 2011

Academic Editor: Ole Nielsen

Copyright © 2011 E. David et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Chondrosarcomas are malignant cartilage-forming tumours representing around 20% of malignant primary tumours of bone and affect mainly adults in the third to sixth decade of life. Unfortunately, the molecular pathways controlling the genesis and the growth of chondrosarcoma cells are still not fully defined. It is well admitted that the invasion of bone by tumour cells affects the balance between early bone resorption and formation and induces an “inflammatory-like” environment which establishes a dialogue between tumour cells and their environment. The bone tumour microenvironment is then described as a sanctuary that contributes to drug resistance patterns and may control at least in part the tumour growth. The concept of “niche” defined as a specialized microenvironment that can promote the emergence of tumour stem cells and provide all the required factors for their development recently emerges in the literature. The present paper aims to summarize the main evidence sustaining the existence of a specific bone niche in the pathogenesis of chondrosarcomas.

1. Introduction

Most chondrosarcomas (90%) are conventional chondrosarcomas which occur in the medullar cavity or at the bone surface. The fact that cartilaginous tumours are mainly observed in bones formed from endochondral ossification strengthens the relationship between the differentiation of normal chondrocytes and these neoplastic cells. Chondrosarcoma cells are cytologically and phenotypically related to the different chondrocyte subtypes observed in the growth plate, and all cell shapes can be observed in the tumour mass [1–4]. Thus, these similarities are in favour of a mesenchymal stem-cell origin for chondrosarcoma cells [1, 5]. The development of cancer cells in bone site responds to several biological mechanisms potentially applicable to numerous other entities. For instance, invasion of bone by a primary or metastatic tumour cell affects the balance between early bone resorption and bone formation. This dysregulation of osteoblast-osteoclast coupling induces the release of factors initially trapped in the bone matrix, which in turn promote tumour cell proliferation [6]. Thus, the bone tumour microenvironment controls the tumour growth and is also described as a sanctuary that contributes to drug resistance patterns [7]. The specific and different bone sites in which the various sarcomas are able to grow reinforce the prominence of the tumour microenvironment. Chondrosarcomas are also characterized by their chemo- and radioresistance leading to a therapeutic surgical approach which remains the only available treatment with a 10-year survival between 30% and 80% depending on the grade [8, 9]. Currently, surgical excision is the main
treatment for all chondrosarcoma subtypes [10], and non-
surgical treatments of their microenvironment are under
investigation. In this context, a better understanding of the
bone niche which interacts with chondrosarcoma is one of
the future therapeutic options. The present paper aims to
describe the bone niche of chondrosarcoma, its role in
tumour growth and drug resistance, and its clinical interest as
a therapeutic target.

2. The Bone Niche Is Composed of
Heterogeneous Cell Types with
Coupled Activities

In 2003, two research laboratories demonstrated that osteo-
blasts formed an osteoblastic niche to sustain hemopoiesis
[11, 12]. Osteoblasts establish an “epithelial-like” tissue
which physically interacts with hemopoietic stem cells and
contributes to their maintenance in a quiescent stage through
the interaction between Tie-2 and angiopoietin-1 [13]. Nils-
son et al. showed that primitive hematopoietic cells resided
close to the bone surface [14]. From these observations, the
concept of bone niche has strongly evolved and has been
applied to cancer stem cells [15]. Indeed, the “niche” is
a functional microenvironment able to promote the emer-
gence of cancer stem cells and to provide all factors required
for their development. Naturally, this concept is well rec-
ognized in the context of hematologic malignancies such as
multiple myeloma [16] or leukemia [17], and these diseases
appear as a stem-cell disease with a hierarchy analogous
to normal hematopoietic development. However, the bone
niche is not limited to osteoblasts and during skeletal remod-
eling, numerous cell types (preosteoclasts, preosteoblasts,
endothelial cells, macrophages, etc.) are closely located in
the bone matrix and their functional coordination is a pre-
requisite to maintain the bone and the bone niche microar-
chitecture. Using three-dimensional visualizations, Andersen
et al. clearly demonstrated the functional relevance of these
cellular interactions in the bone niche [18]. In physiological
conditions in which bone resorption and bone formation
are coupled, the bone surface is always covered by canopy
composed by flat cells expressing osteoblastic markers and
associated with sinusoidal vessels [18]. Disruption of this
canopy results in the dysregulation of the coupled bone-
formation bone-resorption process and leads to a bone
deficiency [18]. These very elegant observations revealed
that the bone niche is composed of multiple cell entities.
Macrophages also contribute to the bone niche as shown by
Chang et al. [19]. Indeed, a discrete population of resident
macrophages has been identified between bone lining cells
within endosteum and periosteum. These osteal tissue
macrophages are involved in bone dynamics by controlling
osteoblast functions and, more specifically, are required for
efficient osteoblast mineralization [19]. Into the bone niche,
self-renewal and differentiation activity are clearly balanced
as shown for hemopoietic stem cells [16, 17], and this
balance is being controlled by the level of hypoxia, which
modulates the interactions between tumour cells and the
components of bone niche. The proliferation stage of stem
cells is predominant with increased levels of oxygen and
hypoxia resulting in opposite effects [20, 21].

The concept of bone niche is also currently discussed for
solid tumours and strengthens the very modern theory of
“seed and soils” proposed by Paget in 1887 in which tumour
cells (“seeds”) would colonize receptive foci (“soils”) [22].
This data is supported by the fact that specific molecules
(e.g., cadherin and osteopontin) contribute to the stabi-
lization of cancer cells in bone niches mimicking the cell
interactions which take place during hemopoiesis [23, 24].
Such interactions have been identified in the premetastatic
niche of breast carcinoma, where carcinoma cells grow avidly
in bone which stores a variety of cytokines and growth
factors and thus provide an extremely fertile environment
for growing cells [25, 26]. The seed and soil theory can be
also envisaged for the primary bone tumours. In a recent
study, we reported an unexpected local osteosarcoma relapse
which occurred at the exact site of autologous fat grafts in
a patient who did not present any predictive factor of local
recurrence [27]. Moreover, we showed that tumour growth
was promoted by fat injection using a human osteosarcoma
model induced in athymic nude mice. We then demonstrated
that the mesenchymal stem cells isolated from adipose
tissue induced exactly the same effect, probably reactivating
quiescent tumour cells locally deposited into the bone tissue
[27]. A recent study reinforces this theory by presenting 8
cases of osteosarcoma development several years after benign
bone tumour treatment by curettage associated with bone
graft. To explain the development of “de novo” sarcomas
in these patients, an attraction mechanism of mesenchymal
stem cells by the scaffold has been hypothesized [28].
Although mechanisms by which cancer stem cells could drive
the tumour growth are still unknown, modulation of the
microenvironment by mesenchymal stem cells may interfere
with the biological behavior of this cell subpopulation.
Similarly, inflammatory process associated with surgery may
be also responsible for the reactivation of dormant tumour
cells [29, 30]. Thus, a disturbance of the microenvironment
and the bone niche modifies the proliferation/differentiation
program of the tumour cells.

3. The Bone Niche of Chondrosarcoma

The key role of bone microenvironment in chondrosarcoma
development has been suspected many years ago. Indeed,
a rat intraosseous model simulating the progression of
human chondrosarcoma has been set up to assess the inter-
actions between bone environment and chondrosarcoma
[31]. Transplantation of swarm rat chondrosarcoma within
bone marrow or in close contact to the bone with induced
periosteal lesions led to extensive bone remodelling with
trabecular bone rarefaction and periosteal apposition asso-
ciated with tumour growth. In contrast with these results,
transplantation in close contact to the bone but without
any periosteal lesion had no effect on bone, suggesting that
bone healing factors interact with tumour development. The
tumours which developed in intramedullary environment
presented different foci with various gradings confirming
that bone environment is an important factor in the pathogenesis of chondrosarcoma [31]. Histological examination of conventional chondrosarcoma reveals the presence of numerous cells types in close contact to the cartilaginous tumour cells (Figures 1(a) and 2). The morphology of cartilaginous tumour cells depends on the grading of the tumour and associated cartilage-like tissue composed by tumour chondrocytes with heterogeneous shapes (Figures 1(b)–1(e)) and tumour cell types with mesenchymal aspect (Figure 1(e)). The tumour mass is characterized by lobular foci separated by vascularized soft tissue, which establishes a continuum with bone marrow or with the surrounding tissues (Figure 1). When chondrosarcoma develops in the medullary space (central or primary chondrosarcoma), the tumour cells induce the dysregulation of the balance between osteoblasts and osteoclasts, degrading the trabecular bone, perturbing the bone marrow environment. When chondrosarcoma develops from the bone surface (peripheral or secondary chondrosarcoma), tumour mass exhibits a similar lobular morphology associated with a periosteal reaction [31]. These peripheral chondrosarcoma develop on preexisting osteochondroma defined as the most common benign bone tumours and characterized by a cartilage-capped exophytic lesion that arises from the bone cortex. Nevertheless, the limit between osteochondroma and chondrosarcoma is still unclear, especially with low-grade chondrosarcoma that is closely related to osteochondroma. These tumours interact with periosteum mimicking the “bone niche”. Periosteum is a continuous membrane intimately linked covering the bone, well vascularized and containing osteoprogenitor cells including mesenchymal stem cells [32–34]. Thereby, peripheral and central chondrosarcoma can interact with the same kind of bone microenvironment. The permeation of tumour cells into the bone tissue is associated with the activation of bone resorption through the induction of osteoclast formation (Figures 1(f) and 2). In fact, the bone niche of chondrosarcoma includes all cell types described in the other neoplastic bone diseases. The narrow relationship between chondrosarcoma cells, soft tissue, vessels, and bone cells strengthens the relevance of a specific bone niche able to sustain tumour growth.

Can we suspect the existence of cancer stem cells in this bone niche which could be at the origin of chondrosarcoma and become quiescent in specific circumstances? Expression of SOX9 in human chondrosarcomas suggests that chondrosarcomas originate from a multipotent stem cell committed to differentiation along the chondrogenic pathway [35]. Moreover, the results of the cDNA array analyses emphasize the heterogeneous nature of chondrosarcoma. Using similar approaches, Boeuf et al. [36] proposed a new classification of chondrosarcoma in two clusters: a prechondrogenic phenotype with immature cells and a chondrogenic phenotype composed of more mature cells. Primary conventional central chondrosarcoma cells could be then grouped into two main clusters with distinctive marker expression signatures: one group clustering together with mesenchymal stem cells (CD49b-high/CD10-low/CD221-high) and a second group clustering close to fibroblasts (CD49b-low/CD10-high/CD221-low) [37]. These data strongly suggest the existence of cancer stem cells possibly with mesenchymal stem cells or fibroblast markers. Although most of the literature on chondrosarcoma has confirmed that adequate surgery is the mainstay of treatment for local tumour control, which itself constitutes a risk factor for survival, an additional feature of chondrosarcoma is also the high level of local recidive even in case of adequate surgery [38–40]. This feature is also in favour of the existence of cancer stem cells in the bone marrow which may remain dormant until some yet unknown signals promote their growth or metastasis formation in bone tissue.

Hypoxia is a signal resulting in a large number of adaptive changes aimed at surviving in the hypoxic environment as well as correcting the oxygen deficit. Hypoxia inducing factor (HIF)-1 is a dimeric transcription factor composed of HIF-1 alpha and beta subunits. HIF-1 protein levels increase as a result of decreased degradation of the oxygen sensitive subunit HIF-1α. HIF-1 modulates changes in gene expression during hypoxia. Although the angiogenesis compound of cartilage tumours is heterogeneous [41], hypoxia modulates the proliferation of chondrosarcoma cells similarly to the other solid tumour types and hemopoietic neoplasia. Thus, there is a significant relationship between the expression of HIF-1α, the microvessel density and the proliferating cell nuclear antigen [42]. Several authors demonstrated that malignant chondrocytes increased HIF-1α expression in an oxygen concentration-dependent manner and increased VEGF expression in response to hypoxia [43–46] which is closely related to the potential malignancy of chondrosarcoma [47, 48]. Hypoxia is also known to increase chemokine receptor expression such as CXCR4 in numerous cell types [49] and CXCR4/SDF1 also indirectly promotes the proliferation and migration of tumour cells and enhances tumour-associated angiogenesis [50]. CXCR4 expressed by tumour cells contributes to their migration into the premetastatic niche [51]. Interestingly, chondrosarcoma cell invasion is increased by hypoxia-induced expression of CXCR4 and MMP1, a process mediated by HIF1α and ERK [52], and CXCL12, also called SDF-1, increases the invasiveness of chondrosarcoma cells [53]. Other chemokine/chemokine receptors couples are also involved in chondrosarcoma progression. Thus, the interaction of CCL5 (RANTES), a product of activated T cells present in bone environment during the tumour process with CCR5 expressed on the cell membrane enhances the migration of chondrosarcoma cells through the increase of MMP-3 production [54]. Overall, these data point out the similarities between the behaviour of chondrosarcoma cells and the invasion of leukaemia cells in the bone niche [51]. Osteopontin is also a typical example of these similarities. Indeed, osteopontin could mediate the anchoring of cancer cells in osteoblastic niches in a manner that mimics the mechanisms used by osteoblast to retain hemopoietic stem cells in these niches and to negatively regulate stem-cell pool size [55]. Osteopontin also influence the behaviour of carcinoma cells (proliferation, invasiveness, etc.) [56]. Similarly, osteopontin located in the bone matrix increases the migration and MMP expression in human chondrosarcoma and contributes to the pathogenesis of chondrosarcoma in its bone niche [57]. More
recently, Vincourt et al. [58] demonstrated not only that the respective levels of C-propeptides of procollagens I and II in chondrogenic tumours but also that the interactions of chondrosarcoma cells with the surrounding extracellular matrix may modulate tumour progression, angiogenesis, and metastasis. C-propeptides of procollagen I favor angiogenesis and tumour progression, whereas C-propeptides of procollagen II exert antitumour and antangiogenic properties through apoptosis induction when they are immobilized, and progression and metastasis when they are soluble [58]. Endostatin derived from collagen XVIII, a potent endogenous antiangiogenic factor that induces regression of various tumours of epithelial origin, prevents the chondrosarcoma growth via its potential activity on endothelial cells [59]. These results demonstrate that bone microenvironment and extracellular matrix establish a very complex bone niche adapted to the tumour progression.

The interactions between the extracellular matrix of bone niche and chondrosarcoma cells are tightly controlled by cytokines and growth factors produced by the environmental cells (osteoblasts, endothelial cells, macrophages, lymphocytes, etc.) and also by tumour cells themselves [60]. Proinflammatory cytokines are particularly associated with the pathogenesis of chondrosarcoma. Interleukin (IL)-1 regulates the expression of a disintegrin and metalloproteinase with thrombospondin motifs 1 (ADAMTS1) and VEGF by chondrosarcoma cells, then contributing to a strong positive impact of IL-1 on vascularization and tumour progression [61]. TNF-α, another proinflammatory cytokine, induced MMP-12 expression in chondrosarcoma cells when chondrocytes undergo malignant transformation [62] and increased also MMP-13 [63]. Members of TGF-β superfamily play also a crucial role in migration and metastasis of human chondrosarcoma. For instance, TGF-β1 and BMP-2 increase
motility of human chondrosarcoma via the PI3K/Akt pathway [64, 65]. Oncostatin (OSM), a member of IL-6 cytokine family, induces a hypertrophic differentiation, with reduced SOX9 and induced Chfa1, Coll10, MMP13, VEGF, and RANKL expression in chondrosarcoma cells. RANKL being a pro-osteoclastogenesis factor and then a proresorptive factor, OSM enhances osteoclast formation at the tumour/bone interface and reduces the ectopic bone neoformation [66].

4. The Bone Niche: A Sanctuary for the Drug Resistance and a Source of New Therapeutic Targets

Although bone niche represents an adequate microenvironment for the survival/proliferation of cancer stem cells and has been identified as a major parameter regulating the metastatic process [67], recent studies also described the tumour microenvironment as a sanctuary contributing to the phenomenon of drug resistance [68]. The process of drug resistance has been shown to be mediated through (i) soluble factors such as cytokines or adhesion molecules constituting de novo drug resistances or (ii) acquired drug resistance linked to resistance mechanisms caused by selective pressure of chemotherapy or other therapeutic drugs [68]. Chondrosarcomas are poorly vascularized in correlation with resistance to systemic chemotherapy and exhibit poor metastatic potential. However, although this poor vascularization represents a first explanation for the drug resistance, the bone niche also contributes to this resistance as observed for other tumour entities. In this context, a better definition of bone niche leads to the identification of relevant drug targets to improve the efficiency of the current treatment. This concept has been already validated in leukemia [69]. In sarcomas, similar approaches have been also envisaged [70]. Targeting of angiogenesis has been assessed in combination of chemotherapy and induced tumour necrosis [71]. Cyclooxygenase-2 (COX-2), a mediator of angiogenesis, is expressed in malignant cartilaginous tumours [72]. In chondrosarcoma, the use of celecoxib, a COX-2 inhibitor, first results in a decrease in tumour volume followed unfortunately by a relapsed tumour growth after 6 weeks [73]. Higher doses of COX-2 may be used, or a combinatory therapy based on this concept may be designed. HDAC4 represses VEGF expression and associated angiogenesis in chondrosarcoma [74]. Similarly, a therapeutic approach of chondrosarcoma based on HDAC inhibitor administration may be interesting [75, 76]. Bisphosphonates and rapamycin and its derivatives have been originally developed, respectively, as antiresorptive and antifungal agents [77, 78]. However, in vitro and in vivo experiments demonstrated that these compounds are multifunctional molecules exerting their effects not only on bone remodelling but also on tumour cell growth. mTOR targeting has been envisaged for numerous cancer types including malignant primary bone tumours [78–80], and a very impressive response of myxoid chondrosarcoma has been obtained
in combination with cyclophosphamide [81]. The main targets of bisphosphonates are bone-resorbing osteoclasts [82] which contribute to the hemopoietic and tumour bone niche [82]. Bisphosphonates also reduce the proliferation and invasion of chondrosarcoma [83, 84]. In preclinical model of chondrosarcoma, zoledronic acid slows down rat primary development and recurrent tumour progression after intralesional curettage and increases overall survival [85]. Thus, osteoclasts targeting may be used in prevention of chondrosarcoma recurrence. Cytokinetic treatment represents another relevant therapeutic approach of chondrosarcoma [2]. Oncostatin M, a member of the IL-6 cytokine family mainly produced by macrophages, neutrophils, and T lymphocytes, is a cytostatic factor for chondrosarcomas in vitro and in vivo [66]. This growth inhibitory effect is also observed with two other cytokines of the same family able to reduce chondrosarcoma expansion but with a lower efficiency: IL-6 in association with its soluble receptor and IL-27 [66]. This list is not exhaustive but gives some evidence of the interest to target or to modulate the bone niche components to improve chondrosarcoma treatment.

5. Conclusion

The treatment of chondrosarcoma is currently based on surgery, radiotherapy, and chemotherapy being occasionally used for metastatic tumours. However, a recent concept has emerged based on the key role played by the tumour micro-environment in the tumour invasiveness and in the drug-resistance phenomenon. This bone niche allows to identify new therapeutic targets for chondrosarcoma, and it appears clearly that a better understanding of the chondrosarcoma bone niche will open nonsurgical therapeutic options for chondrosarcoma which could also be combined with surgery.

Acknowledgments

This work was supported by La Ligue Contre Le Cancer. E. David received a fellowship from the Ministère de la Recherche.

References

[1] S. Boeuf, P. Kunz, T. Hennig et al., “A chondrogenic gene expression signature in mesenchymal stem cells is a classifier of conventional central chondrosarcoma,” Journal of Pathology, vol. 216, no. 2, pp. 158–166, 2008.
[2] J. V. M. G. Bovée, A. M. Cleuton-Jansen, A. H. M. Taminiau, and P. C. W. Hogendoorn, “Emerging pathways in the development of chondrosarcoma of bone and implications for targeted treatment,” Lancet Oncology, vol. 6, no. 8, pp. 599–607, 2005.
[3] T. Aigner, “Towards a new understanding and classification of chondrogenic neoplasias of the skeleton—biochemistry and cell biology of chondrosarcoma and its variants,” Virchows Archiv, vol. 441, no. 3, pp. 219–230, 2002.
[4] H. Gelderblom, P. C. W. Hogendoorn, S. D. Dijkstra et al., “The clinical approach towards chondrosarcoma,” Oncologist, vol. 13, no. 3, pp. 320–329, 2008.
[5] G. De Pinieux and C. Bouvier, “Recent advances in the biology of bone tumors and new diagnostic tools,” in Bone Cancer, D. Heymann, Ed., chapter 19, pp. 225–234, Academic Press, New York, NY, USA, 2010.
[6] Y. Wittrant, S. Théoleyre, C. Chipoy et al., “RANKL/RANK/OPG: new therapeutic targets in bone tumours and associated osteolysis,” Biochimica et Biophysica Acta, vol. 1704, no. 2, pp. 49–57, 2004.
[7] M. B. Meads, L. A. Hazlehurst, and W. S. Dalton, “The bone marrow microenvironment as a tumor sanctuary and contributor to drug resistance,” Clinical Cancer Research, vol. 14, no. 9, pp. 2519–2526, 2008.
[8] M. Campanacci, Bone and Soft Tissue Tumors, Springer, New York, NY, USA, 2nd edition, 1999.
[9] E. L. Staals, E. Palmerini, S. Ferrari, and M. Mercuri, “Non-surgical treatment of chondrosarcoma: current concepts and future perspectives,” in Bone Cancer, D. Heymann, Ed., chapter 31, pp. 375–383, Academic Press, New York, NY, USA, 2010.
[10] J. Zhang, C. Niu, L. Ye et al., “Identification of the haematopoietic stem cell niche and control of the niche size,” Nature, vol. 425, no. 6960, pp. 836–841, 2003.
[11] T. Yin and L. Li, “The stem cell niches in bone,” Nature Medicine, vol. 18, no. 9, pp. 1195–1201, 2006.
[56] J. C. Reichert, V. M. C. Quent, L. J. Burke, S. H. Stansfield, J. A. Clements, and D. W. Hutmacher, “Mineralized human primary osteoblast matrices as a model system to analyse interactions of prostate cancer cells with the bone microenvironment,” Biomaterials, vol. 31, no. 31, pp. 7928–7936, 2010.

[57] Y. J. Chen, Y. Y. Wei, H. T. Chen et al., “Osteopontin increases migration and MMP-9 up-regulation via αvβ3 integrin, FAK, ERK, and NF-κB-dependent pathway in human chondrosarcoma cells,” Journal of Cellular Physiology, vol. 221, no. 1, pp. 98–108, 2009.

[58] J. B. Vincourt, S. Etienne, J. Cottet et al., “C-propeptides of procollagenses Iα1 and II that differentially accumulate in enchondromas versus chondrosarcomas regulate tumor cell survival and migration,” Cancer Research, vol. 70, no. 11, pp. 4739–4748, 2010.

[59] T. Furumatsu, N. Yamaguchi, K. Nishida et al., “Endostatin inhibits adhesion of endothelial cells to collagens I via αvβ3 integrin, a possible cause of prevention of chondrosarcoma growth,” Journal of Biochemistry, vol. 131, no. 4, pp. 619–626, 2002.

[60] P. Rutkowski, J. Kamińska, M. Kowalska, W. Ruka, and J. Steffen, “Cytokine and cytokine receptor serum levels in adult bone sarcoma patients: correlations with local tumor extent and prognosis,” Journal of Surgical Oncology, vol. 84, no. 3, pp. 151–159, 2003.

[61] T. Kalinski, S. Krueger, S. Sel, K. Werner, M. Röpke, and A. Roessner, “ADAMTS1 is regulated by interleukin-1β, not by hypoxia, in chondrosarcoma,” Human Pathology, vol. 38, no. 1, pp. 86–94, 2007.

[62] E. Kerkela, T. Böhling, R. Herva, J. A. Uria, and U. Saarialho-Kere, “Human macrophage metalloelastase (MMP-12) expression is induced in chondrocytes during fetal development and malignant transformation,” Bone, vol. 29, no. 5, pp. 487–493, 2001.

[63] S. W. Yoon, J. S. Chun, M. H. Sung, J. Y. Kim, and H. Poo, “α-MSH inhibits TNF-α-induced matrix metalloproteinase-13 expression by modulating p38 kinase and nuclear factor-kB signaling in human chondrosarcoma HTB-94 cells,” Osteoarthritis and Cartilage, vol. 16, no. 1, pp. 115–124, 2008.

[64] Y. Y. Yeh, C. C. Chiao, W. Y. Kuo et al., “TGF-β1 increases motility and αvβ3 integrin up-regulation via PI3K, Akt and NF-κB-dependent pathway in human chondrosarcoma cells,” Biochemical Pharmacology, vol. 75, no. 6, pp. 1292–1301, 2008.

[65] Y. C. Feng, T. M. Li, C. M. Wu et al., “BMP-2 increases migration of human chondrosarcoma cells via PI3K/Akt pathway,” Journal of Cellular Physiology, vol. 217, no. 3, pp. 846–855, 2008.

[66] E. David, P. Guillard, B. Brouns et al., “Direct anti-cancer effect of oncostatin M on chondrosarcoma,” International Journal of Cancer, vol. 128, no. 8, pp. 1822–1835, 2011.

[67] J. A. Joyce and J. W. Pollard, “Microenvironmental regulation of metastasis,” Nature Reviews Cancer, vol. 9, no. 4, pp. 239–252, 2009.

[68] M. B. Meads, L. A. Hazlehurst, and W. S. Dalton, “The bone marrow microenvironment as a tumor sanctuary and contributor to drug resistance,” Clinical Cancer Research, vol. 14, no. 9, pp. 2519–2526, 2008.

[69] M. Konopleva, Y. Tabe, Z. Zeng, and M. Andreeff, “Therapeutically targeting of microenvironmental interactions in leukemia: mechanisms and approaches,” Drug Resistance Updates, vol. 12, no. 4-5, pp. 103–113, 2009.