OPEN ACCESS

Biomarkers of chondrosarcoma

Wonju Jeong,¹ Ha-Jeong Kim^{2,3}

¹Department of Orthopedic Surgery, Daegu Top Hospital, Daegu, The Republic of Korea

²Department of Physiology, School of Medicine, Kyungpook National University, Daegu, The Republic of Korea

³BK21 Plus KNU Biomedical Convergence Program, Department of Biomedical Science, School of Medicine, Kyungpook National University, Daegu, The Republic of Korea

Correspondence to

Prof Ha-Jeong Kim, Department of Physiology, School of Medicine, Kyungpook National University, Daegu 41944, The Republic of Korea; kimhajeong@knu.ac.kr

Received 31 January 2018

Revised 1 March 2018

Accepted 6 March 2018

Published Online First

28 March 2018

ABSTRACT

Clinical outcome prediction is major concern to patients with cancer. Various molecular markers in various carcinomas have been identified in the past few decades. However, accurate predictors in chondrosarcoma have not been developed, even though chondrosarcoma is the second most common primary bone tumour. Chondrosarcoma is the cartilage-forming malignancy and shows a wide spectrum of clinicopathological behaviours. The majority of chondrosarcoma grows slowly and rarely metastasises, and adequate surgery leads to a good prognosis. However, wide surgical excision is acquired in high-grade chondrosarcoma, because this tumour is highly resistant to chemotherapy and radiotherapy. To decide best therapy, accurate diagnostic markers are also necessary in chondrosarcoma. It is reported that angiogenesis and lymphangiogenesis increase by chondrosarcoma staging, and they are promoted by leptin and adiponectin. Several microRNAs to regulate vascular endothelial growth factor (VEGF)-A and VEGF-C are also reported. Alpha-methylacyl-CoA racemase and periostin are proposed as new biomarkers for differential diagnosis of enchondroma and chondrosarcoma. This review summarises that chondrosarcoma diagnostic markers are currently reported.

INTRODUCTION

Chondrosarcoma is a cartilage-forming bone tumour that is classified into several types based on the pathological lesion, the presence of previous lesion and the histological grade.^{1,2} A majority of primary chondrosarcomas develop de novo, and secondary chondrosarcomas arise from benign precursor lesion such as osteochondroma. Depending on the pathological lesion, chondrosarcomas divide into central chondrosarcomas, arising within the intramedullary space and peripheral chondrosarcoma arising on the bony surface. Histopathological grading is more related to tumour aggressiveness and disease prognosis. It is classified as grade I, II and III (low, intermediate and high grade) chondrosarcoma by H&E staining based on cellularity, matrix protein and mitoses. Because the clinical course of grade I is distinct from grade II and III, it is divided into low-grade (grade I) and high-grade (grade II and III).³ However, it is hard to distinguish between grade I (low-grade) chondrosarcoma and enchondroma based on H&E staining. Radiological findings and clinical information are importantly used to completely distinguish between low-grade chondrosarcoma and enchondroma (table 1).^{4,5}

When osteoid lesion is in chondroblastic mass (chondroid tumour), it is diagnosed as osteosarcoma or dedifferentiated chondrosarcoma.¹ The differential diagnosis between osteosarcoma and

dedifferentiated chondrosarcoma is relatively important issue because of the clinical management difference. Osteosarcoma is very sensitive to chemotherapy but not dedifferentiated chondrosarcoma. Galectin-1,⁶ NELL-1⁷ and SATB 2^{8,9} are reported as biomarkers for differential diagnosis, but they will not be mentioned in this review. In chondroid tumour but not in osteoid tumour, clinical feature and management of dedifferentiated chondrosarcoma is similar to high-grade chondrosarcoma.¹

Surgery is the first choice of treatment for chondrosarcomas because chondrosarcomas are generally insensitive to chemotherapy and radiation therapy. Patients with high-grade chondrosarcomas suffer from local recurrence and distant metastasis after surgical resection. Wide excision is recommended for curative treatment in order to prevent recurrence and metastasis; however, this causes malfunction in patients.^{1,10,11} Conserved excision is enough in patients with enchondroma, because enchondroma is rarely recurrent and metastasis.¹² However, the recurrence and metastasis will happen in patients with low-grade chondrosarcoma after conserved excision. Therefore, there is an urgent need to identify prognostic biomarkers with high accuracy and specificity to determine best clinical management, tumour aggressiveness and disease prognosis in patients.

Several molecules have been recently reported as biomarkers in the diagnosis, prognosis and treatment of chondrosarcomas. In this review, we summarise about these candidate biomarkers.

LEPTIN AND ADIPONECTIN

Leptin is an adipocyte-derived cytokine and binds to leptin receptors (short form (OBR) and long form (OBR1)) in many tissues.^{13,14} It is closely related to obesity and affects tumorigenesis, angiogenesis and metastasis in several cancers.^{15,16} OBR1 expression is increased in chondrosarcoma, but not in OBR.¹⁷ Leptin mRNA¹⁷ and protein¹⁸ expression is also increased in chondrosarcoma tissues. Leptin staining intensity is correlated with chondrosarcoma histological grade.¹⁸ Leptin enhances chondrosarcoma cell migration, angiogenesis and lymphangiogenesis by promoting vascular endothelial growth factor (VEGF)-A and VEGF-C secretion.^{17–19} Leptin-induced VEGF-C expression is negatively regulated by miR-27b.¹⁹ The authors suggest leptin can be used for staging in chondrosarcomas.

Adiponectin is also an adipocyte-derived cytokine like leptin, but with reduced metabolic disorders. Decrease of serum adiponectin increases the risk of obesity, colon, breast, endometrial and prostate cancer.^{20–22} Considering that adiponectin is reversely correlated with several carcinoma, it might decrease in chondrosarcoma. However, Lee *et al* have shown

To cite: Jeong W, Kim H-J. *J Clin Pathol* 2018;**71**:579–583.

Table 1 Compared clinical, radiological and pathological features of enchondroma and low-grade chondrosarcoma

	Enchondroma	Low-grade chondrosarcoma
History and physical examination	Younger patients Rarely pain Appendicular skeleton Phalanx, Ec almost 100%	Patients aged >25 years Inflammatory pain Axial skeleton
Imaging	No periosteal reaction No or minimal endosteal scalloping No changes during follow-up No soft tissue mass	Periosteal reaction and microfractures Endosteal scalloping Malignant change during follow-up Soft tissue mass
Biopsy	Typical encasement pattern No endosteal scalloping Multinodular aspect Surrounded by lamellar bone Not involved in bone marrow	Involved Haversian system Periosteal reaction, endosteal scalloping Occasional necrotic and haemorrhagic foci Involved in bone marrow

that adiponectin staining intensity is correlated with chondrosarcoma stage.²³ They also report that adiponectin promotes VEGF-A expression and angiogenesis, like leptin.²³ Adiponectin suppresses miR-27b expression in chondrosarcoma cell line and increases VEGF-C, like leptin.²⁴ Further studies on the role of leptin and adiponectin in chondrosarcoma oncogenesis and to define the relation between obesity and chondrosarcoma are needed.

PERIOSTIN

Periostin is a stromal-related protein, and exists in several carcinomas. It is well known that periostin enhances tumourigenesis by increasing cancer metastasis, cancer cell stemness, angiogenesis and lymphangiogenesis.²⁵ It is reported that periostin is not in enchondroma but in low-grade chondrosarcoma. In their report, Lai and Chen have suggested that periostin can be used as a biomarker to distinguish enchondroma and low-grade chondrosarcoma.²⁶ Further evaluations about periostin expression in chondroid tumour and long-term follow-up studies about the relation between periostin expression and clinical progression will lead to more knowledge about the chondroid tumour.

S100

S100 is a protein family composed of 21 members. It is characterised by two calcium-binding sites and modulates cellular responses.²⁷ Increased expression of distinct S100 protein has been reported in variety of cancers, and it is reviewed well.²⁷ S100 increase is reported in the chondrosarcoma.²⁸ However, S100 expression in enchondroma and its level by chondrosarcoma staging is not reported.

VASCULAR ENDOTHELIAL GROWTH FACTOR-A

VEGF-A is the essential cytokine for angiogenesis in tumour growth. Its expression is associated with chondrosarcoma grade, and is increased by leptin,¹⁸ adiponectin,²³ CCL5²⁹ and amphiregulin³⁰ in chondrosarcoma cell lines. miR-199a²⁹ and miR-206³⁰ are direct targets of VEGF-A, and they are decreased in chondrosarcoma. Even though VEGF-A is increased by chondrosarcoma staging, it is hard to use as a biomarker because angiogenesis always happens with tumour growth and not with malignant behaviour.

Amphiregulin is an epidermal growth factor receptor (EGFR) ligand, and is increased in chondrosarcoma tissue by its histological grade.³⁰ Amphiregulin-mediated VEGF-A increase is negatively

related to miR-206.³⁰ Amphiregulin is reported as a serological biomarker for evaluation of prognosis and therapeutic response in several carcinomas.^{31 32} Further studies, to define whether amphiregulin can be used in chondrosarcoma, are needed.

CCL5 is an inflammatory chemokine secreted by various cells including cancer cells,³³ and its expression is increased by chondrosarcoma stage.²⁹ Increased CCL5 promotes VEGF-A by suppression miR-119a.²⁹ CCL5 enhances migration through activation of matrix metalloproteinase-3 (MMP-3) and increased CCL5 enhances chondrosarcoma metastasis.³⁴ Taken these, increased CCL5 can be considered a marker of poor prognosis.

VASCULAR ENDOTHELIAL GROWTH FACTOR -C

VEGF-C is the major factor for lymphangiogenesis and also increased in various human carcinomas.³⁵ VEGF-C expression is increased by chondrosarcoma grade, and is increased from chondrosarcoma cells by leptin, adiponectin and brain-derived neurotrophic factor (BDNF), by the inhibition of miR-27b and miR-624-3p.^{19 24 36} miR-27 expression in chondrosarcoma tissues are not confirmed. miR-27 is suppressed by leptin¹⁹ and adiponectin,²⁴ and negatively regulates VEGF-C expression in chondrosarcoma cell line. miR-27b suppression is caused via FAK, PI3K and Akt signalling by leptin, or via CAMK11, AMPK and p38 signalling by adiponectin.^{19 24}

BDNF is known to promote metastasis in human chondrosarcoma cells. miR-624-3p expression is negatively regulated by BDNF via the MEK/ERK/mTOR cascade and directly suppresses VEGF-C in chondrosarcoma cell lines.³⁶ In chondrosarcoma tissues, BDNF and VEGF-C mRNA are increased and miR-624-3p is decreased in chondrosarcoma tissue.³⁶ VEGF-C is hard to use as a biomarker because lymphangiogenesis is also increased by tumour growth like angiogenesis. Even though VEGF-C and BDNF are increased in chondrosarcoma, these are not specific cytokines in chondrosarcoma. BDNF can be used as a biomarker after more evaluations.

SOX4 AND SOX9

Sex-determining region Y (SRY)-related high mobility group-BOX gene 4 (SOX4) is involved in various development processes and in multiple human cancers.³⁷ In chondrosarcoma, SOX4 is overexpressed in patients with chondrosarcoma, and its expression is associated with histological grade. Overexpressed SOX4 enhances cell proliferation and apoptosis in chondrosarcomas.^{38 39} miR-30a³⁸ and miR-129-5p³⁹ directly target on SOX4, and they are downregulated in chondrosarcoma tissues. SOX4 overexpression may serve as a prognostic marker for patients with low-grade chondrosarcoma.

SOX9 is the master regulator of chondrogenesis and increases in chondrosarcoma tissue and is directly targeted by miR-145.⁴⁰ miR-145 is down in chondrosarcoma cell lines, four patients samples and SOX9 is up.⁴¹ In other report, SOX9 is dramatically decreased in grade 1 chondrosarcoma.⁴² Taken these, SOX9 expression level may not be used as a prognostic marker, but can be used as a therapeutic target.

TRANSFORMING GROWTH FACTOR-BETA AND BONE MORPHOGENETIC PROTEIN SIGNAL

Transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs) are members of TGF-β superfamily. They are involve in the wide range of cellular processes, such as proliferation, differentiation, migration and death. TGFBR (TGF-β receptor) and BMPR (BMP receptor) transduce signals by Smads phosphorylation, and the activity of receptor-activated

Smads (R-Smads) in TGF- β and BMP signalling is higher in high-grade chondrosarcoma than in low-grade chondrosarcoma.^{43 44} BMPRs and runt-related transcription factor 2 (RUNX2) signalling in bone development and carcinogenesis are well known but not in chondrogenesis. Shinohara *et al*⁴² have revealed that phosphorylated Smad3 and Smad1/5 is increased in chondrosarcoma, and Yang *et al*⁴⁵ have shown that BMPR2 and RUNX2 expression is correlated with poor prognosis in 57 patients with various grades chondrosarcoma.⁴⁵ BMPR2 downstream Smad1/5 signal promotes tumour growth of chondrosarcoma cells in vivo.

Paternally expressed gene 10 (PEG10), suppressed by TGF- β , is also negatively expressed in chondrosarcoma. Enchondroma exhibited stronger expression of PEG10 compared with chondrosarcoma. Loss of PEG10 suppression causes the increase of phosphorylated Smad3 and Smad1/5.⁴² Taken together, BMPR2 and RUNX2 can be used as potential markers for prognosis.

SIRTUIN-1

Sirtuin (SIRT) is the NAD(+)-dependent histone deacetylase family, and is named SIRT1 to SIRT7.⁴⁶ Increased SIRT1 expression is reported in several cancers including prostate cancer, lung cancer, colon cancer and leukaemia.^{47–49} However, SIRT1 expression is decreased in breast cancer.⁵⁰ In chondrosarcoma, Feng *et al* have reported that SIRT1 is in chondrosarcoma cells and patients with SIRT1-expressed chondrosarcoma have poor prognosis. SIRT1 regulates the metastatic plasticity.⁵¹ Chao *et al* have reported that SIRT1 signalling is induced by resveratrol, a natural phenolic compound found in several plants,⁵² and induces human chondrosarcoma cell apoptosis.⁵³ Taken these reports, the role of SIRT1 in chondrosarcoma is still not clear. Further study is needed to use SIRT1 as a biomarker in chondrosarcoma.

SURVIVIN

Survivin is a member of the inhibitor of apoptosis protein family, and is encoded from baculoviral inhibitor of apoptosis repeat-containing 5 (*BIRC5*) gene.⁵⁴ Overexpression is reported in LNCaP (prostate cancer cell line) cells, osteosarcoma and chondrosarcoma.^{55–57} In high-grade chondrosarcoma, survivin is highly expressed in nucleus and its expression is correlated with p53 expression. YM115, a survivin inhibitor, induces apoptosis of chondrosarcoma cell line. It indicates survivin could be a possible new therapeutic target for chondrosarcoma and could serve as a predictive biomarker.⁵⁷

SPHINGOSINE-1-PHOSPHATE

Sphingosine-1-phosphate (S1P), phosphorylated from sphingosine by sphingosine kinase 1, is encoded by the *SPHK1* gene. ShpK1 is overexpressed in various types of cancers.⁵⁸ However, shpK1 expression decreases in chondrosarcoma tissue, and is negatively correlated with chondrosarcoma progression.⁵⁹ S1P suppresses chondrosarcoma metastasis by upregulation of tissue inhibitor of MMP-2 through suppressing miR-101 expression and increasing metalloproteinase inhibitor 3 (TIMP-3) expression. TIMP-3 is a direct target of miR-101. In chondrosarcoma tissue, ShpK1 and TIMP-3 are decreased and miR-101 is increased.⁵⁹ ShpK1 may be associated with clinicopathological stages in chondrosarcoma.

ALPHA-METHYLACYL-COA RACEMASE

Alpha-methylacyl-CoA racemase (AMACR) is a mitochondrial and peroxisomal enzyme that catalyses R- to S- conversion of 2-methylacyl-CoA derivatives of fatty acids enabling

beta-oxidation. AMACR expression is increased in variable cancers including prostate cancers.^{60–62} AMACR protein and mRNA are detected in enchondroma tissues (88.9%) but not in normal cartilage (0%) and minority of chondrosarcoma (21.1%). However, the specific role of AMACR in enchondroma is not clear.⁶³

HOTAIR

HOTAIR is a long non-coding RNA on human chromosome 12q13 within the antisense strand of HOXC gene cluster. It is highly expressed in metastatic cancers and is a predictor of prognosis.^{64 65} HOTAIR expression is correlated with chondrosarcoma stage and poor prognosis. HOTAIR knockdown leads to inhibition of chondrosarcoma cell growth in vitro and in vivo by the miR-454–3 p increase. STAT3, ATG12 and ATG3 are targets of miR-454–3 p. miR-454–3 p expression is down in chondrosarcoma tissues.⁶⁶ HOTAIR may act as a prognostic biomarker.

MICRORNAS

MicroRNAs (miRNAs) are small endogenous non-coding molecules that alter gene expression by regulating messenger RNA after transcription. Numerous evidences suggest miRNAs play important roles in oncogenesis and can be used for diagnostic, prognostic and predictive biomarkers in variable tumours. Several miRNAs are decreased in chondrosarcoma, and one miRNA is increased. Reported miRNA in chondrosarcoma is listed in table 2, and is explained above. Some miRNA is reported to enhance chemosensitivity in chondrosarcoma.

miR-23b,⁶⁷ which targets src kinase, and miR-100,⁶⁸ which targets mTOR, are downregulated in chondrosarcoma tissues and cell lines. miR-23b and miR-100 increase the sensitivity to cisplatin.^{67 68} miR-125b is also decreased in chondrosarcoma tissues and cell lines.⁶⁹ ErbB2 is a direct target of miR-125b. Overexpression of miR-125b inhibits chondrosarcoma cell proliferation and enhances the sensitivity to doxorubicin.⁶⁹

CONCLUSIONS AND FUTURE DIRECTIONS

Numerous biochemical and genetic biomarkers have been developed for several carcinomas in the last few decades. Biomarkers are used for diagnosis, prognosis and treatment. However, nothing is accurate in chondrosarcoma. Several biomarkers that have been reported recently, are listed in this review (table 3).

Leptin, adiponectin, VEGF-A and VEGF-C are increased in chondrosarcoma by staging. Both leptin and adiponectin promote VEGF-A and VEGF-C for angiogenesis and lymphangiogenesis.

Table 2 miRNAs in chondrosarcoma

miRNA	Target genes	Expression	Reference
miR-23b	Src kinase	Decrease	67
miR-27b	VEGF-C	Decrease	19, 24
miR-30a	SOX4	Decrease	38
miR-100	mTOR	Decrease	68
miR-101	TIMP-3	Increase	59
miR-119a	VEGF-A	Decrease	29
miR-125b	ErbB2	Decrease	69
miR-129–5p	SOX4	Decrease	39
miR-145	SOX9	Decrease	41
miR-206	VEGF-A	Decrease	30
miR-454–3p	stat3, atg12	Decrease	66
miR-624–3p	VEGF-C	Decrease	36

miRNA, microRNA; VEGF, vascular endothelial growth factor.

Table 3 Biomarkers in chondrosarcoma

	Tissue enchondroma	Chondrosarcoma	Cell line
Secreted protein			
Adiponectin		Increased by staging	Exist
Amphiregulin		Increased by staging	Exist
Brain-derived neurotrophic factor		Increased by staging	Exist
Leptin		Increased by staging	Exist
Periostin	No	Exist	
S100		Exist	
VEGF-A		Increased by staging	Exist
VEGF-C		Increased by staging	Exist
Signalling molecule			
AMACR	Exist	No	
BMPR2		Increased by staging	
HOTAIR		Increased by staging	Exist
RUNX2		Increased by staging	
S1P		Decreased	
Sirtuin-1		Exist	Exist
Survivin		Exist	
Nuclear factor			
SOX4		Increased by staging	Exist
SOX9	Exist	Decreased	Decreased

AMACR, alpha-methylacyl-CoA racemase; S1P, sphingosine-1-phosphate; VEGF, vascular endothelial growth factor.

Leptin and adiponectin suppress miR-27b. miR-27b and miR-624-3p target VEGF-C, and miR-119a target VEGF-A. VEGF-A and VEGF-C increase is found in all tumours. To use as biomarkers, further studies on proving the relation with prognosis are needed.

Other cytokines, which are found in any pathological site, CCL5 and BDNF, are also increased and are related to prognosis. SOX9, BMPR2 and RUNX2, which are involved in bone and chondrogenesis, are also increased and are related to prognosis.

Survivin inhibition and miR-23b, miR-100 and miR-125b expression enhance chemosensitivity. These can be used as therapeutic targets.

Ki67 is associated with cell proliferation and is used for prognostic marker in several carcinoma and also in chondrosarcoma.⁷⁰ S100, Sphk1, SOX4, amphiregulin and HOTAIR expression is found in many carcinomas and also in chondrosarcomas. It means these are not specific diagnostic markers in chondrosarcoma, but can be used for staging after further evaluations.

The differential diagnosis between enchondroma and low-grade chondrosarcoma is more important than chondrosarcoma staging because of clinical management. There are only two known biomarkers that can distinguish between enchondroma and chondrosarcoma. They are AMACR and periostin. AMACR is expressed in most enchondromas, but only in a minority of chondrosarcomas. Periostin is only expressed in low-grade chondrosarcomas but not in enchondromas and normal cartilages. This finding promises the possibility for a specific differential diagnostic marker. Further studies on the role of periostin in chondrosarcoma may lead to new knowledge of sarcoma oncogenesis.

In this review, several candidates for chondrosarcoma biomarkers are summarised. The sensitivity and specificity should be >90% to use as a biomarker. In chondrosarcoma,

Take home messages

- Differential diagnosis between enchondroma and low-grade chondrosarcoma is important to determine best clinical management.
- AMACR is expressed in most enchondromas, but only in a minority of chondrosarcoma.
- Periostin is only expressed in low-grade chondrosarcoma but not in enchondroma and normal cartilages.
- Follow-up studies for validation of AMACR and periostin should be facilitated.

nothing is reliable yet. Differential diagnosis between enchondroma and low-grade chondrosarcoma is important to orthopaedic surgeon because surgical excision range is changed. Follow-up study for validation of candidates should be facilitated.

Handling editor Runjan Chetty.

Contributors Both authors were involved in the writing of this review paper.

Funding This work was supported by Biomedical Research Institute grant, Kyungpook National University Hospital (2014).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Gelderblom H, Hogendoorn PC, Dijkstra SD, *et al.* The clinical approach towards chondrosarcoma. *Oncologist* 2008;13:320–9.
- Hogendoorn PC, Athanasou N, Bielack S, *et al.* Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl 5):v204–v213.
- Ahlmann ER, Menendez LR, Fedenko AN, *et al.* Influence of cryosurgery on treatment outcome of low-grade chondrosarcoma. *Clin Orthop Relat Res* 2006;451:201–7.
- Weiner SD. Enchondroma and chondrosarcoma of bone: clinical, radiologic, and histologic differentiation. *Instr Course Lect* 2004;53:645–9.
- Ferrer-Santacru EM, Ortiz-Cruz EJ, González-López JM, *et al.* Enchondroma versus Low-Grade Chondrosarcoma in Appendicular Skeleton: Clinical and Radiological Criteria. *J Oncol* 2012;2012:1–6.
- Gomez-Bouchet A, Mourcin F, Gourraud PA, *et al.* Galectin-1 is a powerful marker to distinguish chondroblastic osteosarcoma and conventional chondrosarcoma. *Hum Pathol* 2010;41:1220–30.
- Shen J, LaChaud G, Shrestha S, *et al.* NELL-1 expression in tumors of cartilage. *J Orthop* 2015;12(Suppl 2):S223–S229.
- Machado I, Navarro S, Picci P, *et al.* The utility of SATB2 immunohistochemical expression in distinguishing between osteosarcomas and their malignant bone tumor mimickers, such as Ewing sarcomas and chondrosarcomas. *Pathol Res Pract* 2016;212:811–6.
- Sangoi AR, Kshirsagar M, Horvai AE, *et al.* SATB2 expression is sensitive but not specific for osteosarcomatous components of gynecologic tract carcinomas: a clinicopathologic study of 60 cases. *Int J Gynecol Pathol* 2017;36:140–5.
- Dahlin DC, Henderson ED. Chondrosarcoma, a surgical and pathological problem; review of 212 cases. *J Bone Joint Surg Am* 1956;38-A:1025–38.
- Jamil N, Howie S, Salter DM. Therapeutic molecular targets in human chondrosarcoma. *Int J Exp Pathol* 2010;91:387–93.
- Nota SP, Braun Y, Schwab JH, *et al.* The Identification of Prognostic Factors and Survival Statistics of Conventional Central Chondrosarcoma. *Sarcoma* 2015;2015:1–11.

- 13 Campfield LA, Smith FJ, Guisez Y, et al. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 1995;269:546–9.
- 14 Tartaglia LA, Dembski M, Weng X, et al. Identification and expression cloning of a leptin receptor, OB-R. *Cell* 1995;83:1263–71.
- 15 Vona-Davis L, Rose DP. Adipokines as endocrine, paracrine, and autocrine factors in breast cancer risk and progression. *Endocr Relat Cancer* 2007;14:189–206.
- 16 Surmacz E. Obesity hormone leptin: a new target in breast cancer? *Breast Cancer Res* 2007;9:301.
- 17 Yang SN, Chen HT, Tsou HK, et al. Leptin enhances cell migration in human chondrosarcoma cells through OBRI leptin receptor. *Carcinogenesis* 2009;30:566–74.
- 18 Yang WH, Chen JC, Hsu KH, et al. Leptin increases VEGF expression and enhances angiogenesis in human chondrosarcoma cells. *Biochim Biophys Acta* 2014;1840:3483–93.
- 19 Yang WH, Chang AC, Wang SW, et al. Leptin promotes VEGF-C production and induces lymphangiogenesis by suppressing miR-27b in human chondrosarcoma cells. *Sci Rep* 2016;6:28647.
- 20 Miyoshi Y, Funahashi T, Kihara S, et al. Association of serum adiponectin levels with breast cancer risk. *Clin Cancer Res* 2003;9:5699–704.
- 21 Goktas S, Yilmaz MI, Caglar K, et al. Prostate cancer and adiponectin. *Urology* 2005;65:1168–72.
- 22 Tang CH, Lu ME. Adiponectin increases motility of human prostate cancer cells via adipoR, p38, AMPK, and NF-kappaB pathways. *Prostate* 2009;69:1781–9.
- 23 Lee HP, Lin CY, Shih JS, et al. Adiponectin promotes VEGF-A-dependent angiogenesis in human chondrosarcoma through PI3K, Akt, mTOR, and HIF- α pathway. *Oncotarget* 2015;6:5479.
- 24 Huang CY, Chang AC, Chen HT, et al. Adiponectin promotes VEGF-C-dependent lymphangiogenesis by inhibiting miR-27b through a CaMKII/AMPK/p38 signaling pathway in human chondrosarcoma cells. *Clin Sci* 2016;130:1523–33.
- 25 Mosher DF, Johansson MW, Gillis ME, et al. and TGF-beta-induced protein: Two peas in a pod? *Crit Rev Biochem Mol Biol* 2015;50:427–39.
- 26 Lai X, Chen S. Identification of novel biomarker candidates for immunohistochemical diagnosis to distinguish low-grade chondrosarcoma from enchondroma. *Proteomics* 2015;15:2358–68.
- 27 Bresnick AR, Weber DJ, Zimmer DB. S100 proteins in cancer. *Nat Rev Cancer* 2015;15:96–109.
- 28 Karamchandani JR, Nielsen TO, van de Rijn M, et al. Sox10 and S100 in the diagnosis of soft-tissue neoplasms. *Appl Immunohistochem Mol Morphol* 2012;20:445–50.
- 29 Liu GT, Huang YL, Tzeng HE, et al. CCL5 promotes vascular endothelial growth factor expression and induces angiogenesis by down-regulating miR-199a in human chondrosarcoma cells. *Cancer Lett* 2015;357:476–87.
- 30 Wang CQ, Huang YW, Wang SW, et al. Amphiregulin enhances VEGF-A production in human chondrosarcoma cells and promotes angiogenesis by inhibiting miR-206 via FAK/c-Src/PKC δ pathway. *Cancer Lett* 2017;385:261–70.
- 31 Yang J, Li S, Wang B, et al. Potential biomarkers for anti-EGFR therapy in metastatic colorectal cancer. *Tumour Biol* 2016;37:11645–55.
- 32 Zaiss DMW, Gause WC, Osborne LC, et al. Emerging functions of amphiregulin in orchestrating immunity, inflammation, and tissue repair. *Immunity* 2015;42:216–26.
- 33 Borsig L, Wolf MJ, Roblek M, et al. Inflammatory chemokines and metastasis—tracing the accessory. *Oncogene* 2014;33:3217–24.
- 34 Tang CH, Yamamoto A, Lin YT, et al. Involvement of matrix metalloproteinase-3 in CCL5/CCR5 pathway of chondrosarcomas metastasis. *Biochem Pharmacol* 2010;79:209–17.
- 35 Dieterich LC, Seidel CD, Detmar M. Lymphatic vessels: new targets for the treatment of inflammatory diseases. *Angiogenesis* 2014;17:359–71.
- 36 Lin CY, Wang SW, Chen YL, et al. Brain-derived neurotrophic factor promotes VEGF-C-dependent lymphangiogenesis by suppressing miR-624-3p in human chondrosarcoma cells. *Cell Death Dis* 2017;8:e2964.
- 37 Kamachi Y, Kondoh H. Sox proteins: regulators of cell fate specification and differentiation. *Development* 2013;140:4129–44.
- 38 Lu N, Lin T, Wang L, et al. Association of SOX4 regulated by tumor suppressor miR-30a with poor prognosis in low-grade chondrosarcoma. *Tumour Biol* 2015;36:3843–52.
- 39 Zhang P, Li J, Song Y, et al. MiR-129-5p Inhibits Proliferation and Invasion of Chondrosarcoma Cells by Regulating SOX4/Wnt/ β -Catenin Signaling Pathway. *Cell Physiol Biochem* 2017;42:242–53.
- 40 Martinez-Sanchez A, Dudek KA, Murphy CL. Regulation of human chondrocyte function through direct inhibition of cartilage master regulator SOX9 by microRNA-145 (miRNA-145). *J Biol Chem* 2012;287:916–24.
- 41 Mak IW, Singh S, Turcotte R, et al. The epigenetic regulation of SOX9 by miR-145 in human chondrosarcoma. *J Cell Biochem* 2015;116:37–44.
- 42 Shinohara N, Maeda S, Yahiro Y, et al. TGF- β signalling and PEG10 are mutually exclusive and inhibitory in chondrosarcoma cells. *Sci Rep* 2017;7:13494.
- 43 Feng XH, Derynck R. Specificity and versatility in tgf-beta signaling through Smads. *Annu Rev Cell Dev Biol* 2005;21:659–93.
- 44 Boeuf S, Bovée JV, Lehner B, et al. BMP and TGFbeta pathways in human central chondrosarcoma: enhanced endoglin and Smad 1 signaling in high grade tumors. *BMC Cancer* 2012;12:488.
- 45 Yang K, Tang XD, Guo W, et al. BMPR2-pSMAD1/5 signaling pathway regulates RUNX2 expression and impacts the progression of dedifferentiated chondrosarcoma. *Am J Cancer Res* 2016;6:1302–16.
- 46 Guarente L. Diverse and dynamic functions of the Sir silencing complex. *Nat Genet* 1999;23:281–5.
- 47 Huffman DM, Grizzle WE, Bamman MM, et al. SIRT1 is significantly elevated in mouse and human prostate cancer. *Cancer Res* 2007;67:6612–8.
- 48 Sun Y, Sun D, Li F, et al. Downregulation of Sirt1 by antisense oligonucleotides induces apoptosis and enhances radiation sensitization in A549 lung cancer cells. *Lung Cancer* 2007;58:21–9.
- 49 Stünkel W, Peh BK, Tan YC, et al. Function of the SIRT1 protein deacetylase in cancer. *Biotechnol J* 2007;2:1360–8.
- 50 Wang RH, Sengupta K, Li C, et al. Impaired DNA damage response, genome instability, and tumorigenesis in SIRT1 mutant mice. *Cancer Cell* 2008;14:312–23.
- 51 Feng H, Wang J, Xu J, et al. The expression of SIRT1 regulates the metastatic plasticity of chondrosarcoma cells by inducing epithelial-mesenchymal transition. *Sci Rep* 2017;7:41203.
- 52 Jiang M, Cai L, Udeani GO, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* 1997;275:218–20.
- 53 Chao SC, Chen YJ, Huang KH, et al. Induction of sirtuin-1 signaling by resveratrol induces human chondrosarcoma cell apoptosis and exhibits antitumor activity. *Sci Rep* 2017;7:3180.
- 54 Altieri DC. Survivin - The inconvenient IAP. *Semin Cell Dev Biol* 2015;39:91–6.
- 55 Zhang M, Latham DE, Delaney MA, et al. Survivin mediates resistance to antiandrogen therapy in prostate cancer. *Oncogene* 2005;24:2474–82.
- 56 Trieb K, Lehner R, Stulnig T, et al. Survivin expression in human osteosarcoma is a marker for survival. *Eur J Surg Oncol* 2003;29:379–82.
- 57 de Jong Y, van Oosterwijk JG, Kruisselbrink AB, et al. Targeting survivin as a potential new treatment for chondrosarcoma of bone. *Oncogenesis* 2016;5:e222.
- 58 Pyne NJ, McNaughton M, Boomkamp S, et al. Role of sphingosine 1-phosphate receptors, sphingosine kinases and sphingosine in cancer and inflammation. *Adv Biol Regul* 2016;60:151–9.
- 59 Tsai CH, Yang DY, Lin CY, et al. Sphingosine-1-phosphate suppresses chondrosarcoma metastasis by upregulation of tissue inhibitor of metalloproteinase 3 through suppressing miR-101 expression. *Mol Oncol* 2017;11:1380–98.
- 60 Jiang Z, Fanger GR, Woda BA, et al. Expression of alpha-methylacyl-CoA racemase (P504s) in various malignant neoplasms and normal tissues: a study of 761 cases. *Hum Pathol* 2003;34:792–6.
- 61 Ananthanarayanan V, Deaton RJ, Yang XJ, et al. Alpha-methylacyl-CoA racemase (AMACR) expression in normal prostatic glands and high-grade prostatic intraepithelial neoplasia (HGPIN): association with diagnosis of prostate cancer. *Prostate* 2005;63:341–6.
- 62 Sekine S, Ogawa R, Ojima H, et al. Overexpression of α -methylacyl-CoA racemase is associated with CTNNB1 mutations in hepatocellular carcinomas. *Histopathology* 2011;58:712–9.
- 63 Aviel-Ronen S, Zadok O, Vituri A, et al. α -methylacyl-CoA racemase (AMACR) expression in chordomas differentiates them from chondrosarcomas. *Sci Rep* 2016;6:21277.
- 64 Rinn JL, Kertesz M, Wang JK, et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. *Cell* 2007;129:1311–23.
- 65 Okugawa Y, Toyama Y, Hur K, et al. Metastasis-associated long non-coding RNA drives gastric cancer development and promotes peritoneal metastasis. *Carcinogenesis* 2014;35:2731–9.
- 66 Bao X, Ren T, Huang Y, et al. Knockdown of long non-coding RNA HOTAIR increases miR-454-3p by targeting Stat3 and Atg12 to inhibit chondrosarcoma growth. *Cell Death Dis* 2017;8:e2605.
- 67 Huang K, Chen J, Yang MS, et al. Inhibition of Src by microRNA-23b increases the cisplatin sensitivity of chondrosarcoma cells. *Cancer Biomark* 2017;18:231–9.
- 68 Zhu Z, Wang CP, Zhang YF, et al. MicroRNA-100 resensitizes resistant chondrosarcoma cells to cisplatin through direct targeting of mTOR. *Asian Pac J Cancer Prev* 2014;15:917–23.
- 69 Tang XY, Zheng W, Ding M, et al. miR-125b acts as a tumor suppressor in chondrosarcoma cells by the sensitization to doxorubicin through direct targeting the ErbB2-regulated glucose metabolism. *Drug Des Deliv Ther* 2016;10:571–83.
- 70 Scully SP, Layfield LJ, Harrelson JM. Prognostic markers in chondrosarcoma: evaluation of cell proliferation and of regulators of the cell cycle. *Sarcoma* 1997;1:79–87.