Biomarkers of chondrosarcoma

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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. Various microRNAs to regulate chondrosarcoma staging, and they are promoted by leptin and adiponectin. Several molecules have been recently reported as 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. 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 different from grade II and III, it is divided into low-grade (grade I) and high-grade (grade II and III). 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). When osteoid lesion is in chondroblastic mass (chondroid tumour), it is diagnosed as osteosarcoma or dedifferentiated chondrosarcoma. 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, NELL-1 and SATB2 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.

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 malformation in patients. Conserved excision is enough in patients with enchondroma, because enchondroma is rarely recurrent and metastasis. 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 the best clinical management, tumour aggressiveness and disease prognosis.

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 (OB-R) and long form (OB-Rb)) in many tissues. It is closely related to obesity and affects tumourigenesis, angiogenesis and metastasis in several cancers. OB-R expression is increased in chondrosarcoma, but not in OBR. Leptin mRNA17 and protein18 expression is also increased in chondrosarcoma tissues. Leptin staining intensity is correlated with chondrosarcoma histological grade. Leptin enhances chondrosarcoma cell migration, angiogenesis and lymphangiogenesis by promoting vascular endothelial growth factor (VEGF)-A and VEGF-C secretion. Leptin-induced VEGF-C expression is negatively regulated by miR-27b. 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. Considering that adiponectin is reversely correlated with several carcinoma, it might decrease in chondrosarcoma. However, Lee et al have shown...
that adiponectin staining intensity is correlated with chondrosarcoma stage. They also report that adiponectin promotes VEGF-A expression and angiogenesis, like leptin. Adiponectin suppresses miR-27b expression in chondrosarcoma cell line and increases VEGF-C, like leptin. 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. 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. 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. Increased expression of distinct S100 protein has been reported in various cancers, and it is reviewed well. S100 increase is reported in the chondrosarcoma. 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, adiponectin, CCL5 and amphiregulin in chondrosarcoma cell lines. miR-199a and miR-206 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. Amphiregulin-mediated VEGF-A increase is negatively related to miR-206. Amphiregulin is reported as a serological biomarker for evaluation of prognosis and therapeutic response in several carcinomas. 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, and its expression is increased by chondrosarcoma stage. Increased CCL5 promotes VEGF-A by suppression miR-119a. CCL5 enhances migration through activation of matrix metalloproteinase-3 (MMP-3) and increased CCL5 enhances chondrosarcoma metastasis. 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. 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-624–3. miR-27 expression in chondrosarcoma tissues are not confirmed. miR-27 is suppressed by leptin and adiponectin, 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. BDNF is known to promote metastasis in human chondrosarcoma cells, miR-624–3 expression is negatively regulated by BDNF via the MEK/ERK/mTOR cascade and directly suppresses VEGF-C in chondrosarcoma cell lines. In chondrosarcoma tissues, BDNF and VEGF-C mRNA are increased and miR-624–3 is decreased in chondrosarcoma tissue. 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. 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. miR-30a and miR-129-5p 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. miR-145 is down in chondrosarcoma cell lines, four patients samples and SOX9 is up. In other report, SOX9 is dramatically decreased in grade 1 chondrosarcoma. 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 involved 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. BMPRs and runt-related transcription factor 2 (RUNX2) signaling in bone development and carcinogenesis are well known but not in chondrogenesis. Shinohara et al. have revealed that phosphorylated Smad3 and Smad1/5 is increased in chondrosarcoma, and Yang et al. have shown that BMP2 and RUNX2 expression is correlated with poor prognosis in 57 patients with various grades chondrosarcoma. BMP2 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. Taken together, BMPR2 and RUNX2 can be used as potential markers for prognosis.

SIRTIUN-1
Sirtuin 1 (SIRT1) is the NAD (+)-dependent histone deacetylase family, and is named SIRT1 to SIRT7. Increased SIRT1 expression is reported in several cancers including prostate cancer, lung cancer, colon cancer and leukaemia. However, SIRT1 expression is decreased in breast cancer. 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. Chao et al. have reported that SIRT1 signalling is induced by resveratrol, a natural phenolic compound found in several plants, and induces human chondrosarcoma cell apoptosis. 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. Overexpression is reported in LNCaP (prostate cancer cell line) cells, osteosarcoma and chondrosarcoma. 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.

SPHINGOSINE-1-PHOSPHATE
Sphingosine-1-phosphate (SIP), phosphorylated from sphingosine by sphingosine kinase 1, is encoded by the SPHK1 gene. ShpK1 is overexpressed in various types of cancers. However, shpK1 expression decreases in chondrosarcoma tissue, and is negatively correlated with chondrosarcoma progression. SIP 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. SphK1 may be associated with clinicopathological stages in chondrosarcoma.

ALPHA-METHYLACLYL-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. 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.

HOTAI
HOTAIR is a long non-codon 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. 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-454–3p increase. STAT3, ATG12 and ATG3 are targets of miR-454–3p. miR-454–3p expression is down in chondrosarcoma tissues. HOTAIR may act as a prognostic biomarker.

MICRONRNAS
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.

| 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 | stath, actg12 | Decrease | 66 |
| miR-624–3p | VEGF-C | Decrease | 36 |

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.
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. SOX4, 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. AMACR is expressed 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.

In this review, several candidates for chondrosarcoma biomarkers are summarised. The sensitivity and specificity should be >90% to use as a biomarker. In chondrosarcoma, nothing is reliable yet. 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.

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**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.
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