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REVIEW ARTICLE

Genetic aberrations and molecular biology of skull base chordoma and chondrosarcoma

Yohei Kitamura[1] · **Hikaru Sasaki**[1] · **Kazunari Yoshida**[1]

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Abstract Chordomas and chondrosarcomas are two major malignant bone neoplasms located at the skull base. These tumors are rarely metastatic, but can be locally invasive and resistant to conventional chemotherapies and radiotherapies. Accordingly, therapeutic approaches for the treatment of these tumors can be difficult. Additionally, their location at the skull base makes them problematic. Although accurate diagnosis of these tumors is important because of their distinct prognoses, distinguishing between these tumor types is difficult due to overlapping radiological and histopathological findings. However, recent accumulation of molecular and genetic studies, including extracranial location analysis, has provided us clues for accurate diagnosis. In this report, we review the genetic aberrations and molecular biology of these two tumor types. Among the abundant genetic features of these tumors, brachyury immunohistochemistry and direct sequencing of *IDH1/2* are simple and useful techniques that can be used to distinguish between these tumors. Although it is still unclear why these tumors, which have such distinct genetic backgrounds, show similar histopathological findings, comparison of their genetic backgrounds could provide essential information.

Keywords Chordoma · Chondrosarcoma · Genetics · Skull base

✉ Yohei Kitamura
ykita@sc4.so-net.ne.jp

[1] Department of Neurosurgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Introduction

Chordomas and chondrosarcomas are two major malignant bone neoplasms occurring at the skull base. Although most of these tumors are slow growing and rarely metastasize, they are locally invasive, highly recurrent, and potentially lethal. Because these tumors are mostly resistant to conventional chemotherapies and radiotherapies, surgical resection plays a crucial role in the treatment of these tumors. However, for chordoma and chondrosarcoma located at the skull base, radical resection is rarely achieved because of challenges associated with the location of the tumors.

In the clinical setting, it is important to distinguish between these two tumor types because they have different prognoses [1, 2]. However, this can be challenging owing to their overlapping radiological and histopathological findings. Indeed, chondroid chordoma, a subtype of chordoma, is a matrix-mimicking cartilaginous tumor [3]. Additionally, in a previous report, 37% (74/200 cases) of skull base chondrosarcomas were initially misdiagnosed as a chordoma [4].

Although chordoma and chondrosarcoma, including those located extracranially, are not as common as other types of cancer, researchers have begun to carry out molecular and genetic studies of these tumors. In this report, we review the genetic aberrations and molecular biology of chordoma and chondrosarcoma, including extracranially located tumors. Because these two types of tumors have distinct genetic backgrounds, molecular and genetic examinations of these tumors are expected to provide useful clues for distinguishing between the two tumor types.

Chordoma

Chordoma accounts for 1–4% of all bone malignancies [5] and 0.5% of primary intracranial central nervous system (CNS) tumors [6]. Chordoma frequently occurs in the sacrum, vertebral body, and skull base, with each of these locations accounting for approximately one-third of all chordomas [7]. Chordoma is thought to be derived from undifferentiated notochordal remnants; this is strongly supported by the fact that aberrations in the *T* gene, which encodes an important transcription factor involved in notochord development, were detected in the germ-line of familial chordoma [8]. The current common therapeutic strategy for the treatment of chordomas is maximal surgical resection followed by unconventional radiotherapy, such as proton beam therapy and carbon ion radiotherapy [9]. Incomplete surgical resection and the absence of postoperative irradiation significantly contribute to the poor prognosis of chordoma [10–13]. Because chordomas are resistant to conventional chemotherapies, researchers have attempted using molecular targeting agents for chordoma treatment.

T (brachyury)

In genetic analysis of chordoma, the *T* gene, located on chromosome 6q27, and its protein product brachyury, have been extensively studied. *T* was originally discovered as a site of mutation in the short-tailed mouse and has been shown to act as a transcription factor in notochord development [14]. Additionally, a recent study showed that brachyury is an essential factor for maintaining notochord cell fate and function [15]. Although brachyury is thought to function in the epithelial-to-mesenchymal transition (EMT) of malignant tumors [16, 17], a recent report showed that *T* function is dispensable for the EMT [15].

Brachyury expression is most frequently observed in chordomas (81–100%); it is less frequent in germ cell tumors and small cell lung cancers, but is rarely present in other types of tumor [12, 18–22]. Immunohistochemical analysis of brachyury is a useful biomarker for distinguishing among similar tumors, such as chondrosarcomas, chordoid meningiomas, and carcinomas, because of its high sensitivity and specificity. Furthermore, in case of skull base tumors, brachyury expression is a prognostic factor; patients having chordomas with brachyury expression exhibit significantly shorter progression-free survival (PFS) than patients having chordomas without brachyury expression [12].

Notably, researchers identified a duplication at the *T* site in the germ-line of familial chordomas [8]. Furthermore, Pillay et al. reported that the common nonsynonymous single nucleotide polymorphism (SNP) rs2305089 on the *T* gene was strongly associated with chordoma risk [23]. These reports suggested that *T* plays an important role in the tumorigenesis of chordoma. Presneau et al. reported that chromosomal aberrations resulting in gain of *T* were common in some sporadic chordomas, and that the down-regulation of *T* using short hairpin RNA (shRNA) in chordoma cell lines decreases cell proliferation and enhances morphological features consistent with a senescence-like phenotype [24]. Additionally, Hsu et al. reported that silencing of brachyury using shRNA led to complete growth arrest in other cell lines [25]. Nelson et al. showed that brachyury activated oncogenic transcription through binding directly to 99 target genes and indirectly affecting the expression of 64 other genes [26]. Based on these studies, the *T* gene (encoding brachyury) is now a promising therapeutic target for the treatment of chordomas [17, 27].

SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1 (*SMARCB1*)/*INI*

Generally, aberrations in *SMARCB1*/*INI1*, located on chromosome 22q11.2, predispose patients to rhabdoid tumors and schwannomatosis. Mutations and deletions in *SMARCB1*/*INI1* have been detected in several pediatric chordoma cases, accompanied by brachyury expression [28–31]. Recently, Hasselblatt et al. reported that these chordomas had a distinct molecular background from conventional chordomas [32], showing poor differentiation, lack of SMARCB1 expression, lack of complex chromosomal alterations as found in conventional chordomas, onset at an early age (young children), and poor prognoses. Furthermore, these tumors had methylation profiles distinct from those of atypical teratoid/rhabdoid tumors, which are commonly found in young children, and lacked SMARCB1 expression. These observations strongly supported the existence of a subtype of chordoma.

Receptor tyrosine kinases (RTKs)

RTKs play an important role in malignant transformation and tumor proliferation in cancers. Many reports have shown that RTKs, such as epidermal growth factor receptor (EGFR) [33–37], platelet-derived growth factor receptor-α (PDGFRα) [33, 37–39], PDGFRβ [35, 37–39], fibroblast growth factor receptor (FGFR) [40], hepatocyte growth factor receptor (MET) [33], KIT [39], p75 receptor [41], tropomyosin-related kinase A (TrkA) [41], and insulin-like growth factor-1 receptor (IGF-1R) [42, 43], are frequently overexpressed and/or activated in chordoma. Additionally, vascular endothelial growth factor (VEGF) [44] and nerve growth factor (NGF) were shown to be overexpressed in chordoma [41]. Although polysomy and amplification of EGFR were frequently detected in chordomas by

fluorescence in situ hybridization [36], no EGFR mutation was detected [36, 45]. Scheipl et al. reported the efficacy of EGFR inhibitors, such as sapitinib, gefitinib, and erlotinib, by demonstrating that these compounds suppressed the phosphorylation of EGFR and activation of its downstream pathways in chordoma cell lines [45]. Sommer et al. reported that patients with chordoma who were positive for phospho-IGF-1R had significantly shorter median disease-free survival [43].

Major downstream pathways

Akt/phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway

The Akt/PI3K/mTOR pathway is activated in various cancers, resulting in hyperproliferation and tumor growth. Phosphoinositide-dependent kinase-1 (PDK1) [46], Akt [34, 35, 43, 46, 47], tuberous sclerosis complex 2 (TSC2) [47], mTOR [47], s6 ribosomal protein (s6) [47], and phosphatase and tensin homolog (PTEN) [48] are dysregulated frequently in chordomas. Schwab et al. reported that PI-103, an inhibitor of Akt and mTOR, blocked proliferation and induced apoptosis in a chordoma cell line [46]. Recently, Tauziède-Espariat reported that *PIK3CA*, which is commonly mutated or amplified in various malignant neoplasms but never detected in chordoma, was mutated in two chordoma cases [44].

Mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway

Activation of the MAPK pathway is common in various types of cancers and has been detected in several studies of chordoma [35, 40, 43]. However, no mutations in *KRAS, NRAS, HRAS*, and *BRAF* have been detected [36, 40]. Long et al. reported that *miR-149-3p, miR-663a, miR-1908, miR-2861*, and *miR-3185* were likely to play important roles in dysregulation of the MAPK signaling pathway, leading to chordoma development [49].

Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway

The JAK/STAT pathway is known to be active in several human cancers and associated with a poor prognosis. Activation of components of the JAK/STAT pathway, such as STAT3 and the proto-oncogene tyrosine kinase Src, has been detected in chordomas [35, 50, 51]. Yang et al. reported that STAT3 inhibitors strongly blocked cell growth and proliferation in chordoma cell lines [50] and suggested that inhibition of the JAK/STAT pathway may represent a potential therapeutic strategy for the treatment of chordoma.

Retinoblastoma (RB) pathway

The RB pathway plays an important role in the control of cell proliferation. Loss of *CDKN2A/p16* with or without the loss of *CDKN2B* has frequently been observed in chordoma [48, 52], and one case with promoter methylation of *CDKN2A/p16* has been reported [48].

Other biomarkers

Triana et al. reported that the downregulation of E-cadherin and upregulation of N-cadherin were correlated with the worse prognosis of clival chordomas [53]. Schoenfeld et al. reported that positive expression of chondroitin sulfate proteoglycan 4 (CSPG4), a membrane-bound proteoglycan expressed in several types of malignant tumors, was associated with a higher risk of mortality and an increased risk of metastasis in chordomas [54]. The expression of fragile histidine triad protein (FHIT), a potential tumor suppressor, was absent or reduced in 98% of sacral chordomas and 67% of skull base chordomas, and the authors suggested that chromosome 3 aneuploidy and epigenetic regulation of *FHIT* contributed to loss of the FHIT tumor suppressor in chordoma [55]. Sa et al. reported recurrent somatic variants, including single nucleotide variations in *MUC4, NBPF1*, and *NPIPB15* and the gene fusion of *SAMD5-SASH1*, in whole-exome and whole-transcriptome sequencing of 13 chordomas [56]. Rinner et al. reported that 20 genes were hyper-/hypomethylated in samples from patients with chordoma compared with those in normal blood; among these epigenetically regulated genes, *C3, XIST, TACSTD2, FMR1, DLEC1, RARB, HIC1,, KL*, and *RASSF1* were suggested to be the most promising candidate genes [57], with the latter three identified as tumor-suppressor genes. Alholle et al. reported several genes (*FAM181B, KANK2, NPR3, PON3, RAB32, RAI1, SLC16A5*, and *ZNF397OS*) that were differentially methylated between recurrent cases and nonrecurrent cases [58]; among these genes, *KANK2* has been shown to be a candidate tumor-suppressor gene.

Cytogenetics

Many researchers have evaluated chromosomal copy numbers in patients with chordoma. These studies have reported similar findings, including losses on chromosomes 1p, 3, 4, 9, 10, 13, 14, and 18 and gains on chromosomes 1q and 7 [12, 48, 56, 59–62]. Of these chromosomes, 1p has been the most intensely investigated chromosome arm, and several studies have suggested that 1p36 may be a putative

tumor-suppressive locus in chordomas, as supported by the finding that loss of 1p36 is associated with poor prognosis [63–65]. Longoni et al. listed tumor necrosis factor (TNF) receptor superfamily member 8 (*TNFRSF8*) as a candidate gene on 1p36. Sawyer et al. reported that isochromosome 1q and monosomy 13 were frequent structural abnormalities in skull base chordomas by spectral karyotyping, supporting the hypothesis that chromosome 1p was a tumor-suppressive locus [66]. Horbinski et al. suggested that loss of heterozygosity (LOH) on chromosome 9p was significantly associated with shorter survival in patients with skull base chordomas [11]. We previously conducted whole genome analyses by comparative genomic hybridization and performed multivariate analyses with genetic and clinical factors; these studies suggested that gain on chromosome 2p was correlated with the prognosis [12].

MicroRNAs (miRNAs)

Several studies have suggested that aberrant miRNAs may play roles in tumorigenesis or progression of chordomas. Duan et al. reported that *miR-1* and *miR-206* were downregulated in chordoma-derived cell lines and chordoma tissue, and *miR-1* expression was inversely correlated with MET expression [67]. In a follow-up study, they showed that *miR-1* expression was correlated with poor prognosis and that induction of miRNA expression suppressed MET expression and inhibited the growth of chordoma cells [68]. Moreover, Osaka et al. reported that overexpression of Slug, a target of *miR-1*, promoted cell proliferation in chordomas [69]. The same team reported that *miR-155* was downregulated in chordomas, resulting poor prognosis [70]. Moreover, Zou et al. reported that overexpression of *miR-140-3p* and downregulation of *miR-1237-3p* were associated with chordoma invasion and poor prognosis in spinal chordomas [71, 72]. Gulluoglu et al. assessed the functions of *miR-31, miR-140-3p, miR-148a*, and *miR-222* by transfecting these miRNAs into chordoma cell lines transiently. These miRNAs were found to target proteins such as MET, MAPK1(ERK2), BCL2L11, and KIT, suggesting that these miRNAs play roles in cell viability, cell cycle, and apoptosis in chordomas [73]. Additionally, as described above, *miR-149-3p* may facilitate chordoma development through the dysregulation of the MAPK signaling pathway [49].

Immune system biomarkers

Checkpoints of programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and PD-L2 have been studied in various malignant tumors, and the expression of these proteins has been implicated in promoting tumor progression. Mathios et al. showed that PD-L1 and PD-L2 were not constitutively expressed in chordoma cell lines, but could be induced by pro-inflammatory cytokines [74]. Using paraffin-embedded tissues, researchers also demonstrated that PD-1 expression could be detected in tumor-infiltrating lymphocytes (TILs) in some cases of chordoma and that PD-L1 was not expressed in chordoma cells but was expressed in tumor-infiltrating macrophages and TILs [74, 75]. Zou et al. reported that the expression of PD-L1 in TILs was associated with a favorable prognosis in spinal chordoma [76]. However, further studies are needed to elucidate the detailed mechanisms and roles of immune checkpoint molecules in chordomas.

Molecular-targeted therapy

Target therapies for these proteins have been carried out using cetuximab (an EGFR inhibitor) [77, 78], gefitinib (an EGFR inhibitor) [77, 78], erlotinib (an EGFR inhibitor) [79–81], lapatinib (an inhibitor of EGFR and HER2) [82], imatinib (an inhibitor of PDGFR, c-Kit, and ABL) [83–85], sirolimus (rapamycin; an mTOR inhibitor) [85, 86], dasatinib (an inhibitor of Src, c-Kit, and ABL) [87], and bevacizumab (a VEGF inhibitor) [79]. Among these reports, the study with the largest number of participants was a phase II study of imatinib in 50 PDGFβ/PDGFRβ-positive patients with advanced chordoma [84]. The results showed that one patient (2%) had a partial response (PR), whereas 35 patients (70%) had stable disease (SD) at 6 months. Hindi et al. reported a retrospective series of 48 PDGFβ/PDGFRβ-positive patients with advanced chordoma treated with imatinib [83]; no patients achieved PR, and 34 patients (74%) showed SD. Stacchiotti et al. tested the efficacy of imatinib plus sirolimus for nine patients with imatinib-resistant advanced chordoma [85]; one patient achieved PR, and seven patients showed SD. Additionally, a phase II trial of lapatinib with 18 patients with EGFR-positive advanced chordoma showed that six patients (33%) achieved PR, whereas seven patients (39%) showed SD at 6 months [82]. A phase II trial of dasatinib in patients with advanced chordoma showed that six patients had an objective tumor response based on Choi criteria [87]. Furthermore, bevacizumab plus erlotinib was administered to three patients with chordoma, resulting in SD for 2–4.5 years [79]. Clinical trials using new targets, including therapeutic vaccines targeting brachyury, PD-1, PD-L1 inhibitors, are planned or underway [88].

Chondrosarcoma

Chondrosarcoma is the third most frequent primary malignancy of the bone after myeloma and osteosarcoma [3]; it is systemically more frequent than chordoma. However, intracranial chondrosarcomas comprise only approximately

1% of all chondrosarcomas [89]; consequently, it is less frequent than chordoma in cases of intracranial location [90]. Chondrosarcomas are graded on a scale of I–III based on histological findings [3], reflecting the rates of local recurrence and metastasis. Almost all chondrosarcomas are grades I or II, and grade III is extremely rare (grade I: 61%, grade II: 36%, grade III: 3%) [91]. A similar distribution has been observed in skull base chondrosarcoma (grade I: 50.5%, contained areas of grade I and II: 28.5%, grade II: 21%, grade III: 0%) [4]. Generally, low-grade chondrosarcomas are locally invasive, but rarely metastasize; thus, surgical resection is the best approach for managing this disease [92]. For chondrosarcomas located in the skull base, however, radical resection is rarely achieved because of the difficulties associated with resection of tumors in this location [4]. Because conventional chemotherapy and radiotherapy are usually ineffective for chondrosarcomas, systemic therapies, including molecular-targeted therapies, have been attempted.

Mutations in isocitrate dehydrogenase 1 (*IDH1*) and *IDH2*

Recent molecular studies showed that there are two major groups of chondrosarcomas with distinct genetic backgrounds: central and periosteal chondrosarcomas, which are related to mutations in *IDH1* or *IDH2*; and peripheral chondrosarcoma, which is related to exostosin-1 (*EXT1*) or *EXT2* inactivation [3]. Because *IDH1/2* mutations have been detected in many cases of skull base chondrosarcoma [93, 94], these chondrosarcomas are thought to be molecularly consistent with a subset of central chondrosarcomas.

Somatic mutations in *IDH1/2* have been identified in gliomas and acute myeloid leukemia (AML). *IDH1/2* mutations are thought to play a tumorigenic role in the development of these tumors. Amary et al. detected mutant *IDH1/2* in central chondrosarcoma, periosteal chondrosarcoma, and enchondroma [95]. The frequency of *IDH1/2* mutations was reported to be 55–66% in central chondrosarcoma [95, 96]. In skull base chondrosarcomas, these mutations were detected in 10 of 20 cases (50%) [93, 94]. Although the vast majority (>90%) of total *IDH1* mutations detected in gliomas involved the R132H substitution, R132H was detected only in 17% of cartilaginous tumors; other substitutions are common in cartilaginous tumors, such as R132C, R132G, R132L, and R132S [93–95]. Accordingly, although immunohistochemical analysis of IDH1 R132H is a useful tool for detection of mutated IDH1 in glioma, this is not the case in chondrosarcoma [3]. Li et al. reported the efficiency of a mutant IDH1 inhibitor in human chondrosarcoma cell lines [97], and phase I/II trials of an IDH1/2 inhibitor for IDH-mutated chondrosarcomas are ongoing [98].

RTKs

RTKs and their ligands have also been extensively investigated in chondrosarcoma and have been shown to play important roles in the progression of chondrosarcoma, including EGFR [99, 100], PDGFR [101], IGF-1 [102, 103], and VEGF [104, 105]. EGFR is expressed in chondrosarcoma, and gefitinib markedly inhibits the growth of chondrosarcoma cell lines [99]. Sulzbacher et al. reported that PDGFR expression in conventional chondrosarcoma was positively correlated with aggressiveness and that PDGFR may be a potential therapeutic target [101]. IGF-1 has been reported to positively regulate mitotic and matrix synthetic activities in chondrosarcoma and to play a role in the progression from chondroma to chondrosarcoma [102, 103]. However, a recent study indicated that the IGF pathway was not expected to be an effective therapeutic target of chondrosarcoma because it was not essential for chondrosarcoma growth, migration, or chemoresistance [106].

Major downstream pathways

RB pathway

Homozygous deletion, methylation, and missense mutations in *CDKN2A/p16* have been detected in central chondrosarcomas [96, 107]. Furthermore, aberrations in CDK4, CDK6, and Cyclin D1 were also reported [96, 108]. The absence of RB and CDKN2A/p16 expression is strongly correlated with higher grade of central chondrosarcoma, implying that loss of RB and CDKN2A/p16 function is an important event during central chondrosarcoma progression [108, 109]. Schrage et al. reported that overexpression of CDKN2A/p16 decreased cell viability and proliferation of chondrosarcoma in vitro [108].

Hedgehog signaling

Tarpery et al. reported that the Indian hedgehog (IHH) signaling pathway is involved in chondrosarcomas [96]. Tiet et al. showed that hedgehog signaling is activated in chondrosarcomas and it plays an important role in tumor cell proliferation. Moreover, treatment with triparanol, an inhibitor of hedgehog signaling, results in decreased tumor volume, cellularity, and proliferation rates in xenografts of human chondrosarcoma in mice [110]. Furthermore, IPI-926 (saridegib; a hedgehog inhibitor) inhibits the hedgehog pathway and blocks tumor growth in chondrosarcoma xenografts in mice [111]; however, in a phase II trial, saridegib did not show efficacy in patients with chondrosarcoma [112]. *miR-30a* has also been shown to be downregulated in chondrosarcoma, promote cell proliferation via the RUNX2 expression, and encode runt-related transcription

factor 2, which is closely linked to IHH signaling [113]; accordingly, *miR-30a*/RUNX2 may also represent a therapeutic target in the treatment of chondrosarcoma.

Akt/PI3K/mTOR pathway

Akt, mTOR, and s6 are also activated in chondrosarcomas [100, 114, 115]. Treatment with BEZ235 (a PI3K/mTOR inhibitor) significantly reduced the growth of chondrosarcoma cell lines [100]. The efficacy of everolimus (an mTOR inhibitor) in the inhibition of cell proliferation and tumor progression has been demonstrated using rats [116].

JAK/STAT pathway

The Src kinase family is also activated in chondrosarcomas [115]. Additionally, dasatinib has been shown to decrease cell proliferation in seven of nine cell lines and primary cultures [115]. Hypoxia-inducible factor 1α (HIF1α), which is induced by Src and Akt, is expressed in high-grade central chondrosarcoma and may facilitate chemoresistance and radioresistance, leading to poor survival [117].

MAPK/ERK pathway

NRAS mutations have been identified in chondrosarcoma cell lines and six patient tissues (12%) [100]. Importantly, the MEK inhibitor ARRY-142886 was effective at inhibiting cell growth only in cell lines with *NRAS* mutations and was not effective in other cell lines.

Other biomarkers

Tarpery et al. reported that hypermutability of the major cartilage collagen gene *COL2A1*, i.e., insertions, deletions, and rearrangements, occurred in 37% of 49 chondrosarcoma cases [96]; it is the second most frequent mutation in chondrosarcoma. The authors also reported the *TP53* was mutated in 20% of cases [96]. Oshiro et al. reported that overexpression and/or structural alterations in TP53 were observed in 38.1% of 158 chondrosarcomas and were correlated with aggressive behavior [118]. van Oosterwijk et al. reported that Bcl-2, which regulates cell death, was expressed in chondrosarcomas and caused chemoresistance to doxorubicin and cisplatin in vitro [119]. Hypomethylation of *maspin* and *14-3-3σ* was detected in chondrosarcoma lines. These genes are epithelial-specific markers that play roles in the mesenchymal-to-epithelial transition during chondrosarcoma development [120]. Bui et al. reported that the 3-O-sulfotransferase gene, which encodes a heparan sulfate biosynthetic enzyme, was abnormally hypermethylated, resulting in altered heparan sulfate proteoglycan sulfation and the invasive phenotype in chondrosarcomas [121]. Jin et al. reported that *RUNX3*, which plays a role in both normal developmental processes and carcinogenesis of the bone, was downregulated in specimens from patients with chondrosarcoma due to hypermethylation of its promoter, resulting in higher proliferation and lower apoptosis rates [122].

Cytogenetics

Although the results of various studies have differed substantially, frequent chromosomal alterations in extracranial chondrosarcomas include gains on chromosomes 2p, 5p, 7, 8q, 14q, 19, 20, and 21q and losses on chromosomes 4q, 6q, 9p, 13q, and 17 [123–128]. Among these aberrations, 8q24.1-qter and 14q24-qter were found to be correlated with shorter overall survival in patients with chondrosarcomas [125]; loss on chromosome 6 and gain on chromosome 12q12 were associated with high-grade chondrosarcomas in one report [128], and losses on chromosomes 5q14.2-q21.3, 6q16-q25.3, 9p24.2-p12, and 9p21.3 were associated with high-grade chondrosarcomas in another [124]. In skull base chondrosarcomas, gains on chromosomes 2q22-q32, 5qcen-q14, 8q21-q22, 15qcen-q14, and 19 were detected, suggesting the absence of distinct chromosomal alterations specific to the skull base localization of the tumors [94].

miRNAs

Many reports have described the expression and roles of miRNAs in chondrosarcomas, most within the last few years. *miR-30a* and *miR-335* are downregulated in chondrosarcomas, resulting in overexpression of SRY-related HMG box (SOX) 4, a member of the SOX gene family, which is related to metastasis and is a poor prognostic factor for low-grade chondrosarcoma [129, 130]. SOX9, which is overexpressed in chondrosarcomas, is induced by downregulation of *miR-145* and *miR-494* [131, 132]. Additionally, *miR-181a*, which plays a role in hypoxic regulation and enhances the expression of VEGF, is overexpressed in chondrosarcoma [104]. Tsai et al. reported that *miR-519d* expression was downregulated in chondrosarcoma, resulting in activation of p38, which is related to tumorigenesis and metastasis [133]. Aili et al. reported that *miR-10b* was significantly downregulated in chondrosarcomas, resulting in chondrosarcoma cell migration and invasion through the overexpression of brain-derived neurotrophic factor (BDNF) [134]; thus, *miR-10b*/BDNF may be potential therapeutic targets for chondrosarcoma.

Immune system biomarkers

PD-L1 expression was absent in conventional chondrosarcomas ($n = 119$), but was detected in some dedifferentiated

Table 1 Summary of genetic profiles of chordoma and chondrosarcoma

Chordoma		Chondrosarcoma
T (Brachyury) [8, 23, 24]	Key tumorigenesis-related genes	*IDH1/2* [93–96]
SMARCB1/INI1 [28–32]	Other key genes	*COL2A1, TP53, CDKN2A/p16* [96]
Gains on 1p, 3, 4, 9, 10, 13, 14, 18 Losses on 1q, 7 [12, 48, 56, 59–62]	Major chromosomal copy number alterations	Gains on 2p, 5p, 7, 8q, 14q, 19, 20, 21q Losses on 4q, 6q, 9p, 13q, 17 [94, 123–128]
EGFR [33–37] PDGFRα [33, 37–39] PDGFRβ [35, 37–39] FGFRs [40] MET [33] IGF-1R, IGF-1 [42, 43] KIT [39] p75 receptor, TrkA, NGF [41] VEGF [44]	Major dysregulated RTKs and ligands	EGFR [99, 100] PDGFRα [101, 146] PDGFRβ [101, 146] IGF-1 [102, 103] VEGF [104, 105]
PDK1 [46] Akt [34, 35, 43, 46, 47] TSC2, mTOR,s6 [47] PTEN [48] PIK3CA [44] ERK1/2 [35, 40, 43] FRS2a [40] STAT3 [35, 50, 51] Src [50] CDKN2A/p16 [48, 52]	Major dysregulated downstream effectors	Akt, s6 [100, 114, 115] mTOR [100, 114] Src [115] HIF1α [117] RB [108] CDKN2A/p16 [96, 107–109] CDK4 [96, 108] CDK6 [96] Cyclin D1 [108] PTCH1, HHIP, GLI1, SUFO [96] RUNX2 [96, 113] NRAS [100] TP53 [96, 118] Bcl-2 [119]
TNFRSF8 [63] *CDKN2A/p16, PTEN* [48] *C3, XIST, TACSTD2, FMR1, HIC1, RARB, DLEC1, KL, RASSF1* [57] *FAM181B, NPR3, PON3, RAB32, RAI1, SLC16A5, ZNF397OS* [58]	Genes with dysregulated methylation statuses	*Maspin, 14-3-3σ* [120] *CDKN2A/p16* [107] *3-OST* [121] *RUNX3* [122]
miR-1, miR-206 (MET) [67–69] *miR-31* (MET), *miR-140-3p* (ERK2, GOLT1B, CBL, SCAMP1), *miR-148a* (BCL2L11, USP33), *miR-222-3p* (KIT, CDKN1B) [72, 73] *miR-149-3p, miR-663a, miR-1908, miR-2861, miR-3185* (MAPK signaling pathway) [49] *miR-1237-3p* (MMP2) [71] *miR-155* (SOCS1, TP53INP1) [70]	Dysregulated miRNAs (predicted target)	*miR-10b* (BDNF) [134] *miR-30a, miR-335* (RUNX2, SOX4) [113, 129, 130] *miR-100* (mTOR) [147] *miR-145, miR-494* (SOX9) [131, 132] *miR-181a* (VEGF) [104] *miR-519d* (p38) [133]

chondrosarcomas [135]. In dedifferentiated chondrosarcomas, PR for anti-PD1 therapy with nivolumub was observed [136].

Molecular-targeted therapies

A tyrosine kinase inhibitor [137, 138], mTOR inhibitor [138, 139], hedgehog inhibitor [140], and Akt inhibitor [112] have been evaluated for applications in the treatment of chondrosarcomas. Additionally, clinical trials of IDH inhibitors and anti PD-1 antibodies are ongoing [98, 141]. Although imatinib has been tested for application in recurrent chondrosarcomas with PDGFRα or PDGFRβ expression as a phase II trial, it failed to show meaningful effects in terms of both obvious responses and blocking progression in patients [137]. A phase II trial of cixutumumab and temsirolimus (inhibitors of IGF-1R and mTOR, respectively) showed that longer PFS occurred in patients with chondrosarcomas showing IGF-1R expression than those without IGF-1R expression [138]. Two phase II studies using multikinase inhibitors (regorafenib [142] and pazopanib [143]) are ongoing. A phase II trial of sirolimus plus cyclophosphamide for 10 recurrent unresectable chondrosarcomas resulted in one patient achieving PR and six patients showing SD for at least 6 months [144]. A phase I/II study of temsirolimus and liposomal doxorubicin for

sarcomas including chondrosarcoma is currently ongoing [139]. Furthermore, a phase II trial of perifosine (an Akt inhibitor) with 33 patients showed that 3% achieved PR (according to Choi criteria) and 25% showed SD [112]. A phase II trial of GDC-0449 (vismodegib; a hedgehog inhibitor) in 45 patients with progressive advanced chondrosarcoma showed no objective response and 10 patients with SD for at least 6 months [140], whereas IPI-926 did not show clinical benefit [112].

Distinguishing between chordoma and chondrosarcoma

The genetic differences between chordoma and chondrosarcoma are summarized in Table 1. Traditionally, immunohistochemical analysis of epithelial markers, such as cytokeratin and epithelial membrane antigen (EMA), has been used to distinguish between chordoma and chondrosarcoma. However, some cases are extremely difficult to judge because of intermediate staining or inconsistencies among these markers. As described above, immunohistochemical analysis of brachyury has become a useful tool for differentiation because of the high positive rate in chordoma (81–100%) and lack of expression in chondrosarcoma [12, 18–22]. Additionally, *IDH1/2* mutations are useful biomarkers to distinguish between these tumors objectively. Because the R132H substitution in IDH1 is not frequently observed in chondrosarcoma [93–95], the usefulness of immunohistochemical analysis of IDH1 R132H is limited. As an alternative to immunohistochemical analysis, direct sequencing of *IDH1/2* could be a simple and useful tool for distinguishing between these tumors because of the higher positive rate for detecting *IDH1/2* mutations in central chondrosarcoma (55–66%) [95, 96]. In previous studies of chordomas, wild-type *IDH1/2* was detected in all 89 cases [94, 95]. In gliomas, genetic findings often provide a better reflection of prognosis than morphological findings, and the importance of genetic findings has been emphasized in the latest World Health Organization (WHO) classification of CNS tumors [145]. Similarly, the results of immunohistochemical examination of brachyury and direct sequencing of *IDH1/2* may provide a more accurate reflection of the prognosis than morphological findings.

Conclusions

In this review, we discussed the genetic profiles of the two major bone tumors of the skull base, chordoma and chondrosarcoma. It is still unclear why these tumors, which have such distinct backgrounds, exhibit highly similar histopathological findings, and comparisons of their genetic backgrounds could provide important insights into the distinct pathologies of these tumors.

Compliance with ethical standards

Disclosure The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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