Biology of Conventional Chondrosarcoma

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Conventional chondrosarcoma (CS) (80–85% of all CS) includes central (85–90%) and peripheral (10–15%) CS subtypes that are characterized by complex karyotype and genetic instability. The presence in their benign precursors of specific gene mutations is considered an early event in tumorigenesis [1], and secondary molecular changes are required for the malignant transformation. Currently, the most clinical reliable prognostic factors are age and grade.

Central CS can arises from or enchondromatosis (up to 40%) in patients with somatic mutations in the isocitrate dehydrogenase genes, IDH1 (R132C and R132H) and IDH2 (R172S) [2].

Wild-type IDH1 and IDH2 are important metabolic enzymes involved in lipid metabolism and in Krebs cycle [3]. Heterozygous somatic IDH1/IDH2 mutations, also seen in many other tumours, cause an abnormal production of the potential oncometabolite D-2-hydroxyglutarate (D-2HG) [4, 5] that leads to genome-wide alteration in DNA methylation, thus supporting the causal role for IDHR132H in driving epigenetic instability [6, 7].

Elevated D-2HG concentration has been detected in acute myeloid leukemia and glioma patients with mutant IDH, confirming the role of this potential biomarker for both diagnosis and therapy [8–10]. An antibody against IDH R132H is currently widely used for the differential diagnosis of glioma.

Peripheral CS arises from osteochondroma (15–20% of cases) or multiple osteochondroma (up to 1–5% of cases) that have genetic abnormalities in EXT1 or EXT2 oncosuppressor genes [11, 12], although some data demonstrate that the pathogenesis of secondary peripheral CS may be independent of EXT mutations [13].

EXT1 and EXT2 are located on the chromosome bands 8q24 and 11p11–12 respectively and the loss of their activity impairs the heparan sulfate (HS) biosynthesis, essential for the diffusion of hedgehog proteins involved in chondrocyte differentiation. A disturbance of Indian Hedgehog signaling pathway (IHH) breaks the negative feedback loop with parathyroid hormone-related protein (PTHrP), resulting in an unbalance between chondrocyte proliferation and differentiation [14].

Reactivation of PTHrP signaling and anti-apoptotic Bcl2 protein overexpression promote the progression toward low-grade and high-grade CS, progressively acquiring p53 mutations, defects in the most important cellular signaling pathways and environment structural changes [14].

Conventional CSs are drug-resistant tumours and surgery remains the primary treatment. However, the knowledge of additional genetic or epigenetic changes during malignant progression led to the identification of potential targets that may be useful for planning new

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adjuvant treatments [14]. In conventional CS, cytogenetic studies showed heterogeneity with respect to karyotype complexity. A positive relation between histological grade and degree of karyotype complexity was found associated with high cellular density, chondroid matrix destruction and vascularization. Chromosome 9p21 and 12q13–15 aberrations resulted in loss of CDKN2A tumour suppressor gene activity and amplification of CDK4 that inhibits pRb activity. P53 is inactivated, while overexpression of prosteoglandin COX2, metalloproteinases MMPs, and pro-hypoxia inducible factor HIF, make them candidate targets for therapeutic approaches [15].

While IDH and EXT mutations are no longer essential for tumour growth, representing the initial phase of malignant progression, the activation of key endpoints controlling tumour cell growth and survival differentiates high-grade CS. The evidence that altered IHH and kinase-dependent signaling pathways drive the increase of malignancy has addressed the preclinical and clinical studies to the use of kinase inhibitors or HH antagonists [16–18].

HH, Bcl2, PDGFR, Src, P13K/Akt pathways are considered candidate targets in conventional CS, but the clinical results are not quite satisfactory [19]. Interestingly, Bcl2-dependent drug-resistance of CS cells could be overcome by the treatment with Src kinase inhibitors and doxorubicin in p53-negative cells [20]. A phase II clinical trial using dasatinib observed a prolonged stable disease in more than 10% of patients, suggesting that further evaluations should be considered in future clinical trials [21].

In contrast, a previous study [22] failed in terms of objective response and disease-free survival by using imatinib mesylate, an anti-PDGFR agent.

Currently, phase I phase II clinical studies with agents targeting IDH mutations, PI3K-Akt-mTOR pathway and angiogenesisis are under investigation with the aim to improve the CS patient survival [23].

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