Isocitrate Dehydrogenase Gene Mutations in Chondrosarcoma: Research Progress and Prospects (Postprint)

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Abstract

Isocitrate dehydrogenase (IDH) is among the genes in human metabolic pathways that are frequently mutated. In the presence of nicotinamide adenine dinucleotide phosphate (NADPH), mutant IDH can bind to α-ketoglutarate (α-KG) and reduce it to 2-hydroxyglutarate (2-HG), thereby participating in multiple biological processes involved in tumorigenesis. While IDH has been extensively investigated in gliomas and acute myeloid leukemia, studies in chondrosarcoma remain limited. Chondrosarcoma is characterized by a high frequency of IDH gene mutations and is prone to recurrence and metastasis. Treatment options are limited following recurrence or metastasis, resulting in poor patient prognosis, and there is an urgent clinical need to identify novel therapeutic strategies. This review summarizes the role of IDH gene mutations in chondrosarcoma pathogenesis, prognosis, differential diagnosis, and treatment, further elucidates the biological functions of IDH mutations in chondrosarcoma development and progression, prospects the development of potent IDH inhibitors and anticancer agents, and aims to provide a reference for clinical treatment decision-making and prognostic evaluation.

Full Text

1 IDH Gene Types and Mutation Sites

IDH is a crucial rate-limiting enzyme in the tricarboxylic acid cycle. The human IDH gene family comprises five distinct genes encoding three different enzyme products: IDH1, IDH2, and IDH3. Mutations are most frequently observed in IDH1 and IDH2, while IDH3 mutations are rare. These mutations occur at different arginine residues within the enzyme's active site, resulting in amino acid substitutions. IDH1 mutations predominantly occur at codon 132, whereas IDH2 mutations are primarily found at codons 172 and 140 . AMARY et al. [3]

identified heterozygous mutations in IDH1 and IDH2 in 56% of chondrosarcoma patients, with an IDH1 R132 to IDH2 R172 mutation ratio of 10.6:1. LUGOWSKA et al. [4] were the first to report concurrent IDH1 and IDH2 mutations in chondrosarcoma patients, as well as the presence of IDH2 R140 mutations. Research indicates that in chondrosarcoma, the most common IDH1 mutation is R132C, followed by R132G and R132L, while the most frequent IDH2 mutation is R172S [5].

The ability of IDH2 mutations to produce 2-HG is independent of wild-type IDH2 alleles, with IDH2 R172 mutations generating 2-HG more potently than IDH2 R140 mutations [3]. In contrast, the 2-HG production capacity of IDH1 mutations depends on the presence of wild-type alleles, with heterozygous IDH1 R132 mutations producing 2-HG at levels comparable to IDH2 R172 mutations.

2 IDH Gene Mutations and Chondrosarcoma Development

IDH gene mutations represent an early event in chondrosarcoma pathogenesis. Studies have identified these mutations in 85% of hereditary enchondromatosis cases, 80% of non-hereditary enchondromatosis (Ollier disease, Maffucci syndrome), and 50% of solitary enchondromas. Furthermore, IDH mutations are present in 60% of chondrosarcomas and 57% of dedifferentiated chondrosarcomas [6]. The risk of malignant transformation from benign enchondromatosis to secondary chondrosarcoma is 40% in Ollier disease and up to 53% in Maffucci syndrome [7]. Investigating IDH mutations may thus elucidate tumor development mechanisms and yield new breakthroughs for chondrosarcoma prognosis and therapy.

2.1 IDH and Epigenetics

Under normal conditions, IDH catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG). Mutant IDH binds to α-KG and reduces it to 2-hydroxyglutarate (2-HG), with isotopic labeling confirming that 2-HG originates from α-KG [3]. In physiological conditions, 2-HG accumulation is limited by endogenous 2-HG dehydrogenase, which converts 2-HG back to α-KG, resulting in extremely low 2-HG levels in normal tissues [8]. However, elevated 2-HG concentrations are detectable in tissues from patients with IDH-mutant tumors. The oncometabolite 2-HG profoundly impacts α-KG-dependent processes, particularly dioxygenases. Over 60 α-KG-dependent dioxygenases have been identified that play crucial roles in epigenetic regulation of tumor cells. 2-HG appears to have two primary targets: the histone lysine demethylase (KDM) family and the ten-eleven translocation (TET) family of 5-methylcytosine hydroxylases [9]. Due to its structural similarity to α-KG [Figure 1: see original paper], 2-HG competitively inhibits histone demethylases and methylcytosine hydroxylases [10], leading to increased histone lysine methylation and global DNA hypermethylation, which suppresses normal cellular differentiation and promotes tumorigenesis [11]. CHOW et al. [7] demonstrated that inducing global demethylation in a Swarm rat chondrosarcoma model inhibited tumor

progression both in vitro and in vivo. LUGOWSKA et al. [4] found that IDH2 mutation expression in mouse mesenchymal progenitor cells induced extensive DNA hypermethylation, impaired differentiation, and loss of cell contact inhibition, ultimately leading to undifferentiated sarcoma formation when grown as xenografts. These findings indicate that IDH mutations promote tumorigenesis through epigenetic regulation and suggest that epigenetic inhibitors may represent novel therapeutic targets for IDH-mutant chondrosarcoma.

2.2 IDH and Hypoxia-Inducible Factor-1α (HIF-1α)

Under hypoxic conditions, HIF-1α regulates tumor cell metabolic processes to maintain growth and proliferation. HIF-1α proteasomal degradation is mediated by prolyl hydroxylases (PHD) through polyubiquitination. α-KG modulates PHD activity; reduced α-KG decreases PHD activity, leading to HIF-1α upregulation that disrupts cellular hypoxia adaptation and promotes tumorigenesis [12]. KOIVUNEN et al. [13] discovered that 2-HG accumulation competitively inhibits PHD activity, resulting in HIF-1α accumulation. HU et al. [14] showed that knocking out mutant IDH downregulated several HIF-1α target genes and reduced HIF-1α levels, attenuating angiogenic marker expression and eliminating tumor cell angiogenic capacity. These studies demonstrate that IDH mutations confer angiogenic and tumorigenic properties through HIF-1α induction.

Beyond affecting dioxygenases and HIF-1α, IDH mutations also influence apoptosis and proliferation signaling pathways. Research indicates that 2-HG directly inhibits cytochrome C oxidase (COX) in the mitochondrial electron transport chain, activating pro-apoptotic proteins Bax and BAK, thereby disrupting normal glutamine metabolism and triggering apoptosis [8,15]. Additionally, evidence suggests 2-HG accumulation exerts immunosuppressive effects, as activated CD4+ and CD8+ T lymphocyte proliferation is reduced under high 2-HG concentrations, promoting tumorigenesis [16].

3 IDH Gene Mutations and Prognosis in Chondrosarcoma Patients

The relationship between IDH mutations and chondrosarcoma prognosis remains unclear based on published data. Some studies [4-5] found that patients with IDH-mutant chondrosarcoma had shorter overall survival and lower 5-year survival rates compared to IDH wild-type patients. VUONG et al. [5] reported that IDH mutation frequency increased significantly with higher histological grade, being highest in dedifferentiated chondrosarcoma, and that IDH mutations were more prevalent in older patients with larger tumors located in long bones (femur, humerus, tibia) and flat bones (pelvis, skull). AMER et al. [17] found that dedifferentiated chondrosarcoma had particularly poor prognosis, with a median survival of approximately 11 months. However, other studies found no correlation between IDH mutations and overall survival, though notably, they

observed that in high-grade chondrosarcoma patients, IDH mutations correlated with longer progression-free survival but significantly increased mortality risk [18]. Further research is needed to definitively establish the relationship between IDH mutations and chondrosarcoma prognosis.

4 IDH Gene Mutations and Differential Diagnosis of Chondrosarcoma

Distinguishing chondrosarcoma from chondroblastic osteosarcoma is a critical and challenging diagnostic problem, as treatment strategies differ significantly. Approximately 25% of conventional osteosarcomas produce chondroid components, making differentiation difficult and subjective on small biopsy specimens [19]. Osteosarcoma patients have high metastatic risk and require combined chemotherapy and surgical treatment, whereas chondrosarcoma patients are relatively chemoresistant and typically treated with surgery alone. IDH mutations are present in over 60% of chondrosarcomas but are rare in chondroblastic osteosarcoma and other mesenchymal tumors. Therefore, IDH mutation testing can aid in distinguishing chondrosarcoma from chondroblastic osteosarcoma.

IDH mutations also play an important role in differentiating skull base chondrosarcoma from chordoma. IDH mutations have been reported in 60% of skull base chondrosarcomas [20] but are rare in chordomas, making high-frequency IDH mutation a useful diagnostic marker. Notably, VUONG et al. [5] found IDH mutations only in skull base chondrosarcomas, not in craniofacial chondrosarcomas. YOU et al. [21] detected no IDH mutations in 25 jaw chondrosarcoma samples, suggesting that IDH mutation testing has important auxiliary diagnostic value specifically for skull base chondrosarcoma.

5 IDH Gene Mutations and Chondrosarcoma Treatment

Chondrosarcoma tissues have poor blood supply and are relatively insensitive to chemotherapy and radiotherapy. Surgical resection remains the primary and optimal treatment, yet some patients experience recurrence or metastasis with limited therapeutic options and poor prognosis [22]. Literature reports indicate that primary chondrosarcoma recurrence rates after initial surgery are approximately 20%, with about 13% of recurrent cases showing higher histological grade than the primary tumor, requiring more extensive resection or becoming inoperable [23]. Therefore, exploring more effective treatment strategies is clinically imperative. The high frequency of IDH mutations in chondrosarcoma has led to the identification of effective molecular targets and new drug candidates, facilitating the development of improved therapeutic approaches.

5.1 IDH Mutation Inhibitors

IDH mutation inhibitors have been successfully developed. AGI-5198 is a specific IDH1 inhibitor that not only reduces 2-HG levels in IDH1-mutant chondrosarcoma tissues [24] but also suppresses tumor cell proliferation and metas-

tasis while inducing apoptosis [25]. DS-1001b is a novel IDH1 inhibitor that decreases 2-HG levels in mutant tumor cells and promotes histone demethylation, thereby inhibiting chondrosarcoma cell proliferation [26]. Currently, IDH inhibitors are primarily used for acute myeloid leukemia (AML) treatment, with applications in solid tumors still in clinical trials [7]. AG-120, an IDH1 inhibitor, achieved a 42% efficacy rate in IDH-mutant relapsed/refractory AML, with complete tumor disappearance in 30% of cases, while AG-221, an IDH2 inhibitor, demonstrated a 56% response rate in relapsed/refractory AML patients [27]. Both inhibitors have received FDA approval for AML treatment harboring IDH1 and IDH2 mutations, respectively.

5.3 Other Therapeutic Approaches

Notably, epigenetic inhibitors also represent therapeutic targets for IDH-mutant chondrosarcoma. VENNEKER et al. [29] found that histone deacetylase inhibitors suppress tumor cell activity. ROY et al. [30] demonstrated that DNA methyltransferase inhibitors effectively induce differentiation and inhibit IDH-mutant cell growth. Additionally, targeting anti-apoptotic genes has emerged as a novel anti-tumor strategy, with studies showing that anti-apoptotic protein inhibitors can reduce proliferation and promote apoptosis in IDH-mutant tumor cells.

In summary, combining IDH inhibitors with epigenetic inhibitors and anti-apoptotic protein inhibitors warrants further investigation for IDH-mutant chondrosarcoma treatment.

6 Summary and Outlook

In conclusion, IDH mutations in metabolic genes are closely associated with chondrosarcoma development and progression, playing important roles in differential diagnosis. IDH has emerged as a promising therapeutic target, with IDH inhibitors and anti-cancer agents demonstrating favorable efficacy in chondrosarcoma treatment. Studies combining IDH inhibitors with epigenetic modulators have been reported. Therefore, continued investigation into the biological mechanisms of IDH mutations in chondrosarcoma, coupled with development of potent mutation-specific inhibitors and anti-cancer drugs from a molecular perspective, will improve clinical management of IDH-mutant chondrosarcoma. We anticipate new therapeutic breakthroughs that may reduce or eliminate the need for surgery while significantly improving patient prognosis.

Note: Figure translations are in progress. See original paper for figures.