IDH Mutations in Chondrosarcoma

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Chondrosarcomas are malignant cartilage-producing tumours that frequently harbour isocitrate dehydrogenase 1 and -2 (*IDH*) gene mutations. Several studies have confirmed that these mutations are key players in the early stages of cartilage tumour development, but their role in later stages remains ambiguous. The prognostic value of the *IDH* mutation in chondrosarcoma seems controversial and (pre)clinical studies that have focused on the direct and indirect targeting of the *IDH* mutation have not yielded novel treatment strategies.

Keywords: sarcoma ; chondrosarcoma ; isocitrate dehydrogenase mutation

1. Frequency and Prognostic Value of *IDH1* and *IDH2* Mutations

IDH mutations are also frequently observed in other tumour types, such as acute myeloid leukaemia (AML), glioma, and cholangiocarcinoma [1]. Interestingly, the most common variant differs between the above-stated tumour types. Cartilage tumours and cholangiocarcinoma mainly have IDH1 p.R132C variants (~60%), glioma predominantly harbours IDH1 p.R132H mutations (~90%), and AML often has IDH2 p.R140Q mutations (~40%) [2][3]. None of the variants are exclusively observed in one tumour type, suggesting that different point mutations can have a similar effect on tumourigenesis, although the level of the oncometabolite D-2-hydroxyglutarate (D-2-HG) produced by these variants differs [4][5][6]. The prognostic value of *IDH* mutations in these tumour types is also diverse, and only glioma patients have a clear favourable outcome when their tumour harbours an *IDH* mutation [7][8][9][10]. Studies that were performed to determine the prognostic value of *IDH* mutations in chondrosarcoma show contradictory results. While it was previously reported that *IDH* mutations do not predict outcomes [2], other studies showed either a worse [11] or better [12] prognosis for *IDH* mutant (IDH^{MUT}) chondrosarcoma patients. The three patient cohorts were similar in size (n = 70 to 80) and median age (50 to 60 years), but the chondrosarcoma subtype inclusion (conventional versus addition of dedifferentiated and mesenchymal cases) and median follow-up time (4.3 versus ≥10 years) differed, which might explain the discrepancy in results. Another factor might be the type of technique used to assign patients to the IDH^{MUT} subgroup. For instance, Sanger sequencing is not sensitive enough to detect mutations when present in less than <30% of the sequenced PCR product, leading to false-negative results in samples with a low IDH^{MUT} variant allele frequency or tumour cell percentage and thereby the assignment of IDH^{MUT} patients to the *IDH* wildtype (IDH^{WT}) subgroup. Despite the lack of prognostic value, the high occurrence rate of *IDH* mutations in all of these tumour types suggests that they have an important role in driving tumourigenesis, already in the early stages of tumour development.

2. Oncogenic Activities of *IDH* Mutations

Both IDH enzymes function in the tricarboxylic acid (TCA) cycle, where they convert isocitrate into α-ketoglutarate (α-KG) and CO_2. Mutated IDH enzymes acquire a neomorphic function, leading to the additional conversion of α-KG into the oncometabolite D-2-HG [13]. The IDH1 p.R132C variant is one of the most efficient D-2-HG producers, while both IDH1 p.R132H and IDH2 p.R140Q produce lower levels of the oncometabolite [4][5][6]. As certain variants are more frequently observed in specific tumour types [2][3], this could suggest that chondrosarcoma and cholangiocarcinoma rely on high D-2-HG levels, while glioma and AML depend on relatively lower levels of the oncometabolite.

Due to the high structural similarity between α-KG and its antagonist D-2-HG, the oncometabolite is able to competitively bind α-KG-dependent enzymes, leading to the overall inhibition of this class of enzymes [14][15]. The inhibition of α-KG-dependent enzymes leads to widespread changes in the epigenomes and metabolomes of cells and affects DNA repair and cellular growth signalling pathways [16][17]. For instance, the D-2-HG-mediated inhibition of α-KG-dependent DNA demethylases (family of TET enzymes, including TET1/2) and histone demethylases (family of Jumonji enzymes, including KDMA4A/B) leads to an overall DNA hypermethylation phenotype, as well as an aberrant histone methylation phenotype in *IDH* mutant tumours. IDH^{MUT} enchondromas and chondrosarcomas are indeed characterised by a CpG island methylator phenotype (CIMP)-positive status, and DNA hypermethylation is present in primary IDH^{MUT}

chondrosarcomas [18][19][20]. The family of Jumonji enzymes is also involved in the regulation of the Mechanistic Target Of Rapamycin Kinase (mTOR) signalling pathway, as well as DNA repair via the homologous recombination pathway. Moreover, IDH^{MUT} enzymes have a reduced ability to produce NADPH and consume high levels of NADPH to produce D-2-HG, resulting in severely reduced overall NADPH levels. This deficiency does not only cause metabolic stress but will also lead to an increase in reactive oxygen species (ROS), making *IDH*^{MUT} tumours more vulnerable to DNA damage. Besides the induction of metabolic stress, *IDH*^{MUT} tumours also undergo metabolic rewiring, including alterations in metabolites of the TCA cycle, a reduced dependency on glycolysis, and alterations in lipid metabolism. Additionally, D-2-HG-mediated inhibition of the prolyl hydroxylase domain proteins (EGLN1 and -2) leads to the upregulation of hypoxia-inducible factors (e.g., HIF1α), resulting in a metabolic switch to maintain oxygen homeostasis. D-2-HG also affects collagen maturation via the inhibition of proline and lysine hydroxylases (P4HA1-3 and PLOD1-3), leading to an impaired extracellular matrix structure. Thus, *IDH* mutations have a wide variety of downstream biological effects; therefore, these mutations are considered as the drivers in multiple tumour types.

3. Inhibition of the IDH^{MUT} Protein

To counteract the oncogenic activity of the *IDH* mutations, several inhibitors targeting either IDH1 p.R132 variants (e.g., ivosidenib) or IDH2 p.R140 variants (e.g., enasidenib) have been developed over the past couple of years [21]. In vitro studies and clinical trials show that AML patients could benefit from IDH^{MUT} protein inhibitors [22][23], although some patients develop resistance against these inhibitors over time. This acquired resistance is multi-factorial and can be caused by second-site mutations in *IDH*^{MUT} genes to prevent the binding of IDH^{MUT} protein inhibitors, *IDH*^{MUT} isoform switching to circumvent the effect of IDH^{MUT} protein inhibitors, or novel acquired mutations in genes encoding for receptor tyrosine kinases (RTKs) [24][25][26]. Direct inhibition of IDH^{MUT} proteins seems less promising for other tumour types that frequently harbour an *IDH* mutation [27][28][29][30]. Especially in chondrosarcoma, the effect of IDH^{MUT} protein inhibitors in in vitro assays seems controversial. While several studies have shown that IDH1^{MUT} protein inhibition does not affect the tumourigenic properties of chondrosarcoma cell lines [27][31], other groups have shown that IDH1^{MUT} protein inhibition causes a decreased proliferation rate in chondrosarcoma cell lines at higher doses or with a different compound [32][33]. Recent results from a phase I clinical trial with the IDH1^{MUT} inhibitor ivosidenib showed that prolonged disease control (i.e., progression-free survival of ~6 months) could be achieved in a subset of patients with advanced chondrosarcoma, predominantly in patients with a minimal number of co-occurring mutations [34].

4. Synthetic Lethal Interactions with the *IDH* Mutation

As IDH^{MUT} protein inhibitors showed limited efficacy in in vitro assays and clinical trials or acquired resistance was observed, a large number of in vitro studies were performed to determine whether directly targeting the downstream biological effects of *IDH* mutations would be more promising. Indeed, multiple synthetic lethal interactions with the *IDH* mutation were reported for AML and glioma, including radiotherapy, chemotherapy, and agents that target poly(ADP-ribose) polymerase (PARP), B-cell lymphoma 2 (Bcl-2) family members, Bromodomain and Extra-Terminal Motif (BET) proteins, DNA methyltransferases (DNMTs), mTOR, Nicotinamide Phosphoribosyltransferase (NAMPT), and glutaminase [27][28][35][36][37][38][39][40][41][42][43][44][45][46][47][48]. However, chondrosarcoma cell lines are variably sensitive to a selection of these therapies, but the effect seems irrespective of the *IDH* mutation status, as *IDH*^{WT} chondrosarcoma cell lines show similar treatment responses [49][50][51][52][53][54][55].

These contradictory findings on synthetic lethal interactions with the *IDH* mutation might be ascribed to different factors. First, the cell of origin and the tumour microenvironment (e.g., cartilaginous matrix formation and hypoxia in chondrosarcoma) of the distinct tumour types that frequently harbour an *IDH* mutation are highly different and could therefore influence the role that *IDH* mutations play in tumourigenesis. Second, the level of the D-2-HG oncometabolite may also influence the downstream biological effects of *IDH* mutations. The most common *IDH* variants in AML and glioma both produce relatively low D-2-HG levels, whilst the most common point mutation in both cholangiocarcinoma and chondrosarcoma produces relatively high levels of the oncometabolite [4][5][6]. It was recently shown that a lower level of DNA hypermethylation was observed for the IDH1 p.R132H variant compared to non-p.R132H variants, irrespective of tumour type [3]. Lastly, the type of in vitro model (endogenous vs. artificially created) might influence whether synthetic lethal interactions with the *IDH* mutation are present or not. The introduction of an *IDH* mutation in a glioma model leads to reduced glutamine and glutamate levels, but this change in TCA cycle metabolites is not present when endogenous *IDH*^{WT} and *IDH*^{MUT} glioma models are compared [56]. Most synthetic lethal interactions with the *IDH* mutation were indeed identified in generic cancer cell lines with an introduced *IDH*^{MUT}. AML and glioma cell lines with an endogenous *IDH*^{MUT} are scarce, but the utilised chondrosarcoma cell lines do harbour endogenous *IDH* mutations and this difference in model type could explain why synthetic lethal interactions with the *IDH* mutation are absent in the chondrosarcoma in vitro

studies. As *IDH* mutations occur early during tumourigenesis, especially in chondrosarcoma, artificial models with an introduced *IDH* mutation may not be representative of the role that *IDH* mutations normally play in tumourigenesis. These studies also introduced the *IDH* mutation in generic cancer cell lines that are easy to transfect (e.g., HeLa, HCT116, and U2OS cells), and these cell lines do not represent the tumour types in which *IDH* mutations frequently occur. Moreover, most studies generated models that overexpressed the IDH^{MUT} protein, whilst the balanced expression of IDH^{WT} and IDH^{MUT} is needed to retain efficient D-2-HG production [57].

5. Putting the *IDH* Mutation into Context to Define Underlying Vulnerabilities

In addition to these factors, it was recently shown that the (epi)genetic landscape in which IDH^{MUT} and IDH^{WT} are embedded is another important aspect to take into consideration when defining underlying vulnerabilities in tumour types that frequently harbour an *IDH* mutation. Studies on AML and glioma have shown that the genetic and epigenetic landscape in which IDH^{WT} and IDH^{MUT} function is highly heterogenous and thereby influences the therapy response and patient outcome [58][59][60][61][62][63][64][65][66][67][68][69]. For instance, mutations in *TP53* and *ATRX* are the underlying denominator in defining which IDH^{WT} and IDH^{MUT} gliomas respond to radiotherapy [58]; the overexpression of BCAT1 in IDH^{WT} AML leads to an IDH^{MUT}-like DNA hypermethylation phenotype [59], and additional mutations in *DNMT3A* cause reduced levels of DNA hypermethylation in IDH^{MUT} AML samples [62]. Furthermore, co-occurring (epi)genetic alterations such as CIMP status [66], 1p19q deletions [68], *CDKN2A* deletions [66][67], *MET* amplifications [66], *PDGFRA* amplifications [67], and *TERT* mutations [68] influence overall survival in IDH^{MUT} glioma patients. Moreover, IDH^{MUT} AML patients with a co-occurring *NPM1* mutation show overall a better response to chemotherapy with or without venetoclax [69]. The influence of co-occurring (epi)genetic alterations may also explain why distinct IDH^{MUT} tumour types differ in therapy sensitivity and underlines the need to use endogenous IDH^{MUT} models, as generic cancer cell lines with an introduced *IDH* mutation do not represent the (epi)genetic landscape in which *IDH* mutations naturally exist. Thus, the *IDH* mutation status does not solely define the underlying vulnerabilities, which is in line with previous findings for chondrosarcoma [49][50][51][52][53][54][55], suggesting that a dichotomy between IDH^{WT} and IDH^{MUT} is too simplistic.

Besides *IDH* mutations, chondrosarcomas frequently harbour mutations in *TP53*, *CDKN2A/B*, *COL2A1*, *YEATS2*, *NRAS*, and *TERT* [70][71][72][73][74]. However, the rest of the previously observed co-occurring mutations seem to follow a more random pattern and are present in less than 10% of the chondrosarcomas [12][71][72][75], leading to a highly heterogeneous genetic landscape in which IDH^{WT} and IDH^{MUT} function in chondrosarcoma. Furthermore, IDH^{MUT} chondrosarcomas are characterised by a global hypermethylation phenotype that changes with increasing histological grade [19][20], and, based on methylation profiles alone, several chondrosarcoma subgroups could be defined, even within IDH^{WT} and IDH^{MUT} tumours [76]. Moreover, using chondrosarcoma transcriptome and methylome data, it was previously shown that different molecular subtypes (i.e., high mitotic state, 14q32 miRNA cluster loss of expression, and IDH^{MUT}-induced DNA hypermethylation) exist, and that these are associated with patient outcomes [77]. Moreover, (epi)genetic alterations in the *TERT* gene (i.e., hypermethylation and promotor mutations) affect the survival probability of $IDH1^{MUT}$ chondrosarcoma patients, whilst this association is absent in IDH^{WT} and $IDH2^{MUT}$ patients [75].

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