DEDIFFERENTIATED AND HIGH GRADE CHONDROSARCOMAS: HOW DOES ISOCITRATE DEHYDROGENASE STATUS APPRISE PROGNOSIS AND THERAPY?

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Introduction: High grade and dedifferentiated chondrosarcomas (CSAs) are frequently associated with isocitrate dehydrogenase (*IDH*) mutations and often exhibit a poor clinical outcome. Treatment is limited mainly to surgery. Defining *IDH* status {wild type (WT) and mutant} and the associated transcriptome may prove useful in determining other therapeutic options in these neoplasms.

Methods: Formalin fixed paraffin embedded material from 69 primary and recurrent grades 2, 3 and dedifferentiated (CSAs) was obtained. DNA sequencing for *IDH1* and *IDH2* mutations (n= 47) and RNA sequencing via Nextseq 2000 (n=14) were performed. Differentially expressed genes (DEGs) were identified and used to predict aberrant biological pathways with Ingenuity Pathway Analysis (IPA) software (Qiagen). Gene Set Enrichment Analyses (GSEA) using subsets C3, C5 and C7 were performed. Differentially expressed genes *WT1*, *AR* and *SATB2* were validated by immunohistochemistry. Outcome analysis was performed using the Wilcoxon Test.

Results: A set of 69 (CSAs), 28 females, 41 males, average age 65, distributed among femur, pelvis, humerus, and chest wall were identified from available clinical material. After further selection based on available *IDH* status, we evaluated 15 *IDH* WT and 32 *IDH* mutant tumors as part of this dataset. 7 of 15 *IDH* WT tumors involved the chest wall/scapula, while 1 of 32 mutants arose in the scapula. There were far more genes overexpressed in *IDH* WT tumors compared to *IDH* mutant tumors (Fig. 1). Furthermore, *IDH* WT and *IDH* mutant tumors were transcriptomically distinct in the IPA and GSEA with *IDH* mutant tumors showing increased activity in methylation pathways and endochondral ossification, while *IDH* WT tumors showed more activity in normal matrix development pathways (data not shown). Validation immunohistochemistry demonstrated expression of WT1 and AR in *IDH* WT tumors, but not in *IDH* mutants. SATB2 was expressed in *IDH* mutant tumors and not in WT tumors. Outcome analysis revealed differences in overall survival between mutant and WT tumors (p=0.04), dedifferentiated mutant and high grade mutant tumors (p=0.03) and dedifferentiated mutant and high grade WT tumors (p=0.03) (Fig. 2). Longest survival times were observed in patients with high grade WT tumors while patients with dedifferentiated mutant tumors showed lowest survival. Generally, patients with *IDH* WT tumors displayed longer survival in both high grade and dedifferentiated groups.

Discussion: High grade and dedifferentiated chondrosarcomas are further characterized by *IDH* status which in turn informs transcriptomic phenotype and overall survival. The transcriptome is distinct depending on *IDH* status and implies different treatment targets.

Significance/Clinical Relevance: Here we show for the first time that high-grade and dedifferentiated chondrosarcomas have distinct prognoses and gene expression patterns vis-à-vis *IDH* status. This may present an opportunity for therapeutic intervention for a deadly disease with no effective adjuvants.

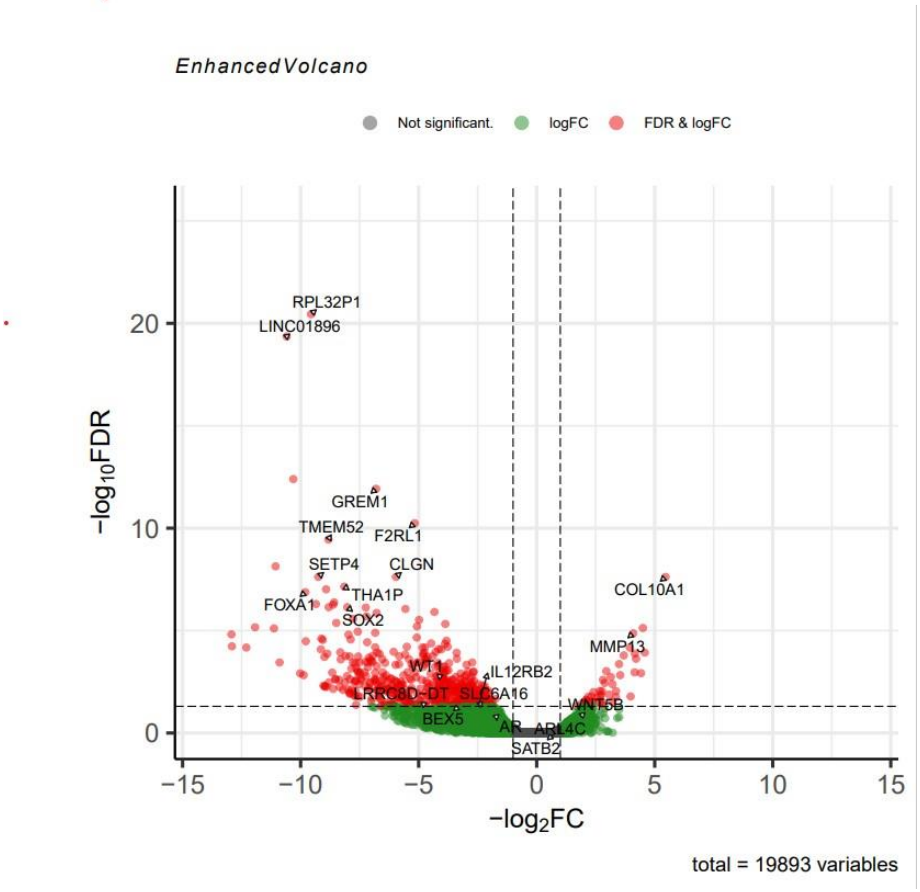

Fig. 1 Volcano plot depicting differences in gene expression between *IDH* WT (left side of graph) and *IDH* Mutant chondrosarcomas (right side).

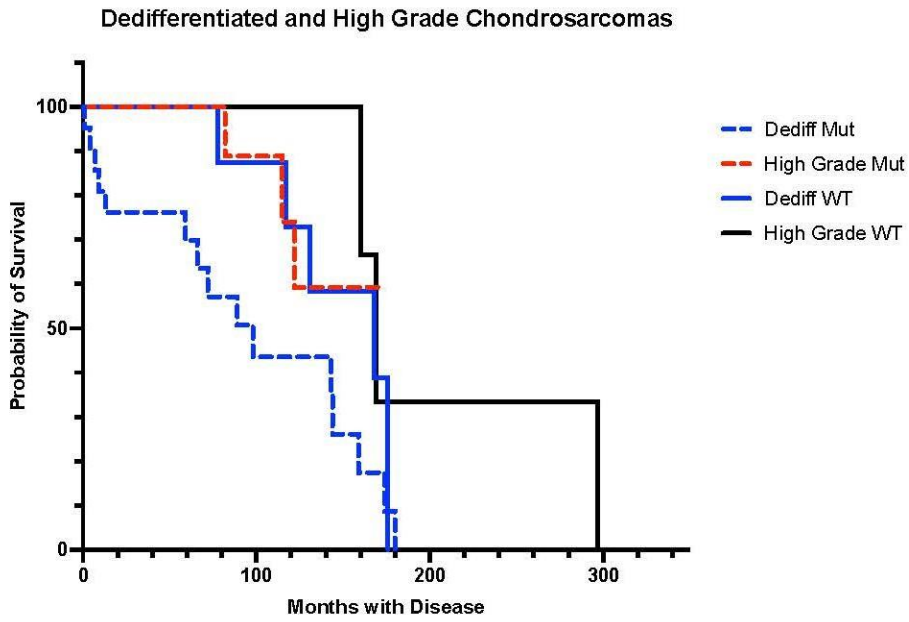

Fig. 2 Kaplan-Meier plot of *IDH* mutant (both *IDH1* and *IDH2*) vs. WT overall survival in dedifferentiated and high grade chondrosarcomas