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The KDM6A/B inhibition affects viability of SMARCB1 deficient tumors through the disruption of autophagy and angiogenesis in pediatric cancer.

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Introduction.

In Pediatric cancer, the traditional cytotoxic therapeutic approaches are always a compromise between treatment efficacy and the risk of developing severe secondary effects, including new tumours during the adulthood. Our previous study demonstrates that *SMARCA4* is necessary to regulate the demethylase activity of H3K27me3 in cancer, we discover that the inhibition of *KDM6A/B* is lethal specifically in *SMARCA4* deficient tumors. This discovery implicates a new synthetic lethality, in which inactivating mutations in SWI/SNF members could sensitize cancer cells to specific epigenetic inhibitors affecting pediatric tumours.

Objectives

In this study our working hypothesis is that the mutational status of different SWI/SNF members will affect the epigenetic regulation of different **KMTs and KDMs** in pediatric tumors. Based on that, our objective is to determine how the specific inhibition of the activity of these histone-modifying enzymes in **SWI/SNF** proficient or deficient cells, affects tumor viability. Here, we have optimized a screening to the selection of genetic alterations **as predictive biomarkers for response**, upon the inhibition of the KDM6A/6B activity in a panel of cancer models with different genetic background. With this we intend to identify whether the molecular mechanisms that conform the basis of the response, are regulated by the components of the SWI/SNF complex and in this way to determine, in which context, the use of epigenetic inhibitors with capability to block a specific enzymatic activity of certain epigenetic effectors, could be of potential interest as new anticancer agents.

Methodology

For this study we integrated state of the art technology like genome-wide transcriptome analysis, (RNA-Seq) using different preclinical cancer models such as in vivo models of mice (i.e., patients derived xenografts-PDXs), to design a target specific epigenetic treatment with **high efficacy and low toxicity**. Also, different types of pediatric cell lines were used for the current project. This includes several cells carrying SMARCB1 biallelic inactivating mutations. Genetically modified pediatric cell lines were also used and cells with restituted *SMARCB1* were also available in the collection, these cells were derived from the cells A204, and G401 that are *SMARCB1*-deficient. In addition, we generate novel models to restitute the expression of SWI/SNF members in the genetically deficient models.

Results.

Here, we show that, unlike the cells with a proficient SWI/SNF complex, pediatric cancer cells carrying a *SMARCB1* genetic inactivation were also refractory to the histone deacetylase inhibitor, SAHA, leading to an aberrant accumulation of H3K27me3. Specifically, *SMARCB1* mutant cells showed an impaired trans-activation and significantly reduced levels of the histone demethylases *KDM6A*/UTX and *KDM6B*/JMJD3. Consequent with this, the viability of *SMARCB1* deficient cancer cells shown a strong dependency on these specific histone demethylases, so its inhibition in this specific genetic background context, compromised cancer cell viability. Notably, *SMARCB1* ectopic re-expression increased cellular viability and promote resistance to the inhibition of *KDM6A/B* by GSK-J4. Related to that, we identified and demonstrate experimentally that the gene expression

signatures after recovering the SMARCB1 function were associated with pathways related with angiogenesis regulation and to the Integrative Stress Response (IRS). The IRS appear to be mediated by direct regulation of ATF4 levels by *SMARCB1* epigenetic activity driving processes such as , apoptosis, cell cycle arrest, and senescence. Importantly in the study it was also observed changes of gene expression after GSK-J4 treatment and after *SMARCB*1 re-expression of autophagy-related genes such as *SQSTM1*, ATF4, and *MAPL1LC3B* (LC3). Furthermore, administration of the KDM6s inhibitor GSK-J4 in vivo, demonstrated and a **strong anti-tumor effect and therapeutic potential** in mice orthotopically implanted with *SMARCB1*-deficient Malignant Rhabdoid Tumors (MRT) derived from pediatric patients.

Main Conclusions.

Overall, these findings suggest a potential role of the *SMARCB1*genetic inactivation and the inhibition of *KDM6A/6B* activity in modulating autophagy flux providing insights into the intricate workings of **autophagy in *SMARCB1*-deficient tumors**, especially in the context of pediatric cancer. This innovative epigenetic-based therapeutic strategy, together with a unique collection of patients derived Orthoxenografts (PDOXs) models, constitute an extraordinary opportunity to set the basis for the stratification of tumors according to their genetic and epigenetic background for tailor treatments, matching the patients with specific therapies, generating a model of **precision medicine in pediatric cancer.**