Epigenetic Compound Screening Reveals New Therapeutic Targets for Chordoma
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Chordoma is a rare cancer, with an incidence of 1 in 800,000 of the population, showing notochordal di□erentiation and with a median survival of 7 years. We have previously demonstrated that EGFR inhibitors represent almost uniquely the family of compounds to exert an e□ect on chordoma cell lines proliferation, however not all cell lines respond and drug resistance is likely to occur. Genomic studies have revealed that chordomas do not harbour recurrent alterations in kinases whereas chromatin-remodelling genes are altered in at least 20% of cases. The transcription factor brachyury (T), the diagnostic hallmark of chordoma, is strongly implicated in its pathogenesis and is regulated during embryonic development at the epigenetic level, suggesting that epigenetic inhibitors may represent a therapeutic approach for this disease. In this study we have undertaken a medium throughput focused compound screen using validated small molecule inhibitors of enzymes involved in chromatin biology (n=91) targeting readers, writers and erasers of the “chromatin code”. Compounds were assessed for their ability to decrease cell viability in an Alamar blue assay in □ve chordoma cell lines (UCH1, UCH2, MUG-Chor, UM-Chor, UCH7). Screening revealed activity in a range of compounds targeting the jumonji domain-containing lysine demethylases including GSK-J4 and KDOBA67, two structurally closely related compounds that mainly target KDM6A (also known as UTX) and KMD6B (JMJD3). The compounds were e□ective in all cell lines tested and, in contrast to EGFR inhibitors, promoted a
strong downregulation of brachyury at the transcriptional and protein level. Chordoma cell lines were also sensitive to halofuginone, a highly speci□c inhibitor of the enzyme glutamyl-prolyl tRNA synthetase that has already been assessed in phase I autoimmunity clinical trials. In conclusion, we have identi□ed epigenetic and metabolic pathways that represent potential novel targets for the treatment of chordoma.
E□ects of Glycation on Degradation of Collagen: An In Vitro Investigation