OFFICIAL ABSTRACT and CERTIFICATION

Endogenous Roles of NT5C2 Identified with Genetic Screening and Treatment Implications

Margarita Bogdanova-Shapkina
Oceanside High School, Oceanside, NY, USA

Aberrant over-expression of NT5C2 has been linked to chemoresistance in relapsed acute lymphoblastic leukemia (ALL). Multiple gain-of-function NT5C2 mutations have been identified that account for post-relapse chemoresistance in ALL patients. Preliminary data has shown that mutant NT5C2-containing ALL cells have demonstrated increased sensitivity to treatment with mizoribine, and that knockout and knockdown of NT5C2 has little effect on cell homeostasis and growth. In addition, NT5C2 splicing variants have been associated with hereditary spastic paraplegia. These indicate that there may be unknown compensatory mechanisms and/or endogenous roles of NT5C2. The purpose of the study was threefold: first, to identify the extent, if any, of the effects of NT5C2 KO on the cell (NT5C2 CRISPR KO and rescue and MTT/growth curve analysis of the effect on cellular population, and comparison of RNA sequencing between the variants to identify compensatory mechanisms); second, to identify any other genes that interfere with NT5C2 ' s role in the purine biosynthesis pathway (investigated through whole genome mizoribine CRISPR screening); and third, to identify pathways directly affected by treatment-like pharmaceutical inhibition of NT5C2 through whole-genome CRISPR screening with HTP-2, an early-stage NT5C2 inhibitor. While the RNA sequencing and HTP-2 screen failed to yield results, mizoribine screening identified several pathways in which NT5C2 may be involved, whole growth curve comparison confirms the absence of any inherent cytotoxicity to NT5C2 inhibition or knockout. These results offer several potential new avenues besides direct NT5C2 inhibition for combating chemoresistance in ALL, and confirm NT5C2 as a viable treatment option where feasible.

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