NUDT2 at the Interface of RNA Decapping and Disease: Expression and Post-Transcriptional Regulation

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Background: The nucleoside diphosphates linked to moiety-X (NudiX) hydrolase family comprises twenty-four enzymes in humans that catalyze the hydrolysis of nucleoside diphosphates linked to other moieties. A subset of NudiX enzymes participates in RNA cap metabolism, directly influencing RNA stability and translation. However, the role and regulation of NudiX hydrolases in non-canonical RNA decapping remain poorly understood. Preliminary findings from our laboratory suggest that NUDT2 preferentially targets Ap_4A-RNA over free Ap_4A, supporting a potential role in RNA cap regulation. NUDT2-mediated Ap_4A decapping may therefore influence RNA half-life, stress responses, and cellular adaptation, with dysregulation potentially contributing to disease development and progression. contribute to disease development, progression, or treatment. Method: We analyzed NUDT2 expression using the recount3 framework across 27,884 RNA-seq samples from 73 projects. NUDT2 protein levels were examined in HepG2 and THLE-2 cell lines. Predicted miRNAs targeting NUDT2 were explored with MIENTURNET and TargetScan. Results: Analysis of recount3 RNA-seq datasets revealed disease-specific patterns of NUDT2 expression. NUDT2 was upregulated in liver hepatocellular carcinoma (LIHC) and cholangiocarcinoma (CHOL) compared to normal tissue. In contrast, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) samples show reduced NUDT2 expression. Interestingly, although NUDT2 mRNA is broadly expressed, reported protein levels in healthy tissues are markedly low. This discordance between transcript and protein levels is consistent with tight post-transcriptional regulation. The potential involvement of miRNA-mediated regulation in health and disease is currently being explored, particularly through hsa-miR-744-5p and hsa-miR-423-3p. Conclusion: Collectively, these findings support a context-dependent role for NUDT2. In LIHC, NUDT2 may contribute to RNA degradation and cellular adaptation, whereas in chronic metabolic disease states such as NAFLD and NASH, it appears to be downregulated. The observed discordance between NUDT2 transcript and protein levels further suggests that NUDT2 may be tightly controlled by post-transcriptional regulatory mechanisms, including potential miRNA-mediated repression.