Deciphering the impact of 2’-O-methylation on lung cancer growth and treatment response

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Abstract**:** Tumors co-opt evolutionarily conserved mechanisms of viral sensing and innate immune signaling to enhance growth, evade the immune system and avoid the effects of therapy. Under normal circumstances, endogenous “host” RNA does not activate cellular RNA sensors that recognize foreign viral RNA. A recently identified mechanism to define host mRNA is Cap2 methylation, which comprises 2’-O-methylation of the ribose of the second nucleotide mRNAs and small nuclear RNAs (snRNAs) by CMTR2 (Cap methyltransferase 2). Cap2 prevents host RNAs from binding the viral RNA sensor RIG-I. Recently, inactivating mutations in CMTR2 were found to be prevalent in lung cancer. Preclinical studies have shown that loss of CMTR2 leads to exaggerated interferon-stimulated gene expression in response to intracellular stimuli, as well as promoting cancer growth in mice. In this project, we will investigate the mechanisms by which CMTR2 regulates lung cancer tumor growth and treatment response. We will use in vivo CRISPR screening to identify genes that mediate the tumor growth-promoting effects of CMTR2 loss and determine whether this is dependent upon loss of Cap2 methylation of mRNAs or snRNAs. We will investigate the mechanisms by which CMTR2 loss perturbs mRNA processing and expression via snRNAs, expanding a role for 2’-O-methylation beyond cytosolic RNAs. Finally, we will investigate whether CMTR2 restrains induction of interferon-stimulated genes following targeted therapy treatment, and determine whether 2’-O-methylation modulates the development of drug resistance. These studies will reveal how RNA 2’-O-methylation impacts the clinical behavior of lung cancers and open new avenues for therapeutic discovery.