High-throughput analysis reveals miRNA up & down regulating α-2,6-sialic acid

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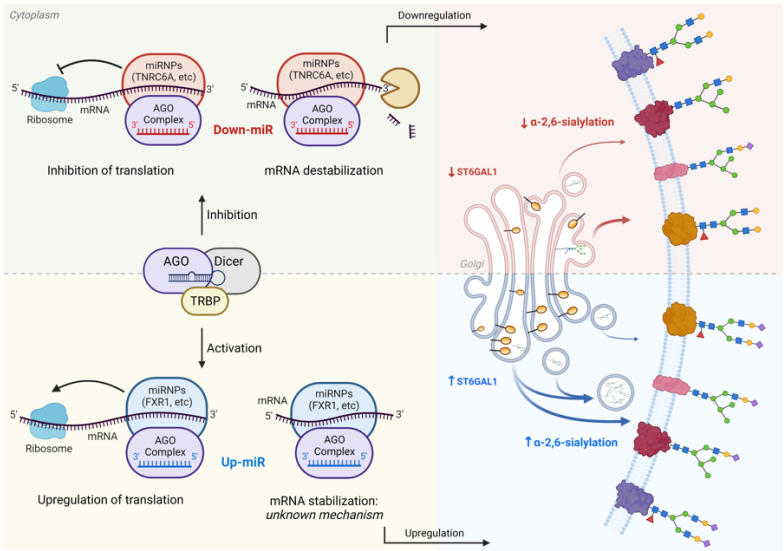
Chemical biology tools have increasingly revealed the importance of sialic acids as a major signal in physiology and disease. α-2,6-Linked sialic acids on galactose drive cancer development and metastasis, immunological recognition, and microglial phagocytosis (1). This modification is biosynthesized by two enzymes: ST6-β-galactoside-α-2,6-sialyl- tranferase-1 (ST6GAL1), and ST6GAL2. Although this modification is critical in both health and disease, the regulation and dysregulation of these enzymes and thus α-2,6-linked sialic acid are poorly understood.

microRNAs (miRNAs, miRs) are small non-coding RNA that tune protein expression through modulation of mRNA. The canonical view of miRNAs is that they are posttranscriptional repressors, binding to the 3'-UTR of mRNA within RISC complex and causing mRNA destabilization and/or loss of translation (2). Using our recently developed high-throughput fluorescence assay (miRFluR) (3), we comprehensively mapped the miRNA regulatory landscape of α-2,6-sialyltransferases ST6GAL1 and ST6GAL2. We found, contrary to expectations, the majority of miRNA upregulate ST6GAL1 and α-2,6-sialylation in a variety of cancer cells. In contrast, miRNAs that regulate ST6GAL2 were predominantly downregulatory (4). Mutational analysis identified direct binding sites in the 3'-untranslated region (UTR) responsible for upregulation, confirming it is a direct effect. The miRNA binding proteins AGO2 and FXR1 were required for upregulation. Our results upend common assumptions surrounding miRNA, arguing that upregulation by these non-coding RNA is common. Indeed, for some proteins, upregulation may be the dominant function of miRNA. Our work also suggests that upregulatory miRNA enhance expression of ST6GAL1 and α-2,6-sialylation, providing another potential pathway to explain their dysregulation observed in cancer and other disease states (4).



miRNA regulation of α-2,6-Sialic acids

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