Sialic acid is a critical component of many mammalian glycans and serves a variety of roles. Sialylated glycoconjugates mediate essential recognition events in the immune system and also act as receptors for many pathogens and their toxins. Sialylated molecules are abundant in the nervous system, where they coordinate cell-cell interactions. Finally, many recognized tumor markers are composed of sialylated molecules.

Given the critical roles of sialic acid, it is intriguing to note that humans differ from other primates in certain aspects of sialic acid biology. Notably, humans are incapable of synthesizing a hydroxylated version of sialic acid known as N-glycolylneuraminic acid (NeuGc) and make only the non-hydroxylated form, N-acetyll neuraminic acid (NeuAc). The NeuGc deficiency in humans is attributed to a truncation in the gene encoding cytidine monophosphate sialic acid hydroxylase (CMAH). Despite their inability to make NeuGc, humans can incorporate this sialic acid into glycoconjugates through dietary acquisition. These NeuGc-containing glycoconjugates can be immunogenic in humans and are implicated in chronic inflammatory states, including those associated with cancer progression. Moreover, the presence of NeuGc-containing glycoconjugates predisposes humans to infectious diseases where the pathogens or toxins bind to NeuGc. Because the incorporation of NeuGc carries negative consequences for humans, we hypothesized that human cells may employ mechanisms to discriminate against NeuGc incorporation.

To track the metabolism of NeuAc and NeuGc, we prepared cell-permeable forms of N-acetylmannosamine (ManNAc) and N-glycolylmannosamine (ManNGc). ManNAc and ManNGc serve as metabolic precursors to NeuAc and NeuGc. We discovered that both human and rodent cell lines preferentially metabolize ManNAc to NeuAc while ManNGc serves as a metabolic precursor to NeuGc. Given the critical roles of sialic acid, it is intriguing to note that humans differ from other primates in certain aspects of sialic acid biology. Notably, humans are incapable of synthesizing a hydroxylated version of sialic acid known as N-glycolylneuraminic acid (NeuGc) and make only the non-hydroxylated form, N-acetyll neuraminic acid (NeuAc). The NeuGc deficiency in humans is attributed to a truncation in the gene encoding cytidine monophosphate sialic acid hydroxylase (CMAH). Despite their inability to make NeuGc, humans can incorporate this sialic acid into glycoconjugates through dietary acquisition. These NeuGc-containing glycoconjugates can be immunogenic in humans and are implicated in chronic inflammatory states, including those associated with cancer progression. Moreover, the presence of NeuGc-containing glycoconjugates predisposes humans to infectious diseases where the pathogens or toxins bind to NeuGc. Because the incorporation of NeuGc carries negative consequences for humans, we hypothesized that human cells may employ mechanisms to discriminate against NeuGc incorporation.

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