S.18 SIALIC AND POLYSIALIC ACID

S18.1
New Insights into the Mode and Role of Enzymatic Sialic Acid Modifications

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The considerable structural variety exhibited by sialic acids makes them unique among the sugars of glycoconjugate oligosaccharides. Recent investigations have revealed that the various enzymatic derivatisations of Neu5Ac occur at different stages in the biosynthesis of glycoconjugate-bound sialic acid, involving several cellular compartments. Thus, the formation of Neu5Gc results from the cytosolic hydroxylation of CMP-Neu5Ac, while the *O*-acetylation of the glycerol side chain occurs at the level of glycoconjugate-linked sialic acid within the Golgi apparatus. Similarly, the methyltransferase catalysing the formation of 8-*O*-methyl Neu5Gc in starfish also acts on glycan-bound sialic acid and is located in a particulate cellular fraction.

The biological significance of the various sialic acids is the subject of much research. Neu5Ac linked to cell surface glycoconjugates has been suggested to mediate a number of cell-cell interactions via receptors such as the selectins, sialoadhesin and CD22. Recent investigations on the sialoadhesin of mouse macrophages revealed that this receptor is highly specific for Neu5Ac and does not tolerate Neu5Gc or *O*-acetylated sialic acids. The interaction of certain pathogens with their target tissues can also be influenced by modification. Thus, the binding of the malaria parasite, Plasmodium falciparum, to erythrocytes is greatly reduced by the presence of 9-*O*-acetylated sialic acids. In contrast, Influenza C virus haemagglutinin exploits 9-*O*-acetyl sialic acids as a receptor for infection. These are only a few examples of how the functional diversity of sialic acids can result from their structural heterogeneity.

S18.2
Structure-Activity Relationship in the Interaction Between Influenza Virus and its Host Cell Receptor

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Before influenza virus enters the cell to initiate infection the virus must attach to the surface of the host cell. Sialic acid is recognized as a receptor determinant by more viruses than any other determinant known. Influenza A and B virus specifically identify *N*-acetylneuraminic acid on the host cell surface, whereas influenza C virus recognizes 9-*O*-acetyl-*N*-acetylneuraminic acid. For influenza A virus we have synthesized novel sialic acid analogues to probe, by use of two independent methods, the strength of interaction between virus and receptor determinant. Distinct differences in activity were observed which allowed to develop a structure-based rationale for further studies.

Employing synthetic sialic acid analogues we have analysed the specificity of the receptor-destroying enzyme of influenza C virus. After enzymatic transfer to surface glycoproteins, 9-acetamido-*N*-acetylneuraminic acid was able to mediate the binding of the virus to cultured cells. However, containing an amide linkage instead of an ester the synthetic receptor determinant resisted the enzyme, yet allowed the cell to be infected. Interestingly, a structurally related analogue, though equally active as receptor determinant, did not sustain infection of the cell.

Because of their inhibitory activity such analogues promise to be powerful chemotherapeutic agents.

S18.3
Polysialic Acid: From Microbes to Man

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Polysialylated neural cell adhesion molecules (N-CAMs) are oncodevelopmental antigens in human kidney and brain, and may enhance the neural invasion of some human cancers, including multiple myelomas and T-cell lymphomas. Polysialic acids (polySia) are a structurally unique group of carbohydrate chains that consist of *N*-acetylneuraminic acid (Neu5Ac) or *N*-glycolylneuraminic acid (Neu5Gc) joined internally by α-2,8-,α-2,9, or alternating α-2,8/α-2,9-ketosidic linkages. 2-keto-3-deoxy-D-glycero-D-galactononulosonic acid (KDN) is a special deaminoneuraminic acid, and its polymers share many properties in common with polySia. PolySia covalently modify surface glycoconjugates on cells that range in evolutionary diversity from microbes to man. Thus, these molecules function in a remarkably diverse range of important biological contexts. As a consequence, polysialylation has emerged as an exciting new area of glycoscience that continues to impact on contemporary studies in micro-biology, molecular, cell and developmental biology, neuro-biology and oncology.

Our studies seek to understand the unresolved problem of how surface expression polySia chains is regulated in neuroinvasive *Escherichia coli* K1, developing chick brain, human cancers (neuroblastomas, myelomas, T-cell lymphomas), sea urchins, and trout egg polysialoglycoproteins. The objective of my seminar will focus on three areas: First, to summarize the occurrence, structural diversity and possible functions of polySia chains with an emphasis on human tumors. Second, to describe the development of prokaryotic-derived reagents to identify polySia residues on various surface glycoconjugates from bacteria to brains, and to illustrate how the *E. coli* K1 polysialyltransferase can be used as a synthetic reagent to synthesize structurally unique polysialylated neoglycosphingolipids. Third, to review recent developments that have emerged regarding the specific proteins and genes required for the synthesis, transmembrane translocation and export of the polySia capsule in neuropathogenic *E. coli* K1. A surprisingly complicated genetic and biochemical pathway is involved in regulating expression of this neurovirulent capsule, in that the *kps* gene complex is encoded in ca 17 kb of DNA that codes for at least 14 proteins required for capsule expression. The complexity of polySia chain synthesis and expression in prokaryotic cells underscores the probable complexity to be found in eukaryotic cells, a biosynthetic pathway that is beginning to emerge.