



# Sialic acids as regulators of molecular and cellular interactions

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The wide occurrence of sialic acids (Sia) in various chemical forms linked as monomers or polymers in an outstanding position in a multitude of complex carbohydrates of animals and microorganisms renders them as most versatile function modulators in cell biology and pathology. A survey is presented of recent advances in the study of the influences that Sias have as bulky hydrophilic and electronegatively charged monosaccharides on animal cells and on their interaction with microorganisms. Some highlights are: sialylation leads to increased anti-inflammatory activity of IgG antibodies, facilitates the escape of microorganisms from the host's immune system, and in polymeric form is involved in the regulation of embryogenesis and neuronal growth and function. The role of siglecs in immunoregulation, the dynamics of lymphocyte binding to selectins and the interactions of toxins, viruses, and other microorganisms with the host's Sia are now better understood. *N*-Glycolylneuraminic acid from food is antigenic in man and seems to have pathogenic potential. Sia *O*-acetylation mediated by various eukaryotic and prokaryotic *O*-acetyltransferases modulates the affinity of these monosaccharides to mammalian and microbial receptors and hinders apoptosis. The functionally versatile *O*-acetylated ganglioside GD3 is an onco-fetal antigen.

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### Introduction

Sialic acids (Sia), a large family of neuraminic acid derivatives, are acidic monosaccharides common in higher animals and some microorganisms. They are found in cellular secretions and on the outer surface of cells, mostly as terminal components of glycoproteins and glycolipids (gangliosides) [1\*]. Sia are exposed to the cellular environment functioning in intrinsic and extrinsic communication and in defense. The same holds for mucin secretions, in which Sia not only increase viscosity but

also help to protect epithelia from harmful substances and pathogens [2,3]. It is not easy to describe a general role of Sia because these monosaccharides participate directly or indirectly in multiple and diverse cellular events. However, in addition to their negative charge, it is useful to divide their functions into two groups that explain many phenomena. Firstly, Sia act as a biological mask, that is an antirecognition agent by shielding recognition sites such as penultimate monosaccharides of glycan chains or (antigenic) proteins and other macromolecules of cell membranes including receptor molecules. In this way Sia contribute to cells being 'self'. This may be possible by their electronegative nature together with their bulky, hydrophilic chemical structure (Figure 1). Secondly, Sia operate in the opposite way by being biological recognition sites, that is ligands for a great variety of molecules such as hormones, lectins, antibodies, and inorganic cations. Especially the latter two protein classes have been recognized recently as being involved in most important phenomena of cellular and molecular interactions in both physiological and pathological processes. In this respect, polysialic acids (PSA) are presently drawing much attention [4]. Furthermore, many microorganisms infect cells by binding to Sia and thus exploit the host organism. Elucidation of the underlying mechanisms will enable the development of therapeutic or prophylactic strategies [5].

These dual properties of Sia can be influenced strongly by different substituents on the neuraminic acid moiety. About 50 Sia types are known, with *N*-acetylneuraminic acid (Neu5Ac), followed by *N*-glycolylneuraminic acid (Neu5Gc) and *O*-acetylated derivatives, mostly *N*-acetyl-9-*O*-acetylneuraminic acid (Neu5,9Ac<sub>2</sub>) as most frequent forms [6] (Figure 1). This Sia variability can be increased by metabolic incorporation of non-natural substituents into cell membrane Sia, which also modulate their functions [7].

### The antirecognition effect of sialic acids

The first example of this phenomenon was the uptake of desialylated serum glycoproteins by hepatocytes observed by G. Ashwell and A.G. Morell 35 years ago (summarized in [1,6]). The reason for this was the exposure of Gal residues and trapping of unmasked glycoproteins by a Gal-recognizing receptor. This finding tremendously influenced not only sialobiology but also the whole area of protein (lectin)-carbohydrate interaction studies [8\*]. In a similar way desialylation of erythrocytes, lymphocytes, and thrombocytes leads to sequestration from circulation by a galectin on liver and spleen macrophages [6]. Also tumor cells may be