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Review

Short Article

Role of Sialic Acids in Central Nervous System Immune Response

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ABSTRACT

Sialic acids (Sia) are a structurally diverse family of nine-carbon sugars that play a crucial role in cell–cell communication, immune modulation, and neurodevelopment. Their unique ability to form homo- and oligo-polymers, along with a variety of linkages and chemical modifications, contributes to the complexity of glycosylation patterns on cell surfaces. Particularly enriched in the Central Nervous System (CNS), polysialic acids are involved in processes such as synaptogenesis, neuroplasticity, and modulation of neurotransmitter activity. This study explores the biosynthesis, recycling, and functional roles of Sia in the CNS, emphasizing their involvement in immune regulation via SIGLEC receptors and complement system modulation. It also addresses the pathological implications of Sia mimicry by pathogens such as Neisseria meningitidis and E. coli, which exploit sialylation to evade immune responses.

Keywords: CNS, Sialic Acids, immune system, sialylation, sialyltransferases, SIGLEC

INTRODUCTION AND PURPOSE

Sialic acids occur in over 50 forms of nine carbon monosaccharaides [1], the most common in vertebrates are Neu5Ac, Kdn and Neu5Gc acids, which are synthesized in the cytosol [2]. The unique aspect is that Sia, not like other sugars are responsible to form a homo/oligo polymers, such as diSia, oligoSia and polySia. The degree of polymerization [DP], various intersialyl linkage types- α2,4, α2,5Oglycolyl, α2,8, α2,9 and also possible modifications, like sulphation, methylation, lactylation, lactonization and acetylation are the reasons of a great diversity of this molecules [3]. The Sia residues are part of glycocalyx, determining its unique glycosylation pattern by sialylation process. As a result of sialylation, carried by sialyltransferases, the cell surface is terminated by sialoglycoproteins' and sialoglycolipids' chains [2]. Sialic acids have strong anionic charge, it determinate glycocalyx's

chemical properties also secondary and tertiary structure of glycoproteins thus it regulate various functions of local environment including protein reactions, such as trafficking, folding, signaling and stability which provides to further consequences in many fields of the human physiology [2,4]. Sia are included from local to systemic actions like controlling glycoconjugates , microdomain formation, cell communication- with other cells [like ligand receptors], with extracellular matrix and also pathogens; recognition of self and non- self-molecules [regulating innate immune response] , cellular and tissue development [especially CNS], growth factor retention, tissue homeostasis, cellular aggregation and differentiation [2,5,6,7]. The aim of the study is to show the Sialic acids' role and circulation in the Central Nervous System.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Sialic Acids circulate in the cycle which include a few stages; production, expression on cell surface, desialylation [removal of Sia residues], endosomal uptake, lysosomal degradation and reuse [2]. The production of Sia starts from UDP-GlcNAc [8], nucleotide synthetized in cytosol, containing D-glucosamine [9]. First, two reactions including transformation from UDP-G1NAc to ManNAc-6- phosphate are catalyzed by GNE, ManNAc kinase [other name is UDP-GlcNAc 2-epimerase]. Next, ManNAc and phosphoenolopyruvate are condensed by Neu5Ac-9-phosphate synthase, forming Neu5Ac-9-phosphate. Then, the molecule is dephosphorylated by Neu5Ac-9-phosphate phosphatase. 4 steps of Neu5Ac production take place in the cytosol and the final form CMP-Neu5Ac is formed in nucleus, by CMP-Neu5Ac synthetase [8]. Activated Neu5Ac is transported to the Golgi apparatus, where it can be used by sialyltransferases to polymerization process [polySia formation] [10]. The Sia synthesis pathway is regulated by feedback inhibition mechanisms, as its crucial role for cell functioning. [10].Sialyltransferases are transmembrane glycosyltransferases occurring in 20 forms [11]. STs belong to the four families; ST3Gal, ST6Gal, ST6GalNAc and ST8Sia. Its main function is to catalyze the reaction of transfer Sia residues onto glycoconjugates [the type of linkage is dependent on ST type], forming sialoglycoconjugates, which are further transported on the cell surface [2]. Then, as described above, it is participating in various important physiological and pathological processes.

The greatest amount of polySia is found in Central Nervous System, particularly in the embryonic life. The detection of it is possible from day 9.5 and reaches the highest

concentration before the labor [2]. Sialic acids play significant role in development of Central Nervous System including synaptogenesis and neuronal transmission. Glycolipids are dominating the brain's glycome, whereas gangliosides are the form which occur the most often [4]. Gangliosides regulate the flexibility and fluidity of neuron's membrane. One of the most important molecules is PSA-NCAM, known as a modulator of structural plasticity in neurons [12]. Also we have knowledge that higher amount of glycosylation in CNS is the reason of better brain's functioning, especially in case of learning and memory because gangliosides take part in memory formation mechanisms, such as binding calcium ions which are necessary to synaptic transmission, second messenger release and regulation of membrane excitability. Gangliosides are also necessary in the process of membrane extension associated with growth of axons and dendrites [9]. In addition, polySia take part in binding neurotransmitters, neurotropic and growth factors, such as BDNF [2]. Sia's amount is increased in the saliva and plasma of pregnant women. High concentration of Sialic acids occurs in human milk which was the reason of conduction of research comparing breastfed children with those who were fed by infant formula. Findings showed that breastfed children achieve higher scores in tests checking intelligence [9]. The expression of polySia in adulthood is significantly reduced but there are regions where it is detectable, such as synapses, the whole retina and also neurogenic zones of dental gyrus and hippocampus [2].

Sialic acids residues also regulate the innate immune response of Central Nervous system, its most important role is taking part in the process of recognizing molecules. The main cells with phagocytic properties are microglia. Its activation depends on ''switch'', which is turned ''off'' most of the time, in a state of homeostasis. Microglia recognize unique configuration of Sialic acids as a ''intact self'' which stops its activation and further processes, protecting neurons from degeneration. Sialic acids prevent the attack in several mechanisms, such as complement system inhibition [alternative C3- convertase]. What is more, desialylated structures trigger the classic pathway of complement activation, thus the sialylation is critical for preventing the attack. Also the genetic defects of FH [the complement factor with regulatory properties, binding to Sia and competing with complement active factors] provide to neurodegeneration. The next, important mechanism of immune regulation is recognizing Sialic Acids by SIGLEC receptors located on surface of immune cells, particularly microglia, macrophages and monocytes [2], except SIGLEC-4 found on myelinating cells involved in neurodegeneration. Humans express 14 types of SIGLEC, 9 of immune SIGLECS carry ITIM-domain, causing response breaking [by thyrosine phosphatases shp1/2] and 3 provides to association with DAP10/12, which activates immune response [13,14]. Unfortunately, this

immune regulation is also a reason of possible pathological processes. Some bacteria take advantage of human Sia, incorporating it into cell membrane which leads to escape the immune defense [2]. The Neisseria Meningitidis [serogroup B], resistant to normal human sera [NHS] express the (α2→8)-linked polySia and research showed that desialylation carried by α2, 3 sialyltransferase gene interruption changed resistance to 50 % NHS [17]. E.Coli, serogroup K1, use molecular mimicry and escape immune response by exploiting human Sia by S-O-acetylotrasferases and sialidases. What is more, the pathogenesis of many bacterial and viral infections with affinity to other human systems, like digestive system [for example Salmonella Typhi, Vibrio Cholerae] [16] is based on Sia metabolism. Likewise, Trypanosoma [parasitic protozoans] use trans- sialidase with opportunity to run donor- acceptor Sia reaction which cleaves Sia residues from human cell and transfers it to parasite surface. [17]

SUMMARY

Sialic acids (Sia) are a diverse group of over 50 nine-carbon monosaccharides, with Neu5Ac, Kdn, and Neu5Gc being the most common in vertebrates. Unique among sugars, Sia can form polymers like diSia and polySia, which vary in linkage types and modifications, contributing to their structural diversity. Sialylation, catalyzed by sialyltransferases, plays a key role in forming the glycocalyx and influences many cellular processes by affecting glycoprotein structure and function. In the Central Nervous System (CNS), polySia is particularly abundant during embryonic development and is involved in synaptogenesis, neuronal plasticity, and memory formation. Sialic acids regulate immune responses in the CNS, notably through interactions with microglia and SIGLEC receptors, helping to distinguish self from non-self and prevent unwanted immune activation. However, some pathogens exploit Sia to evade immune detection, contributing to infections and disease. This study focuses on the synthesis, function, and immunological importance of Sialic acids within the CNS.

AUTHOR'S CONTRIBUTION

Conceptualization -K.N., M.N., Formal Analysis-.K.N., M.N., Investigation-K.N., M.N. , Data curation - K.N.,M.N., P.D.,S.K.,Writing- through preparation- K.N.,M.N., P.D.,S.K.,A.U.,A.J.M.W., Writing- review and editing-K.N.,M.N., P.D., Supervision-K.N. All authors have read and agreed with the published version of the manuscript.

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