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SIALIC ACID AND ITS ROLE IN HEALTH - A SHORT REVIEW

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ABSTRACT

On the surface of numerous body cells, sialic acid, a form of polysaccharide molecule, can be found. It has been discovered to contribute to the growth and spread of malignancy, and therefore has been studied as a potential diagnostic marker for cancer. Earlier diagnosis may increase the life expectancy and normal functioning of the patient. Our body is a complex machine with advanced mechanism. It contains various fluids like blood, saliva,serum,urine,etc. Each of them has their own role and functions. But they also react to each and every simple alterations in the body and we humans can make use of it for earlier and accurate diagnosis through its changes from its normal pattern and composition. One among them is saliva. Saliva is a complex fluid with number of components which aids in various purposes like hydration, lubrication and also diagnosis. This study aims in diagnosis using one such component called Sialic Acid. It is a nine carbon compound found at the terminal end of the chain. This article aims in concluding the various diagnostic purposes of sialic acid in dentistry and also other health related issues. Sialic compounds are a type of acidic sugars that can be found in some bacteria and on the external layer of cell membranes in mammals. They are essential for cell-to-cell transmission and classification and changes in their levels or composition can be indicative of various diseases. Overall, sialic acid measurement has the potential to provide valuable diagnostic information in dentistry, particularly in the areas of periodontal disease and oral cancer. However, further research is needed to fully understand its clinical utility and to develop standardized protocols for its use in clinical practice.

INTRODUCTION:

"Sialic acid" is the term first coined in 1952.It describes N-acetylneuraminic acid which is the main product released due to the low-level acid reactions of glycolipids in brain or the salivary mucins.[1] Sialic acid which is a nine-carbon compound is an acute phase reactant. It helps in diagnosis of different oral pathologies as it plays the role of bio markers. They can be used in some pathological circumstances during which there is less of a need for accuracy than there currently is for particular diagnostics in order to improve diagnosis, staging, as well as tracking of therapeutic response[1]. Brain is the only organ in humans with large amount of sialic acid present in it mainly in the form of gangliosides. Since various gene products frequently create the same glycosidic linkage , sialyltransferases exhibit some degree of redundancy and are essential for the development of cancer. A class of glycosyltransferases known as sialyltransferases catalyses sialic acid gets transmitted to a carbohydrate molecule from a frequently used substrate (CMP-sialic acid).

The sugar elements of glycoproteins as well as glycolipids are generally referred to as sialic acids (Sia), which are polysaccharides with an electrical charge that is negative. These sugars play a crucial role in modulating intracellular along with biochemical connections [1-3]. N-acetyl glucosamine (GalNAc) or N-acetyl galactosamine (GalNAc) are bound together by a 2- 6 bond. (GlcNAc), To create polysialic acids, sialic acids can be joined to sub terminal sugars using a 2, 3, or 2, 6 bond to a substance called gal (Gal), or a 2-8 bond with an additional sialic acid .[7] Sialic acid measurement has also been studied as a potential diagnostic tool for oral cancer. In its early stages, oral cancer can be challenging to detect and is a serious, possibly fatal condition. Patients with oral cancer have been discovered to have higher salivary levels of sialic acid and some studies have suggested that measuring these levels could be a useful screening tool for the disease.

STRUCTURE OF SIALIC ACID:

3-deoxy-Non2ulo5NAc-onic

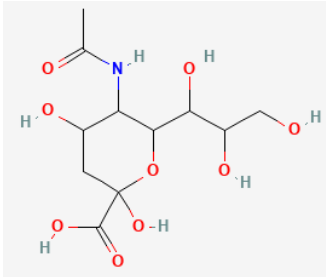

Image reference:;National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 906, Sialic acid. Retrieved March 25, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Sialic-acid.

Sialic Acid comes in two varieties:

I. Glycolipid-bound SA makes up LIPID BOUND SIALIC ACID(LSA).

ii. SA that is linked to glycoproteins and glycolipids makes up TOTAL SIALIC ACID(TSA).

The usual range of TSA concentration in serum or plasma is 1.58 to 2.22 mol/L, while the free form of SA only amounts to 0.5 to 3 mol/L and the LSA forms at 10 to 50 mol/L.[16] These Sialic Acids are 9carbon carboxylated monosaccharides synthesized in animals, also present at the outer most end of N and O linked carbohydrate chains.

Sialic acids are usually seen as end components of glycoproteins and glycolipids, it also plays a major role in the chemical and biological diversity of glycoconjugates.[3]

Recent studies showed increased correlation of sialic acid and prevalence of cancer in general population. It also plays a major role in diagnosis of periodontal conditions. It is an acidic sugar with a nine-carbon carboxylated chain which pays major pathway for various patho- physiological processes .[10]

Saliva is a multifaceted fluid made up of numerous organic and inorganic components along with salivary sialic acid that function together to modify the environment of the oral cavity. It is a fluid especially found in Oral cavity, and in recent years, interest in using it as a diagnostic instrument has grown significantly. Biological markers can be used to track cancer, forecast its prognosis and therapeutic response, and in some cases, even identify it. These molecules are also known as tumour markers that can be detected in serum, blood, plasma fluid, or other fluids of the body and also modifications in the amount of the concentration levels of cancer. They may be naturally existing or normally modified molecules.[14]

FUNCTIONS OF SIALIC ACID:

The Cell-to-cell interactions, cell-to-cell transmitting signals, carbohydrate-protein exchanges, cellular accumulation, processes of development, responses from the immune system, reproduction, in addition to the neuroscience and medical conditions in humans, where it allows for infection by bacteria, are the the main stream ways that sialic acid performs in human physiology.[3] Sialic acid having the capacity to both symbolize targets in biological systems that can be acknowledged by proteins called receptors and function as ligands, and also to cover up recognition sites. By obscuring antigens that would not normally trigger an immunological reaction, sialic acid can shield cells from immune system assault. This is important for the brain for the reason of the barrier between the blood and the brain stops numerous immune cells from penetrating and possibly harming vulnerable neural tissue there as well.

Desialylation and sialylation are dynamic modifications that sialyltransferases and sialidases control in reaction to internal or external stimuli .[1] Sialic acid can help to lubricate and protect the surfaces of cells and tissues, particularly in the respiratory and digestive tracts, which are exposed to potentially damaging substances and pathogens. By exposing galactose (Gal) residues and making it easier for receptors to recognize and phagocytoseasialoglycoproteins, the loss of Sialic acid shortens the lifetime of platelets. Identical to erythrocytes, intended platelets are swiftly eliminated from circulation in vitro.

Natural killer (NK) cells contribute to two antagonistic receptors for the CK-binding immunoglobulin-like glycoprotein (Siglec): Siglec-7 and Siglec-9. It is speculated that sialic acid on the outermost layer of tumour cells modulates NK-mediated cellular damage through interaction with Siglec-7 and Siglec-9 and suppressing the NK cell stimulation mechanisms. Additionally, Sialic acid serve as places in which different receptors, including selectins and siglecs, can be located.[1] Universal chemicals called Sialic acid can very precisely alter both healthy and unhealthy cellular processes. Sialic acid as a result, the most visible agents of molecular and cellular recognition.[1] Sialic acid is often found on the outer branches of complex carbohydrate structures on the surface of cells and proteins, where it can help to stabilize these structures and protect them from degradation. Overall, sialic acid is a key player in many important biological processes, and its presence and function are essential for proper health and development in humans.

SIGNIFICANCE IN DIAGNOSTIC PURPOSE IN ORAL CANCER:

Oral cancer is one of the most commonly seen cancer which is often treated with resection of the malignant part which is followed by chemotherapy and radiotherapy.Whereas the life after resection doesn't appear to be same as before or easy to accept. Various difficulties are encountered by the patient as well as their family as the resection saves the life and affects the function, aesthetics etc. Squamous cell carcinoma, malignant melanoma, basal cell carcinoma are some of the common oral malignancies. The sialic acid found in saliva has been acting as a possible value for diagnostic indication of cancer. Additionally, there are few studies that use saliva as a screening tool for oral cancer. [6] The amount of total and free Sialic acid in the blood and tissues increased almost invariably in response to extreme bodily effects and inflammatory processes, according to a number of scientific studies. However, it was unclear how they contributed to the emergence of pathological processes and the mechanisms underlying variations in the concentrations of different Sialic acid components.[1] The expression "tumour hyper sialylation" corresponds to a 40–60% boost in remnants of sialic acid on the outermost layers of cancer cells. Hyper sialylation, which may end up in either an overexpression of sialyltransferases, a decreased activity of neuraminidases, or a combination of both, leads to an overabundance of negatively charged sialic acid on the outermost layer of the cell. The enhanced transcription of sialyltransferases has been linked to oncogenes like Ras and c-Myc, among other things. Sialic acid the accumulation has been linked to immune evasion, suppresses crucial signalling routes, and decreases the therapeutic effects of chemotherapy and irradiation.[5] Total sialic acid (TSA) is comprised of a mixture of glycoprotein and glycolipid-bound sialic acid, in contrast lipid-bound sialic acid (LSA) is composed of glycolipid-bound sialic acid.

These glycoconjugates are discharged into the bloodstream by malignant cells' enhanced secretion, shedding, and/or turnover. Individuals with OPC as well as carcinoma of the mouth had substantially greater blood concentrations of TSA and LSA when contrasted with controls. Elevated blood sialic acid levels might have been correlated to the clinical preparation, outcome, and eventual recurrence of carcinomas, in relation to specific research.[13] Based on the outcomes of these investigations, oral cancer patients have considerably greater concentrations of both free and attached to proteins sialic acid in their saliva than their non-infected peers. In recent times, it was discovered that OSCC cases had substantially greater concentrations of free sialic acid and protein-bound sialic acid, whereas there had been no important to note results in regard to the various OSCC staging.This indicates a connection between increased levels of sialic acid in saliva and the development of precancerous and cancerous conditions, such as OSCC and leukoplakia.[14]

IN BREAST AND GYNECOLOGICAL CANCER:

The most common cancer that can be treated on early detection is the breast cancer which is often neglected from early detection. In order to decrease the mortality rate and to aid in early diagnosis concentration of sialic acid may play a vital role. By interacting with Siglec-7 and Siglec-9 and reducing the NK cell activation pathways, it is proposed that Sialic acid on the surface of tumour cells controls NK-mediated cytotoxicity. Additionally, Sialic acid serve as places in which different receptors, including selectins and siglecs, can be located .[1] These selectin ligands function to bind circulating cancer cells to the endothelium in close proximity to the target organ, preventing extravasation, once the cells have reached the circulation or lymphatic system. A distinctive marker for P-selectins encountered on blood platelets and endothelial cells, termed CD24, has been modified by sLex in P-selectin-dependent sliding of breast and bladder malignancies throughout progression to the lungs. Furthermore, sialylation accumulates on the cell surface protein CD133, a cancer precursor cell biomarker. Migration and propagation have been strongly associated to this sialylation of CD133. According to a 2019 study by Scott and Drake, breast tumours with high sLex levels exhibit an

affinity for endothelial cells' E-selectins, which can cause extravasation at potential secondary locations.[5] Irrespective of the underlying glycan structure, carcinoma can be identified by the proliferation and reorganization of the terminal sialic acid structures (Sia). (Amon et al. 2014).Traditionally, this has the effect of reducing the tumour cell's adherence to the ECM. It is possible for tumour cells to become more plastic inside the tissue matrix, which can also help to obstruct the alternate pathway of complement activation from detecting the tumour.[14] Sialoglycans on its outermost layer of hypersialylated malignant cells hyperlink with siglecs on immune cells in order to trigger immune suppression by limiting NK cell cytotoxicity and T cell activation thereby promoting a cancerous-associated macrophage phenotype, which subsequently turn encourages ongoing tumour development. [16] The early awareness and early diagnosis are the key points of the study in which the role of sialic acid plays the lead. As further investigation and research on the same trend will lead to a persistent diagnostic method the mortality can be widely decreased all over the world.

IN PERIODONTITIS AND FLUOROSIS:

Periodontitis is a most common inflammatory conditions found among more than one third of the population. It depicts the information of periodontium which helps in positioning and functioning of the tooth structures.While fluorosis in India is most commonly due to decreased fluoride intake. One of the most common uses of sialic acid measurement in dentistry is in the diagnosis of periodontal disease. A long standing persistent inflamed disorder, periodontal disease damages the soft tissues and the underlying bone surrounding dentition. It is then transported on by an infection from bacteria and, if left untreated, may culminate in teeth loss. In accordance with studies, people who have periodontal disease have an elevated amount of sialic acid in the fluid that accumulates between the tissues of the gums and the tooth (gingival crevicular fluid).Therefore measuring sialic acid levels in this fluid can provide information about the severity of the disease and guide treatment decisions. Sialic acid and chondroitin sulphate (CS) are two indicators that have been linked to fluorosis and periodontitis.[15] High SA levels found in the patient's saliva and blood showed that periodontal pathogens triggered the immune system. The immune system's main response is inflammation, which aims to get rid of triggers and pathogen bacteria in order to get the injured host cells back to normal.[2] Because of the pathogenic microorganisms that cause periodontitis, there is a rise in the secretion of proinflammatory cytokines, which causes oxidative stress. As a result, radical production rises, and glycoprotein terminal SA residues start to disappear. As a result of increased levels of acute phase glycoproteins that have been heavily sialylated following inflammation and injury processes, SA concentration increases quickly, acting as an acute phase protein to prevent further damage and promote healing. The fact that SA levels are markedly elevated in inflammatory conditions like periodontitis supports the notion that saccharides are essential for the immune system. The production of sialoproteins and the cleavage of globulins from injured tissue were thought to be the causes of increased SA levels.[2]

In patients with periodontal disease, oral bacteria that enter the circulation system through lymph vessels may also trigger an immune reaction and raise blood SA levels .[2]

METHODS OF EVALUATION OF SA:

According to the procedure described by Sydow G, et al. in 1988, Ehrlich's method was used to quantify the serum sialic acid.

- 400 ml of serum were spun at 2000 rpm for 5 minutes after being combined with 1.2 ml of 5% perchloric acid for 5-10 minutes at 100°C.
- 400 ml of the supernatant and 400 ml of the Ehrlich solution (5 g of p-dimethylaminobenzaldehyde/50 ml of HCl/50 ml of distilled water) were combined.
- The optical density at 525 nm was measured using a spectrophotometer following a 15-minute warming period at 100 °C.[17]

LIMITATIONS OF SIALIC ACID:

SA has the following drawbacks:

I. Diabetes, cardiovascular disease, and inflammatory disorders all result in higher serum SA levels.

ii. Remarkably elevated concentrations of Sialic acid up to (10–30 fold) have been observed as well in numerous types of genetic variants of metabolic conditions, which includes sialidosis, Salla disease, infantile SA storage disease, and neuraminidase deficiency.

iii. Patients suffering from persistent glomerulonephritis and prolonged renal failure have been reported to have significantly elevated TSA values.[16]

CONCLUSION:

Studies have demonstrated that those diagnosed with numerous types of carcinomas, including oral squamous cell carcinoma, have significantly higher serum levels of TSA, LSA, and TSA/TP ratio. Serum sialic acid levels have gone up substantially based on an article from 2005 that apprximated the importance of SA as tumour indicators all over the body. Rajpura K.B. et al. (2005) derived the serum concentrations of SA in pre-malignant conditions, malignant patients, and normal subjects. They observed that these concentrations were considerably improved in cancer patients in comparison to both healthy people and people with oral precancer. Previous examinations have established the value of SA as a specific tumour indicator. Its preciseness is in contradiction, though. Furthermore, it was previously established that various physiological conditions may result in elevated serum sialic acid levels.[14] The goal of this initiative of the current research is to show the manner in which sialic acid can be used as a method of diagnosis for a variety of oral health issues. There are positive aspects to using sialic acid for the identification of oral malignancy and a number of other oral health issues, but more study is required.[14] Science demonstrated that a wide range of experimental procedures, including mass spectrometry and lectin-based assays, are able to identify modifications to both the amounts and kinds of sialic acids that exist on the surface of cancer cells.These improvements might be distinctive to a specific case cancer varieties, facilitating the establishment of more sophisticated diagnostic tests.

Despite the truth that SA has the possibility as a tumours biomarker, its implementation in medical practice for early detection of cancer is still comparatively restricted. The precision and sensitiveness of sialic acid-based assessments, in addition to their likelihood for being employed in conjunction with other methods for diagnosis, require a greater understanding.

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