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Neuraminidase Function in Bacteria as a Virulence Factor

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The factor of virulence has become inherent among a multitude of bacterial populations surviving on pathogenic mode of life. To this end, 'Neuraminidase' is an important enzyme reported to execute the virulence mechanism. It accomplishes this task by acting on glycosidic linkages of terminal sialic acid residues in glycoconjugates and synthetic substrates. Exo and endo-α-neuraminidases are the two types identified so far based on the neuraminidase led glycosidic cleavage of sialic acid. The key mandatory event for the commencement of virulence is the bacterial acquisition of sialic acid through scavenger pathway by neuraminidases. As virulent factor, neuraminidase contributes to a variety of perturbations like high viscosity of blood, thrombocytopenia, hemolytic anemia, loss of circulating factors, increased immune complex, auto immune conditions, deficiency of mucus viscoelasticity etc.

The existence of neuraminidase in several functional forms of '*Nan*' and its contribution to 'biofilm formation' appears to influence the evolving mechanisms and survival rates of pathogenic bacteria. With this, neuraminidase involvement in many diseases has shed much light and increased research attention has further widened its exploration as virulent factor in bacteria.

Key words: Neuraminidase,Virulence, Enzyme, Sialic acid.

Microorganisms like bacteria have emerged to contribute to a variety of infections by putting human life at risk. As such, there has been a growing research attention on mechanisms to understand the virulence and its mode of introduction in the host organism. In this regard, 'Neuraminidases' have been identified as important candidates. Neuraminidase, also known as Sialidase or Exo-alpha-sialidase is an enzyme (EC 3.2.1.18) [1], that cleaves α-(2→3)-, α-(2→6)-, α-(2→8)-glycosidic linkages of terminal sialic acid residues in glycolipids, glycoproteins,oligosaccharides, glycoproteins, colominic acid and synthetic substrates[2]. So far, two types of neuraminidases have been reported that hydrolyse glycosidic linkages.

They include exo-±-neuraminidase, for α-(2-3)-, α-(2-6)-, and α-(2-8)-glycosidic linkages of terminal sialic acids[3], the other is endo neuraminidase for α-(2-8)-sialosyl linkages in oligo- or poly-sialic acids[4]. Apart from their existence in diverse microorganisms that behave as pathogens or animal commensals, neuraminidases are found very frequently in descendants of deuterostomate organisms (Echinodermata through Mammalia)[5]. Neuraminidase function is better connected with Sialic acid . Sialic acids constitute the family of nine-carbon acidic monosaccharides present at the sugar chain ends and their most wide spread form is N-acetylneuraminic acids (Neu5Ac, NANA, Sia)[6] .

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Association between neuraminidase utilization by bacteria and virulence

Neuraminidase has been utilized by several bacteria as contributor of virulence in establishing infection[7,8]. They include *Vibrio cholerae,*[9] *Pseudomonas aeruginosa,* [10] and *Streptococcus pneumonia*[11] and others.[29,31,32]

The acquisition of sialic acid, using neuraminidases by pathogenic bacteria, can be considered as the prerequisite for virulence. In fact, to acquire sialic acid bacteria follow *de novo* biosynthesis or scavenger pathway (environmental source e.g. mammalian host).[12,13] Pathogenic bacteria secreted neuraminidases follow the scavenger pathway to liberate sialic acid from a variety of host sialoglycoconjugates.[14] Here, sialic acid is metabolized when extracellular sialidase catalyses sialo-glycoprotein to produce sialic acid (Neu5Ac) . Subsequently, free monosaccharide is transported into the cell by the action of sialic acid permease and finally gets degraded to to N-acety I mannosamine (ManNAc) by acylneuraminate pyruvate lyase.[14]

This biochemical pathway reflects a system where sialic acid is transported into cells, degraded for utilizing the carbon backbones as energy providers. Certain structure driven properties binding neuraminidase were considered crucial for infection acquirement. These include glycoconjugate nature and the presence of glycosidic linkage types, like α 2 - 3, α 2-6, α 2-8, to the next glucose in the chain of oligosaccharides.[16-19] Secondly, the substitution of hydroxyl groups at C7-9 positions and their increased O-acetylation lessens sialidase activity.[20, 21] Thus, neuraminidases of bacterial pathogens could serve as potential virulence factors by successfully competing with the host.[22]

Significance of Neuraminidase virulence

Neuraminidases uncover the cell structures of the host subterminally which later act as receptors for toxins and parasites.[23] It was reported that these enzymes contribute to host tissue toxicity or interfere with the host immunological machinery and supplementary protective mechanisms which results in several life threatening conditions. They include a) alterations at blood cell level ; thrombocytopenia, hemolytic anemia, erythrocyte pan agglutination, lessening of erythrocyte and leukocyte circulating half –life b) alterations in soluble blood conjugates; high viscosity of blood, low circulating glycoconjugate half life, loss of circulating factors erythropoietin and erythropoiesis, increased immune complex formation, increased auto antibody titres like that of anti T antigen leading to auto immune conditions c) alterations in vascular cell: deficiency of endothelial cell surface negative charge , deficiency of cell surface receptor specificity for cells enzymes and hormones d) mucosal surface defects; deficiency of mucus viscoelasticity and protective features, invasion due to bacterial binding site formation on epithelial cells.[24]

Neuraminidases strip of sialic acids surrounding erythrocytes and make galactose residues exposed on erythrocyte surface thus providing a sign to the hepatocytes for degradation, as observed in anemic animals.[25] Similarly, for pneumococcal invasion, glycosylation pattern variations of the host induced by neuraminidase enables the interaction between surface receptors and pneumococci leading to high adherence and other series of actions.[26]

Pathogenic forms of Neuraminidase

The function of neuraminidase as a virulent factor in bacteria is also better associated with their existence and mode of colonization. For example, in all strains of *Streptococcus pneumoniae*, neuraminidase exists as Nan A and Nan B whose genes have been cloned and sequenced.[27, 28] Among *two neuraminidases possessed by Tannerella forsythia, one enzyme (NanH) is involved in* bacterial colonization and invasion.[29, 30]. *Porphyromonas gingivalis* encodes a neuraminidase, PG0352 (SiaPg) that is mainly involved in biofilm formation , capsule synthesis, and infection.[31] Neuraminidase led biofilm production has also been reported in the *H.influenzae,* S. *pneumoniae*,and *Pseudomonas aeruginosa* which are pathogens of respiratory tract.[32] In *Vibrio cholerae,* neuraminidase (NANase) functions as an accessory virulent factor to improve pathogenicity by facilitating erythrocyte uptake of cholera toxin (CT) through increased binding and penetration.[33]

CONCLUSION

It can be concluded that, neuraminidase function as virulent factor is vast and

interassociated with bacterial physiology. Importantly, pathogenic bacteria have possessed neuraminidases to evolve and adapt to the host environment and continue virulence. As a result, several routes have been chosen by neuraminidases to keep alive the factor of virulence as an important function. A concrete evidence is warranted to further determine the neuraminidase virulent role in bacterial populations.

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