Neuraminidase gene: a target for influenza antivirals and vaccines

Highly contagious nature and fast transmissibility, mark Influenza as one of the most infectious diseases. According to WHO, annual Influenza epidemic tolls up to 3-5 million cases of serious illness, culminating in half a million death worldwide. To fight this dreadful disease, the anti-Influenza arsenal is equipped with therapeutic drugs and prophylactic vaccines. Present on the Influenza virus envelope, are two major surface glycoproteins, namely, hemagglutinin (HA) and neuraminidase (NA), which substantially influence the mutation dynamics associated with the Influenza virus, apart from facilitating virus-host fusion and serving as determinants in virus subtype identification. This review consolidates the evolutionary journey of the therapeutic NA inhibitors, resistance concerns with the use of these drugs and the several possibilities of designing NA centric vaccines.

The therapeutic drugs chiefly comprise of NA inhibitors, which function by blocking the enzyme active site of NA, thereby preventing the release and spread of virions. The potential of NA inhibitors as effective anti-influenza therapeutics was identified at the outset of emerging resistance to the adamantane group of influenza antivirals targeting the M2 gene. The Centres for Disease Control (CDC) recommends the use of three influenza antivirals, which include oseltamivir, zanamivir and peramivir. Studies have shown that the amino acid residues, involved in the catalytic function of NA, are conserved among all the NA subtypes of the influenza viruses. Geometry of the catalytic site is stabilized by yet another set of amino acid residues called as the framework residues. Mutations in the catalytic site and the framework residues are linked with drug resistance. A large cluster of NA-inhibitor resistant influenza viruses were detected in Japan, China and the USA. Though the number of resistant viruses seems less in the present scenario, this figure is likely to rise in the coming future owing to the increasing use of NA inhibitors.

Influenza virus alters its antigenicity dynamically by accumulating mutations in the surface glycoproteins, HA and NA. Minor changes in the protein structure are referred as antigenic drift whereas major changes are called antigenic shift. These antigenic shifts and drifts drive the emergence of new strains that cause pandemics, thereby rendering the development of newer drugs and vaccines challenging. Effective global monitoring and vaccine updating are crucial in strategically dealing with this disease. CDC recommends the use of live attenuated influenza vaccine, inactivated influenza vaccine and recombinant influenza vaccine to prevent influenza. Current vaccines chiefly constitute HA with varying amounts of NA and thus the standardization of these preparations is primarily based on HA content. Immune response to vaccination is estimated by measuring antibodies against HA. However, reduced inhibition due to amino acid changes in the HA protein in one study led to changes in the WHO vaccine strain recommendations for the 2015-2016 season.

A study on the evolution of hemagglutinin and neuraminidase genes depicted a slower rate (0.45-

1%) of amino acid substitutions in NA than in HA (1-2%), rendering NA antibodies capable of providing long-term protection. In addition to displaying an immunogenic profile similar to HA, NA glycoproteins have been also found providing both homologous and heterologous protection against influenza viruses. NA-specific antibodies may not be effective in preventing infection, but they do play crucial role in inhibiting the virus spread, thereby reducing the disease severity. In the face of these evidences, standardizing amounts of NA along with HA protein in influenza vaccine formulations appears to be a viable option towards compensating the variations due to HA and could be helpful in reduction and better containment of the influenza epidemic severity.

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