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Editorial

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Alternative Roles of Neuraminidase in Influenza a Viral Propagation

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Influenza A is an envelope virus containing a segmented negative RNA genome. The viral envelope has two major surface glycoproteins, Hemagglutinin (HA) and Neuraminidase (NA) of which there are 16 and 9 subtypes respectively [1,2]. While HA has been well characterized and shown to be essential for viral fusion and entry into host cells, the functional roles of NA in viral replication are much less understood.

Some previous reports suggest that NA exerts its primary role during viral exit from the cell by enzymatically cleaving sialic acid and facilitating the release of viral particles from the host cell [3-5]. Indeed this role is supported by the observation, that NA-defective viruses, or wild type (WT) viruses in the presence of NA inhibitors, form aggregations on the apical surface of the cells [6-8]. Although there is consensus regarding this primary role of the NA protein, other studies suggest that the functional role of NA may extend beyond viral exit from the host cell. Specifically, these reports indicate that NA may also play pivotal role(s) in viral spread through the airways and viral entry and fusion into target host cells [9-12].

Mastrosovich et al. suggest that in addition to viral particle release from the cell, NA is also essential in removing decoy receptors on mucins, a necessary step to perpetuate viral spread [13]. This role is particularly important within the airway, where mucins are produced by the epithelium and impede viral binding to the host cells at the primary site of infection. These results are largely consistent with those obtained by de Vries et al. who demonstrate that in the presence of serum rich in decoy receptors, NA is necessary for viral infection of host cells [14]. Furthermore, Ohuchi et al. [11] demonstrated NA facilitates virus entry in both MDCK and A549 lung carcinoma cell lines. Here it was found that NA could destroy decoy receptors on the cell surface and direct the virus to endocytic sites where the virus can be effectively internalized [15]. This observation was supported by results reported by Su et al., who developed a reporter gene system designed to detect viral entry and fusion [12]. Collectively these studies demonstrated that both viral entry and fusion were significantly enhanced by NA. However, since pseudotyped virus is used in the majority of entry and fusion studies [12], it is unclear how this type of the viral replication system may faithfully reflect the replication of the normal WT virus. Yet, it may be feasible to address this issue by quantitatively determining viral gene products of the WT viruses at early time points following infection. Alternatively, employing mutant virus incapable of replicating beyond viral fusion would also be an option. As the cells used in the virus infection study may differ in glycosylation, this could also contribute to the difference in cell susceptibility to virus infection. Finally, another important question remaining to be answered is the drastic difference in ratio between HA and NA among different virus strains. The observations that the increased levels of NA induced enhanced immune responses necessitate further investigations into such fundamental issues. Clearly, better understanding of all these issues is critical for the development of new antiviral strategies and vaccine evaluation processes through selective use of appropriate cell substrates for vaccine seeds and quantification of NA in human vaccine preparations [16].

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