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Choose your enemies wisely

Influenza virus has two major surface glycoproteins: haemagglutinin (HA), which promotes viral entry into host cells, and neuraminidase (NA), which facilitates the release of newly formed viral particles. Current influenza vaccines have focused on inducing HA-reactive antibodies; however, Chen *et al.* have found that influenza infections in humans induce antibodies against NA that provide protection against divergent virus strains.

Previous studies have suggested that immunity to NA protects against influenza virus, but little has been known concerning human antibody responses to NA. Chen *et al.* characterized plasmablasts from patients infected with H1N1 and H3N2 strains of influenza virus and found a surprisingly high proportion of these cells were NA-reactive. Indeed, plasmablasts from H3N2-infected patients predominantly targeted NA. Overall, they found that around 25% of plasmablasts induced by natural influenza virus infection targeted NA, whereas only 1–2% of plasmablasts induced by influenza vaccination were specific for NA. This suggested that current influenza vaccines do not induce NA-reactive antibodies efficiently. In agreement with this, NA-reactive antibodies were induced in mice infected with live or inactivated influenza virions but not in mice vaccinated with commercially available vaccines.

Characterization of monoclonal antibodies obtained from patients infected with influenza virus showed that NA-specific antibodies were more broadly cross-reactive against a range of influenza virus strains than HA-specific antibodies. Additional analyses indicated that several NA-reactive antibodies inhibit the enzymatic activity of NA from divergent strains of influenza virus. Furthermore, almost half of the NA-reactive antibodies tested were able to inhibit viral replication *in vitro*. Epitope mapping studies identified four amino acids in the head of N1 and three amino acids in the conserved enzymatic domain of N2 that were crucial for the binding of NA-inhibiting antibodies. Of note, these epitopes are disrupted in the available influenza vaccines.

Treating mice prophylactically with patient-derived NA-reactive monoclonal antibodies protected against lethal challenge with influenza virus. Almost all (11 of 13) of the N2-reactive monoclonal antibodies tested provided protection against an H3N2 influenza strain, whereas 5 of 8 tested N1-reactive monoclonal antibodies protected against an H1N1 strain; 4 of these 5 protective N1-reactive antibodies also protected against an engineered H5N1 avian influenza virus strain. Moreover, the protective antibodies were effective when delivered therapeutically to mice 48 hours after infection.

The efficacy of current seasonal influenza vaccines has ranged from 19% to 48% during the past three seasons. This study suggests that optimizing the NA component in the next generation of influenza vaccines could greatly enhance their protective capacity, particularly as the rate of NA antigenic drift is slower than that of HA.

Yvonne Bordon

> “optimizing the NA component in the next generation of influenza vaccines could greatly enhance their protective capacity”

ORIGINAL ARTICLE Chen, Y. *et al.* Influenza infection in humans induces broadly cross-reactive and protective neuraminidase-reactive antibodies. *Cell* **173**, 417–429 (2018)