because TGFβ1 is an essential regulator of immune responses in severe respiratory infections.[5] Notably, Carlson and colleagues[5] reported that injection of TGFβ1 delayed mortality and reduced viral titres of mice infected with H5N1 influenza virus, whereas neutralisation of TGFβ1 during H5N1 and pandemic 2009 H1N1 infection had opposing effects.

As a caveat, a side-effect of DPP4 inhibitor treatment could be suppression of immunity mediated by effector T cells. This action could limit their use in severe infection because it might inhibit the protective antiviral immune response.

In sum, it could well be worthwhile to establish the antiviral action of various DPP4 inhibitors through in-vitro and preclinical testing and, depending on the results, cautiously to examine their potential therapeutic effect in severe viral infections, including infection by MERS-CoV.

We declare that we have no conflicts of interest.

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Age and different influenza viruses

We read with interest the Comment by Guus Rimmelzwaan and colleagues[1] explaining the different age distribution of cases caused by avian influenza A viruses of the H5N1 and H7N9 subtypes. They proposed that the low incidence of severe H5N1 infections in elderly people compared with that in younger people might be related to the presence of cross-protective antibodies to neuraminidase that had been induced by seasonal influenza A H1N1 viruses. There is another type of cross-reactive antibody that might contribute to protection against the H5N1 subtype. By contrast with conventional neutralising antibodies binding to the globular head of the haemagglutinin, which are subtype-specific or even strain-specific, antibodies binding to the stalk region of the haemagglutinin are broadly neutralising. Some antibodies to the haemagglutinin stalk are subtype-cross-reactive.[2]

Previously, Smallman-Raynor and Cliff[3] suggested the possibility that people born before 1969 have immunity to the H5N1 subtype, which might have been associated with geographically widespread influenza A events before the late 1960s. We proposed[4] that widespread influenza A events before the late 1960s could have been attributable to the H2N2 pandemic starting in 1957, based on and expanding the hypothesis suggested by Palese and Wang.[5] The stalk-specific neutralising antibodies induced against H2 subtype viruses in 1957–68 might be more cross-reactive to the H5 subtype than those induced against the H1 subtype (the H1, H2, and H5 subtypes belong to group 1 haemagglutinins, but the H5 subtype is more similar to the H2 subtype than to the H1 subtype). This cross-reactivity could have rendered the population born before 1968 more resistant to the H5N1 subtype than are people born after 1968, who have only been exposed to seasonal H1N1 and H3N2 subtypes.

Because the H7 subtype belongs to group 2 haemagglutinins, most stalk-specific neutralising antibodies induced against the H2 subtype are unlikely to be cross-reactive to the H7 subtype. Therefore, the older group might have no more resistance against the H7 subtype than do the younger age group, resulting in the more typical age distribution of H7N9 subtype as an infectious disease. Although the H3 subtype belongs to the same group 2 haemagglutinin as H7, in view of the fact that the H3 subtypes have been circulating since 1968, it is difficult to know the effect of antibodies generated against the H3 subtype on resistance against the H7 subtype. We think our hypothesis is not mutually exclusive with that offered by Rimmelzwaan and colleagues.

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