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Missing information in animal surveillance of MERS-CoV

Chantal Reusken and colleagues have identified neutralising antibodies against Middle East respiratory syndrome coronavirus (MERS-CoV) in dromedary camels, suggesting the role of camels in harbouring the virus and infecting human beings. The study findings suggest that bats and camels jointly play an important part in the persistence and evolution of MERS-CoV, resulting in spillover to the human population. Theoretical epidemiologists refer to such combinations of animal hosts as the reservoir community.

To confirm that the two animal species constitute a reservoir community, two conditions should be objectively examined. First, the combination of reservoir hosts should permit persistence of the virus in natural settings (e.g., by frequently transmitting the virus to other hosts), which is the necessary condition. Second, in the absence of the reservoir community, transmission cannot be maintained (by definition), which is referred to as the sufficient condition. If other animal hosts can also maintain transmission, the reservoir community will have to include these hosts. In view of these conditions, although the identification of antibodies in camels is remarkable, an explicit assessment of the epidemiological role of camels has yet to be made to elucidate the mechanism of emergence in human beings.

How can a complete view of reservoir dynamics be achieved? The series of transmission in a population could be traced with serological techniques. Rather than doing a cross-sectional survey (to take a snapshot of prevalence), the identification of the reservoir host requires understanding of the incidence (i.e., rate of new infections) to measure transmissibility. Serial cross-sectional surveys or large-scale follow-up of cohorts (of susceptible camels, not of those already infected) would be required. Alternatively, implementation of a transmission experiment with uninfected camels could also be useful, because the transmissibility of infected camels can be objectively quantified. Even a simple one-to-one transmission experiment could inform about the presence of substantial transmissibility.

Of course, identification of the route of transmission from camels to human beings would also be of utmost importance, and could directly lead to prevention. In addition to such preventive effort, clarification of reservoir dynamics should be given a high priority, because identification of the major route of animal-to-human transmission, without an understanding of the overall picture of persistence and evolution in different hosts, is difficult.

We declare that we have no conflicts of interest.

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1 Reusken CBEM, Haagmans BL, Müller MA, et al. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study. Lancet Infect Dis 2013; 13: 859–66.
2 de Wit E, Munster VJ. MERS-CoV: the intermediate host identified? Lancet Infect Dis 2013; 13: 827–28.
3 Nishiura H, Hoje B, Klaassen M, Bauer S, Heesterbeek H. How to find natural reservoir hosts from endemic prevalence in a multi-host population: a case study of influenza in waterfowl. Epidemics 2009; 1: 118–28.
4 Funk S, Nishiura H, Heesterbeek H, Edmunds WJ, Checchi F. Identifying transmission cycles at the human-animal interface: the role of animal reservoirs in maintaining Gambian human african trypanosomiasis. PLoS Comput Biol 2013; 9: e1002855.
5 Nishiura H, Yen HL, Cowling BJ. Sample size considerations for one-to-one animal transmission studies of the influenza A viruses. PLoS One 2013; 8: e55358.

DPP4-directed therapeutic strategies for MERS-CoV

Christian Drosten and colleagues provided the first complete virological profile of a patient infected with Middle East respiratory syndrome coronavirus (MERS-CoV). Previous study findings have shown that dipeptidyl peptidase 4 (DPP4; also known as CD26) serves as the functional receptor for MERS-CoV. In view of the importance of DPP4 in regulating immune responses, inhibitors of DPP4 binding and activity could modulate the pathogenesis of viral infection and serve as potential therapeutics.

Targeting of the site between the binding domain on the virus surface and the receptor might provide pharmacological action to suppress MERS-CoV infection. Studies have provided new insights into DPP4 interaction with substrates and inhibitors, and numerous inhibitors with varying selectivity have been characterised in DPP4 binding and functional assays. Additionally, on the basis of our work on the use of DPP4 inhibitors as a treatment for autoimmune disease, DPP4 inhibition could suppress the damaging aspects of the body’s own antiviral immune response by modulating inflammation. Reversible inhibitors of DPP4 enzymatic activity suppress T-cell proliferation and production of proinflammatory cytokines as well as interleukin 10. As we have shown, DPP4 inhibitor-mediated suppression acts partly through the induction of transforming growth factor β1 (TGFβ1) production by effector T cells. Consistent with this mechanism, we noted a significant increase of TGFβ1 concentrations in tissue and plasma of mice treated with DPP4 inhibitors. TGFβ1 induction at the site of inflammation could be an additional therapeutic benefit of DPP4 inhibitor treatment.
because TGFβ1 is an essential regulator of immune responses in severe respiratory infections.\textsuperscript{3} Notably, Carlson and colleagues\textsuperscript{3} 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.

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1 Drosten C, Seilmaier M, Corman VM, et al. Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection. Lancet Infect Dis 2013; 13: 745–51.

2 Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013; 495: 251–54.

3 Reinhold D, Bank U, Tager M, et al. DP IV/CD26, APN/CD13 and related enzymes as regulators of T cell immunity: implications for experimental encephalomyelitis and multiple sclerosis. Front Biosci 2008; 13: 2356–63.

4 Mandiuta L, Tarrago T, Giralt E. Recent patents of dipeptidyl peptidase IV inhibitors. Expert Opin Ther Pat 2011; 21: 1693–741.

5 Carlson CM, Turpin GA, Mozer LA, et al. Transforming growth factor-beta activation by neuropeptides and role in highly pathogenic H5N1 influenza pathogenesis. PLoS Pathog 2010; 6: e1001236.

**Age and different influenza viruses**

We read with interest the Comment by Guus Rimmelzwaan and colleagues\textsuperscript{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.\textsuperscript{7}

Previously, Smallman-Raynor and Cliff\textsuperscript{2} 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\textsuperscript{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.\textsuperscript{5} The stank-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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1 Rimmelzwaan GF, Fouquier RA, Osterhaus AD. Age distribution of cases caused by different influenza viruses. Lancet Infect Dis 2013; 13: 646–47.

2 Laursen NS, Wilson IA. Broadly neutralizing antibodies against influenza viruses. Antiviral Res 2013; 98: 476–83.

3 Smallman-Raynor M, Cliff AD. Avian influenza A (H5N1) age distribution in humans. Emerg Infect Dis 2007; 13: S10–12.

4 Terajima M, Babon JA, Ennis FA. Epidemiology of the influenza A virus H5N1 subtype and memory of immunity to the H2N2 subtype. MBio 2012; 3: pii e00138-12.

5 Palese P, Wang TT. Why do influenza virus subtypes die out? A hypothesis. MBio 2011; 2: pii e00150-11.