New flu strains and old antibodies: How sinful is 'original antigenic sin'?

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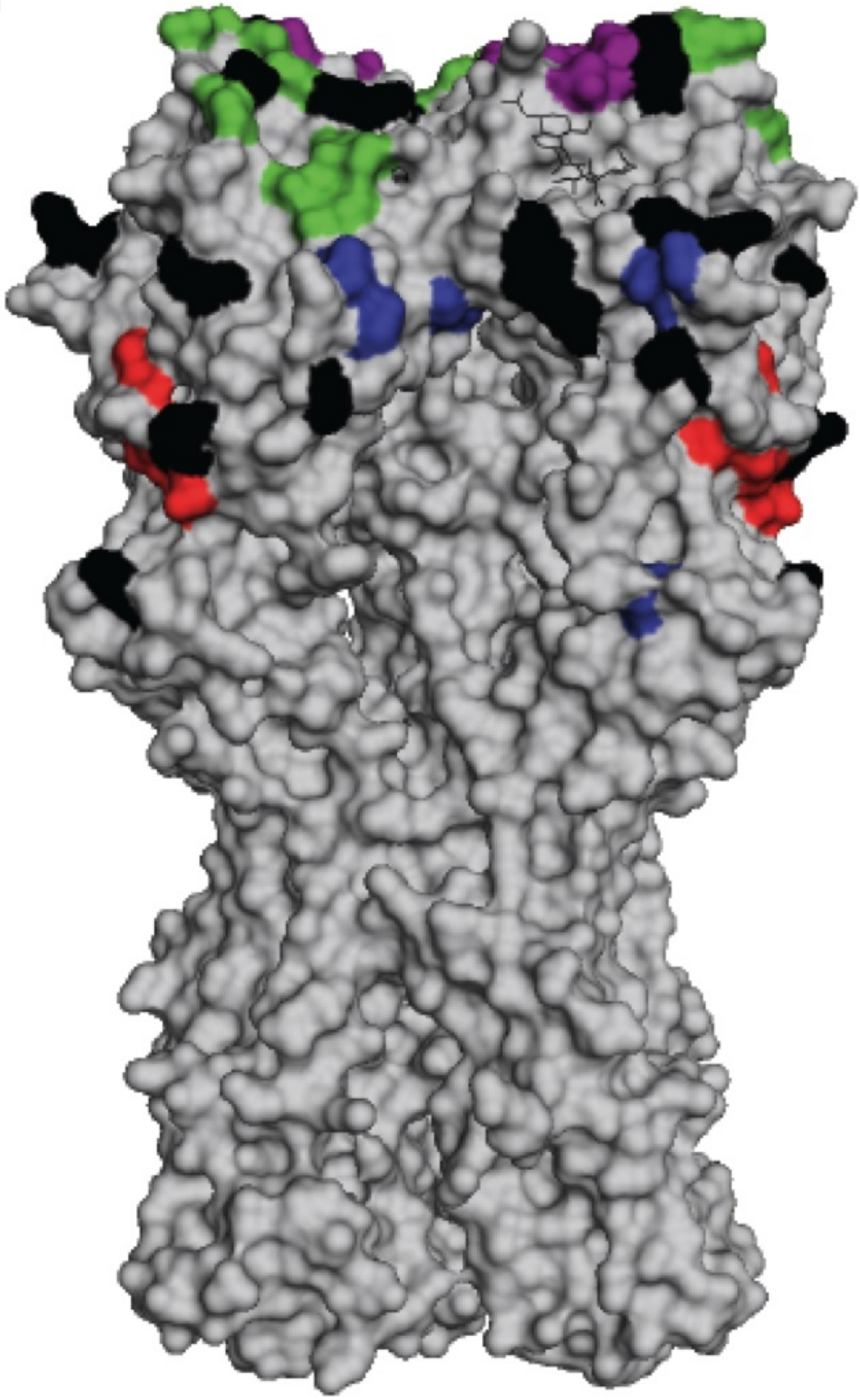

Structure of HA from H1N1 virus. The trimer of hemagglutinin (HA) of an H1N1 virus is shown (Protein database number 1RVX). Different antigenic sites are colored and differences between PR8 and S12a HA are shown in black. Credit: Susanne Linderman and Scott Hensley

Immune memory ensures a quick and specific response to previously encountered pathogens. However, for rapidly evolving pathogens like influenza virus, there is concern that recalled ('old') antibodies dominate and compromise the response against a changed ('new') infectious strain. A study in mice published on August 18th in *PLOS Pathogens* reports that while influenza exposure history does influence the antibody response to a circulating flu virus, this does not appear to compromise the defense against the new strain.

The concept of 'original antigenic sin' for influenza—which proposes that immune memory of previously encountered older flu strains weakens the response against threats from current strains—has been around since the 1960s. The idea is that, because some parts of a current flu virus are familiar to the immune system, antibodies specific to older flu strains are 'recalled' and produced at the expense of the creation of new antibodies specific to the current strain, and that these 'original antigenic sin' antibodies are detrimental to the host since they react poorly with the current strain against which defense is needed.

To study 'original antigenic sin' antibodies, Scott Hensley and Susanne Linderman, from the Wistar Institute and the University of Pennsylvania in Philadelphia, USA, dissected antibody responses in mice that were sequentially exposed to different influenza strains. Most antibodies against influenza viruses recognize one of two highly variable proteins

on the virus surface. The researchers focused their analysis on the antibody repertoire against one of them, hemagglutinin, or HA.

The researchers infected mice sequentially with two different flu strains called PR8 and S12a. The HA proteins of the two strains differ by 13 mutations, and most antibodies generated against one HA protein do not recognize the other. The researchers vaccinated mice with PR8 followed four weeks later either by a repeat vaccination with PR8 or with a vaccination with the antigenically distinct S12a virus.

As expected, PR8-reactive antibodies were strengthened (or boosted) upon re-exposure with PR8. Although S12a is much different compared to PR8, this virus was also able to boost PR8-reactive antibodies in animals previously exposed to PR8. The researchers created cell lines from individual antibody-producing B cells from mice exposed sequentially to PR8 and S12a. When they analyzed the monoclonal antibodies produced by these cell lines, the researchers found that approximately half of the antibodies from mice sequentially exposed to PR8 and S12a had an 'original antigenic sin' phenotype—they bound with high affinity only to PR8 but not to S12a. The other half were either cross-reactive with strong binding to both PR8 and S12a, or bound exclusively to S12a.

Antibodies with an 'original antigenic sin' phenotype are thought to be detrimental to the host. To address this, the researchers passively transferred antibodies to mice without prior exposure to any influenza strain and subsequently challenged them with either PR8 or S12a. They found that, as expected, PR8-specific antibodies protect against PR8 virus, and cross-reactive antibodies protect against both PR8 and S12a. But, in addition, PR8-specific antibodies with very weak binding to S12a nonetheless protected against S12a challenge, and did so as effectively as S12a-specific antibodies elicited in a previously naïve host.

Acknowledging that most humans have been exposed to multiple different influenza strains (not just two viral strains), and that age might also play a role in humans, the researchers conclude that their data nonetheless "indicate that Abs elicited by sequential exposures can be highly effective at protecting against the virus that recalls them, even though they often bind with a much higher affinity to the first viral strain that the host encountered". Rather than being a problem, they propose that "[antibodies] classically associated with original antigenic sin might play an important role in protecting the host against secondary encounters with antigenically drifted viral strains".

More information: Linderman SL, Hensley SE (2016) Antibodies with 'Original Antigenic Sin' Properties Are Valuable Components of Secondary Immune Responses to Influenza Viruses. *PLoS Pathog* 12(8): e1005806. DOI: 10.1371/journal.ppat.1005806