Permissive Secondary Mutations Enable the Evolution of Influenza Oseltamivir Resistance
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Improve Evolutionary Forecasting by Examining Both Sides of the Coin

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Predicting the evolution of oseltamivir resistance in influenza virus strains by mining the neuraminidase genes for permissive mutations is groundbreaking and exciting ("Permissive secondary mutations enable the evolution of influenza oseltamivir resistance," J. D. Bloom *et al*., Reports, 4 June 2010, p. 1272). Unfortunately, the contribution of the influenza hemagglutinin to the sequence and functional diversity of the neuraminidase was completely overlooked.

"Fitness" was equated with in vitro replication in this study; however, the concept of "evolutionary fitness" as determined by functional balance between attachment and detachment (*1*) would have been a measurement much better suited to the title and theme of this work. A decrease in neuraminidase functionality can be compensated for in terms of evolutionary fitness by proportional changes in the hemagglutinin such that the two functions remain in a balanced state. This has been observed both in vitro (*2*, *3*) and in vivo (*4*) with influenza viruses. It should therefore be plausible that mining the hemagglutinin protein sequence for permissive mutations in oseltamivir-resistant strains possessing the H274Y genotype may provide the answer to the looming question of how these resistant yet apparently unfit variants emerged.

The possibilities raised by E. C. Holmes (*5*) for identifying influenza lineages at high risk for antigenic shift, becoming neuraminidase inhibitor resistant, or developing the ability to infect new species are exciting and potentially very powerful. In the case of oseltamivir resistance, however, an evolutionary driver far more constant than oseltamivir itself was not regarded. To feel confident in the vigor of any predictions that are made, we must consider every driver and passenger contributing to the evolutionary process.

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Response to M. May and D. R. Brown's E-Letter

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M. May and D. R. Brown suggest that mutations to hemagglutinin (HA) could play a role in the evolution of influenza oseltamivir resistance by reducing receptor affinity to balance reduced neuraminidase (NA) activity. We agree with the plausibility of their suggestion. We wrote in our Report that the evolutionary spread of NA mutations "could be the result of...tuning of the NA/HA balance" ("Permissive secondary mutations enable the evolution of influenza oseltamivir resistance," J. D. Bloom *et al.*, 4 June 2010, p. 1272). However, experimentally we found that in human seasonal H1N1 influenza, the H274Y oseltamivir-resistance mutation was preceded by permissive secondary mutations that countered the deleterious effect of H274Y on total surface-expressed NA activity. Therefore, resistance in this strain did not lower NA activity relative to earlier variants lacking both the permissive and resistance mutations.

It remains possible that HA mutations played some role. For example, it has been noted that many seasonal H1N1 variants with H274Y also contain the A193T HA mutation (*1, 2*). This could be evolutionary coincidence or a signature of genetic hitchhiking, but it has also been conjectured that these two mutations promote better NA/HA balance. However, we are unaware of any published experimental evidence on this point.

We also acknowledge that the future spread of resistance to neuraminidase-inhibitors might be enabled by other mechanisms, including reduced HA receptor-affinity. As May and Brown note, reduced HA affinity can rescue the in vitro and in vivo growth of resistant viruses.

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However, at least so far, these resistant viruses with reduced HA affinity have not spread widely in the human population.
An unavoidable peril of experimentally studying natural evolutionary processes is that it is impossible to be certain that all relevant factors have been considered. We believe that our work made a substantial contribution by demonstrating that oseltamivir resistance in seasonal H1N1 was preceded by secondary mutations that rescued both total surface-expressed NA activity and in vitro viral fitness. We did not intend to imply that the story is necessarily complete, and concur that there is ample room for further experimental work on this topic.

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