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The mechanistic basis of hemoglobin adaptation in the high-flying barheaded goose: insights from ancestral protein resurrection

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Abstract:

The bar-headed goose (‘BHG’, Anser indicus) is renowned for its trans-Himalayan migratory flights, and the elevated hemoglobin (Hb)-O2 affinity of this species is thought

to make a key contribution to its capacity for powered flight at elevations of ~9000 m. Here we revisit the molecular basis of this text-book example of biochemical adaptation. Previous hypotheses about the molecular basis of the evolved increase in Hb-O2 affinity were tested by engineering BHGspecific mutations into recombinant human Hb. This approach can provide important insights, but one problem with such ‘horizontal’ comparisons – swapping residues between proteins of contemporary species – is that the focal mutations are introduced into a sequence context that may not be evolutionarily relevant. If mutations have context-dependent effects, then introducing BHG-specific substitutions into human Hb may not recapitulate the functional effects of causative mutations on the genetic background in which they actually occurred during evolution (i.e., in the BHG ancestor). An alternative ‘vertical’ approach is to reconstruct and resurrect ancestral proteins to test the effects of historical mutations on the genetic background in which they actually occurred. We used this approach to measure the independent and joint effects of amino acid substitutions that occurred in the reconstructed BHG ancestor. Measuring the additive and nonadditive effects of these substitutions enabled us to address several important evolutionary questions about molecular adaptation: (1) Do each of the substitutions contribute to the increased Hb-O2 affinity? If so, what are their relative effects? (2) Does the sequential order in which they occur make a difference? In other words, do the functional effects of mutations depend on which other substitutions have already occurred?