Simultaneous Viral Exposure and Protection from Neanderthal Introgression

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In this issue, Enard and Petrov present intriguing results on the possibility of genetic traces left behind in our genomes from adaptation to past viral epidemics that may have been initiated by interaction with Neanderthal archaic hominins. The work highlights how powerful infectious agents can act as a selective force to shape our genetic makeup.

Less than 10 years ago, a study provided the first genomic evidence that Neanderthals interbred with modern humans outside of Africa (Green et al., 2010). From the fossil record, we knew of the geographical and temporal colocalization of the two groups, but the discovery of Neanderthal DNA from fossils and the subsequent generation of their reference genomes allowed the comparison of archaic and modern human genomes necessary to identify surviving remnants of Neanderthal DNA in modern humans today (Prüfer et al., 2014). Surprisingly, sequencing DNA from fossils also revealed the existence of other previously unknown hominins, the Denisovans (Meyer et al., 2012), and recently an offspring of a Neanderthal and a Denisovan (Slon et al., 2018). While the amount of archaic admixture in present-day humans is small (1%–5%; Prüfer et al., 2014), many loci exhibit strong signatures of adaptive introgression (archaic sequences at high frequency), suggesting that archaic DNA facilitated adaptations to various selective pressures, including infectious diseases, climate, sun exposure, altitude, and diet (Racimo et al., 2015, 2017).

In this issue of *Cell*, Enard and Petrov (2018) hypothesize that archaic hominins, as well as exchanging DNA with a recipient *Homo sapiens* population tens of thousands of years ago, may have concomitantly introduced viral infections into the recipient population (and vice versa). Under the assumption that the archaic hominins were already genetically predisposed to be resistant to the viral pathogens they carried, a unique situation occurred in that both the selective pressure (the virus) and the genetic material (the hominin variants) that facilitates adaptation to that selective pressure were introduced simultaneously into the recipient population (Figure 1). The genetic signature resulting from such an effect is characterized by the presence of a long initial block of archaic sequence that, although degraded by recombination over time in individual sequences, is still in sufficiently high frequency in the modern human population due to positive selection to be reconstructed from current DNA sequences.

To test their hypothesis that adaptation occurred in response to a viral selection pressure in this scenario, they draw on prior work (Enard et al., 2016) cataloging and curating viral interacting proteins (VIPs) in the human genome, and they hypothesize that if these proteins are under positive selection immediately after introgression, they should be enriched within archaic introgressed segments (ISs). Their previous work suggested that 30% of all human protein adaptation was due to viral interactions, supporting the hypothesis that genetic changes after archaic admixture may also in part be driven by viral infection. Determining statistical enrichment of VIPs in ISs is complicated, however, because VIPs are generally subject to purifying selection (mutations in them tend to be rare, as they are in the process of being eliminated from the population), and so are IS regions. In addition, there are a number of other co-varying genomic features and processes between VIPs and ISs that could give a false signal of adaptive introgression, including heterosis. Therefore, the authors lay out a methodology to carefully adjust for these covariates when comparing VIP to non-VIP proteins and subsequently determining enrichment in ISs. With this analysis, they convincingly highlight the dominant force played by viral infection, particularly from RNA viruses, in driving a considerable proportion of the observed adaptation that can be traced to Neanderthal introgression into modern humans in Europe. They are able to identify particular RNA viruses in the same family as influenza and HIV that are enriched for interacting human proteins and associated long archaic ISs. While that cannot realistically identify a particular epidemic or outbreak, given the uncertainty in estimation of the timing of archaic admixture and selection, the study convincingly highlights the complexity of population interactions and the substantial genetic impact that past human admixture has had during our evolution.

Their methodology is general enough that, as a follow-on work, it could readily be applied to Denisovan segments, which are even more commonly seen than Neanderthal segments in some populations, particularly Melanasians, and where a comparative analysis could be performed to look for archaic population-specific viral exposure.

While in this particular instance, it is not possible to pinpoint a specific epidemic, now that studies of ancient DNA and temporal DNA sampling of modern humans are becoming more commonplace, their

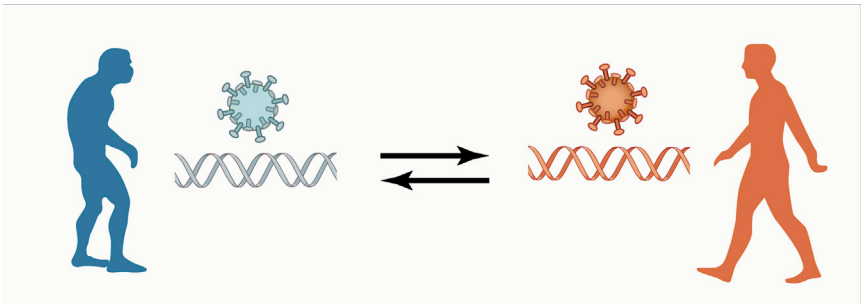

Figure 1. Host DNA and Viral Pathogen Exchange
Archaic and anatomically modern humans carry distinct DNA and infectious organisms, and they are already genetically adapted to the pathogens in their local environment. With introgression, both viruses and host DNA are exchanged.

proposed methodology has significant potential to identify past epidemics in human history based on the dynamics of host VIP adaptation. Furthermore, while most studies of ancient pathogens focus on relatively more stable DNA viruses (Andam et al., 2016), applying their approach may reveal insights on rapidly evolving pathogens, like HIV and influenza. Obtaining insights into ancient outbreaks and epidemics is important in light of strong genetic evidence suggesting that pathogens have been a major driver of human evolution.

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Aster: A New Star in Cholesterol Trafficking

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Life evolved in an aqueous environment, necessitating the evolution of carrier proteins to shuttle lipophilic molecules within and between cells. Sandhu et. al. (2018) report the discovery of a long-sought-after cholesterol carrier protein, named Aster, which transports cholesterol from the plasma membrane to the endoplasmic reticulum.

Lipid membranes are essential for cellular life as we know it, enabling the subdivision of the cellular space into membrane-encapsulated organelles with specialized functions. This innovation of nature, however, presents significant challenges. Transport of lipophilic molecules between membrane compartments must overcome the intervening aqueous environment, requiring specialized carrier proteins. One of the most important transported molecules is cholesterol, a key structural component of lipid membranes and also the precursor for steroid hormones and bile acids in steroidogenic organs and liver, respectively (Ikonen, 2008). Uptake of cholesterol in these tissues occurs primarily from high- and low-density