HOW MIGHT UNDERSTANDING OF THE CO-EVOLUTION OF HLA AND VIRUSES INFORM CONTEMPORARY CLINICAL ISSUES

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Class I MHC molecules are under diversifying selection but share the preference for binding to conserved areas of human proteins, and most target human viruses with similar efficiency. However flaviviruses, such as Hepatitis C, are unusual in that non-conserved areas may be preferentially targeted. MHC binding can therefore be considered as 'nature's estimator of sequence conservation/functionality' and this acts a fundamental force shaping the adaptation of pathogens and different viruses have taken different strategies to escape these selective pressures.

Some individuals exposed to Hepatitis C clear the virus during acute infection while others become chronically infected and there is also intra-patent variability in the response to therapy. This is likely to be determined by both variability in host alleles and the degree to which the infecting virus has adapted to those responses. However, to predict likely clinical outcomes it is also essential to first understand which responses are effective and constraining the virus from those host responses which are being elicited by the virus and are non-effective or even harmful to the host.

The failure of the STEP trial of the Merck developed Ad5-based HIV vaccine, which demonstrated that HIV acquisition was unexpectedly enhanced in vaccinated individuals despite evidence of good immunogenicity has created new challenges in HIV vaccine research. We have found evidence of characteristic HLA allele-specific adaptations that induce T cell responses that are not just ineffective or neutral but actively enhancing to viral infection and harmful to immune control. These responses may appear strong by standard measures but they represent the consequence rather than the cause of adaptation and as such, serve the interests of the virus rather than the host. These findings support the concept that the more generally 'immunogenic' a vaccine is to this highly adaptable pathogen, the greater harm the vaccine may do unless the enhancing viral elements are pre-emptively identified and excluded from the immunogen.