Source of immune polymorphism - from population dynamics to data-driven models

Yoram Louzoun

Bar-Ilan University

The Major Histocompatibility Complex (MHC) is a central component of the vertebrate immune system and hence evolves in the regime of a host-pathogen evolutionary race. The MHC is associated with quantitative traits which directly affect fitness and are subject to selection pressure.

The evolution of haplotypes at the MHC human leukocyte antigen (HLA) locus is generally thought to be governed by selection for increased diversity that is manifested in over-dominance and/or negative frequency-dependent selection (FDS). We here show that a model combining purifying selection on haplotypes and balancing selection on alleles is most consistent with the data.

We then compare the predictions of several population dynamics models of haplotype frequency evolution to the distributions derived from 6.59 million donor HLA typings from the National Marrow Donor Program registry. We show that models that combine a multiplicative fitness function, positive FDS, extremely high mutation and recombination rates, and exponential fitness decay over time, but not overdominance, produce the best fit to the data. In contrast, population sub-structure does not explain the observed haplotype frequencies.

To study the specific elements that can explain this selection, we follow the locations on the sequence that can predict the fitness, using a combination of phylogenetics and population dynamics model. These results present a data-oriented comprehensive view of the population dynamics of the MHC locus.

Joint work with: Alexander E. Lobkovsky[1], Lee Levi[2], Yuri I. Wolf[1], Martin Maiers[3], Loren Gragert[3,4], Idan Alter[2], Eugene V. Koonin[1].

[1] National Center for Biotechnology Information, National Library of Medicine. National Institute of Health, Bethesda, MD.

[2] Department of Mathematics, Bar-Ilan University.

[3] National Marrow Donor Program, Minneapolis, MN.

[4] Tulane University School of Medicine, New Orleans, LA.