

Gene conversion and diversification of antigen repertoires

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Parasites that cause chronic infections in vertebrates use a variety of strategies to evade the adaptive immune responses mounted by their hosts. One strategy, called antigenic variation, relies on the parasite surface being coated by one or a small number of proteins, which change over the course of the infection. Typically, these surface proteins are encoded by multiple genes belonging to a gene family (the antigen repertoire), only one of which is expressed at a time by each parasite and only a few of which are expressed at a time in the entire parasite population infecting a host. Although host immune responses will eventually develop against these antigen types, the infection can persist if small numbers of parasites randomly change to new antigen types. Examples of parasites that rely on antigenic variation include the bacterium *Borrelia burgdorferi*, which causes lyme disease, and the protozoan *Trypanosoma brucei*, which causes African sleeping sickness.

Comparisons of antigen repertoires from different strains of the same parasite suggests that antigen genes evolve exceptionally rapidly. There are a variety of reasons why this might be so. For example, it could be the case that mutation rates are exceptionally high in antigen genes, perhaps because they are often located in chromosome subtelomeres. Another possibility is that diversification is favored by natural selection to facilitate superinfection, i.e., parasites will be able to transmit to a previously or currently infected host only if they express antigen types that have not already been expressed in that host.

The aim of this project will be to explore a third possibility, namely, that rapid diversification is an indirect consequence of gene conversion within antigen repertoires. Gene conversion occurs when one stretch of DNA sequence is copied onto another, creating two copies of the template sequence. Gene conversion plays an important role in the evolution of some gene families and is also a key part of the system regulating the expression of some antigen genes. We might expect gene conversion to accelerate the rate of evolution of antigen repertoires for the following reason. For antigenic variation to work, the antigen repertoire must contain genes that code for distinct antigen types. If a parasite expresses an antigen type that has already been expressed in that infection, then it will be killed by existing antibody responses. However, gene conversion will erode diversity within an antigen repertoire whenever one antigen gene is copied onto a gene coding for a distinct antigen type. In general, such duplications will be harmful to the parasite, but because selection is delayed until the duplicated copy is expressed, antigen repertoires can accumulate sets of similar or identical genes. Should this occur, there will be selection for diversification of the members of these subfamilies, resulting in an increase in the overall rate of evolution of the repertoire.

The goal of this project will be to use simulations and, if possible, mathematical analysis to quantify the effect of gene conversion on antigen repertoire diversification. This project would suit someone keenly interested in evolutionary biology who either knows or is willing to learn to program in C/C++ or some comparable language.

References:

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antigenic variation. *Trends in Parasitology* 23: 408-413.

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