A NOTE ON THE POSSIBLE EFFECT OF VIRAL MIMICRY ON THE FREQUENCY-DEPENDENT SELECTION OF MAJOR HISTOCOMPATIBILITY COMPLEX ALLELES

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ABSTRACT. It is argued that viral expression of its host's Major Histocompatibility Complex molecules hinders transmission to new hosts with different MHC molecules. This leads to an advantage of MHC "rarity" and thereby to frequency-dependent selection of MHC coding genes.

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INTRODUCTION

One of the most striking features of the Major Histocompatibility Complex (MHC) System[1], a part of the immune system that plays a role in the recognition of antigens, is its polymorphism. Approximately one hundred different alleles for the class I MHC A, B and C loci together are known. Similar polymorphisms exist for type II and type III MHC sub-systems. This polymorphism is remarkable because MHC alleles determine the type of (human) immune response to infectious pathogens and the occurrence of many autoimmune disorders, and can therefore *a priori* be expected to cause heterogeneity in life expectancy and thus in fitness. It is well known that alleles which cause inferior fitness in both homozygotes and heterozygotes, will become extinct rapidly[2], and only a rapid mutation rate can maintain a significant Hardy-Weinberg equilibrium[3]. Thus one would expect selection pressure to eliminate much of the MHC polymorphism very rapidly.

STABILIZATION OF GENE RATIOS

In the absence of equal fitness two different mechanisms may stabilize gene ratios.

1. **Overdominance**, superior fitness of heterozygous individuals compared with homozygous ones. This mechanisms maintains the sickle cell gene in populations exposed to *Plasmodium falciparum* infections. Although homozygous sicklers have a high mortality rate of this hereditary disease, heterozygous individuals are partially protected against the consequences of malaria. As MHC

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heterozygous individuals are able to present a wider range of antigens to the immune system than homozygous individuals, it is likely that overdominance is one of the mechanisms which maintains the MHC polymorphism.

2. **Frequency-dependent selection**, an advantage of rarity. A fitness advantage of a rare gene over a more common one can arise in the context of the co-evolution of a predator (or parasite) and a prey (or host). It is an advantage (and thus selection pressure) for predators to be able to catch the more common types of prey. Similarly, there is selection pressure on prey animals to develop skills in avoiding capture by common types of predator. Thus individuals (either predator or prey) with uncommon "behaviour" have an advantage over individuals with more common types of behaviour. The same applies to pathogens. The survival of pathogens depends on their ability to evade, at least until transmission to other hosts have taken place, elimination by the immune system of a sizable proportion of their hosts. Thus having an "uncommon" immune system may facilitate elimination of pathogens which have become successful in evading elimination by individuals with common immune systems, i.e. common MHC molecules. It is possible that this mechanism of adaptation of pathogens to hosts plays a role in stabilizing the polymorphism of the MHC system.

Empirical evidence of an advantage of rarity has recently been found in a cohort of female prostitutes from Nairobi, Kenya, who are heavily exposed to Human Immunodeficiency Virus type I (HIV-1)[4]. Among women who entered the cohort those with rare MHC class I molecules were much less likely to be HIV-1 seropositive than women with more common class I molecules. Also, during follow up of this cohort, initially HIV-1 seronegative prostitutes with rare MHC class I type molecules were much less likely to seroconvert than those with more common types. Prostitutes with "rare" class I MHC molecules (defined as the lowest 25 percentiles of a rarity score which measures the expected number of class I molecules an individual shares with a randomly chosen individual from the population) had a 3 fold reduction in HIV-1 incidence compared to those with more common MHC types. The same phenomenon was later observed in initially HIV-1 seronegative men followed-up after treatment for genital ulcers[5].

SIMILARITY DEPENDENT DISEASE TRANSMISSION

Although it is possible that the above noted mechanism of co-evolution of pathogen and host explains this observation, this is not likely, as HIV-1 appears to be a relatively new virus and has had little time to become adapted to "common" hosts. As an alternative explanation of this phenomenon we believe that some host specific adaptation of the virus occurs. More specifically we refer to the recent discovery that certain enveloped viruses can express host MHC molecules when budding from the membrane of the infected cell[6]. This expression of host MHC molecules may be a form of mimicry to evade recognition by the immune system of the host. However, this chameleon type of behaviour, which is an adaptation of the virus to an *individual* host, may also have disadvantages for the virus as those camouflage MHC molecules may

well provide a barrier against transmission of free virus to a new host, provided such a new host recognizes those molecules as non-self. The same, of course, applies to cell-bound transmission of viruses in which the intracellular virus is transmitted through host cells, and infection with the virus takes place when it buds from the invading cells before they have been recognized and eliminated by the immune system of the new host; a process whose efficiency is likely to be determined by how different the MHC molecules of the invading cells are from those of its new host. As almost all cells express MHC molecules, possession of uncommon MHC molecules should thus confer protection against viral infections.

It is difficult to assess the extent to which this mechanism plays a role in stabilizing MHC gene frequencies. It is not yet known which viruses are able to perform this "trick" of MHC mimicry. Neither is it known what role such viruses have played in morbidity and mortality in the past. The finding that MHC "rarity" protects against HIV-1 infection suggests that this mechanisms will play a role in the HIV-1 pandemic. Thus one may expect HIV-1 to influence MHC gene ratios, even without heterogeneity in the ability of different MHC alleles to mount an effective immune response against this virus.

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