Diseases and sex: The cocktail maintaining immune gene variation

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Sticklebacks show the same polymorphism of immune genes as humans and thus make excellent research models. Credit: Milinski/MPI for Evolutionary Biology

The great variation of a specific form of immune genes makes organ transplants so complicated. On the other hand, we need such a great variability in order to resist infectious diseases. This is why it also plays a major role in the selection of sexual partners. Up until now, the mechanisms for maintaining this standing genetic variation have remained an evolutionary puzzle. In a study of sticklebacks, researchers from the Max Planck Institute for Evolutionary Biology in Plön, together with colleagues from the Helmholtz Center for Marine Research in Kiel, have now shown that reoccurring infectious diseases determine which individuals produce a particularly large number of offspring in a population, and which immune genes increase in frequency in the next host generation. Infections are thus the drivers for this variability.

We have all read and heard of successful organ transplants. Despite the technical improvement, this clinical achievement is rendered extra complicated by the difficulty in finding a fitting donor to a receiver. This is because the genes at the root of the immune system (called HLA [Human Leucocyte Antigens] in human) are extremely diverse within the population but must not differ between the donor and the receiver for successful transplant. If the HLA differs, the HLA molecules will recognize the new organ as non-self, triggering an immune response against the implanted liver or heart for instance. With more than 1000 HLA immune gene versions (called "alleles") present in the human population any two individuals are likely to differ and thus to be incompatible.

Interestingly, what is a problem for transplanting a liver is an advantage when humans choose their mating partners. As human, we prefer, by smell, those who offer the best complement to our own set of HLA-alleles. This is because we have evolved behaviours to provide our children with the best set of genes to resist infectious diseases. In order to be able to choose the best fitting partner, it is good that there are many possible partners with different mixtures of HLA alleles "on the market". This high variability in individuals' HLA alleles, called polymorphism, is exceptional. In all other genes any two individuals are extremely similar. Which forces maintain this polymorphism that is so badly needed for providing our offspring with optimal mixes of immunogenes but renders transplant so complicated still remains a mystery.

Nicely for scientists, the HLA polymorphism is very similar in other vertebrates where it is called MHC (Major Histocompatibility Complex) polymorphism, including the three-spined stickleback - a small fish found in all lakes and rivers in the northern hemisphere. As is true for the HLA, the primary function of MHC genes is to fight against diseases. It has been suggested that MHC polymorphism is maintained in

natural populations by diseases changing from one generation to the next and thus those individuals that happen to have the resistance MHC allele are healthy and thus have more offspring carrying that beneficial allele. To test this idea, scientists from the Max Planck Institute for Evolutionary Biology in Ploen and the Helmholtz Center for Marine Research in Kiel (both in Germany) set up genetically identical experimental populations of three-spined sticklebacks in huge outside mesocosms where each population was exposed to one of two parasite diseases. The fish were allowed to display natural breeding behaviours and females could choose the best partners for reproduction. It is interesting to know that male three-spined stickleback display an intense red coloration on their throat during the mating season- a sign of their health. Changes in MHC allele frequencies were tracked between two generations. Supporting their hypothesis, the scientists found that only those MHC alleles providing resistance to the respective specific parasite disease, that the parental generation had been exposed to, increased in frequency in the next host offspring generation.

The conclusions, exposed in a new article published in Nature Communications this week, are that MHC variation is needed to resist diseases and that the currently adaptive MHC allele spreads in the population so that the next generation is better equipped against this disease – until another disease shows up and other individuals with another MHC allele are healthy and produce more offspring. Now this new adaptive MHC allele will spread. In this way the enormous MHC polymorphism is maintained causing continuous problems with transplantation, but also helping us to produce stronger children every generation.

More information: Eizaguirre C., Lenz T. L., Kalbe M., & Milinski M. Rapid and adaptive evolution of MHC genes under parasite selection in experimental vertebrate populations. *Nature Communications*. DOI: 10.1038/ncomms1632