Abstract for the general public

Complexity of the vertebrate immune system was formed by millions of years of evolution. Pressure of pathogens have been the main force shaping this system, but neither its structure nor function can be fully understood without the consideration of the evolutionary trade-offs constraining its development. Perhaps the most noticeable example, reflecting both of those aspects, is the major histocompatibility complex (MHC). MHC is a key for a differentiation of healthy molecules of 'self', from possibly harmful and dangerous 'non-self' or 'altered-self' that foreshadow an infection or a cancerous transformation. MHC specifically binds fragments of proteins (antigens), and presents them to T cells. When a T cells recognizes a foreign particle, using T-cell receptors (TCRs), it initiates adaptive immune response: against a virus or bacteria, but also against transplanted organs, as they are also recognized as 'non-self'. Rejection of a graft is related to an incompatibility of MHC between the donor and the recipient (hence the name: histocompatibility complex). It is so difficult to find a suitable donor, because the MHC is extremely polymorphic, that means, there are numerous variants of those molecules in populations; thousands of them have been described for humans. Of course, the remarkable variability of the MHC was not meant to make life of transplantologist difficult – it is a result of an evolutionary arms race between hosts and pathogens. New MHC variants appear, to bind antigens of quickly changing pathogens. Pathogens, in turn, modify their molecules, to avoid recognition by the immune system of the hosts. It would seem that a high within-individual MHC diversity (which could be achieved by gene duplication and diversification) should be beneficial for the host, so that it could recognize all possible pathogens. Yet, individuals usually possess just a few, functional loci, that can accommodate a tiny fraction of the diversity present at the population level. A *TCR depletion hypothesis* tried to explain this surprising observation, by pointing to an evolutionary trade-off between an increased potential for pathogen recognition and mechanisms preventing autoimmune diseases. During maturation, T cells go through a process of negative selection, that removes cells strongly recognizing self-antigens bound to MHC. The more MHC variants one have, the more antigens (both self and non-self) it can present, and theoretically – the more T cells will turn out to be self-reactive, and would have to be deleted. This hypothetical explanation was first proposed over 30 years ago, but only recently a direct test of the predictions of this hypothesis became feasible. With development of new sequencing techniques, it was possible to check whether individuals that had more MHC variants, indeed had smaller TCR repertoire sizes. Results of this test partially supported the *TCR depletion hypothesis*, but they also highlighted important gaps in our understanding of these processes. Specifically, they showed a disparity between two MHC classes: MHC class I, that presents intracellular pathogens (e.g. viruses), and MHC class II, that present extracellular pathogens (e.g., most of bacteria, fungi, parasitic warms). More variants of MHC class I, but not of class II, correlated with the smallest repertoire size – however, we still do not know why.

In this project, I want to better understand what causes the observed differences. I will check how TCR repertoires differ between subpopulations of T cells interacting with particular MHC classes; how individual MHC diversity affects the size of these populations; whether high numbers of MHC class II variants, despite a lack of influence on the TCR repertoire size, invoke other changes in the T cell functional subpopulations (e.g., expansion of regulatory subsets); and how all those aspects are affected by sex. In my research, I will use a species characterized by a high, between-individual variation in the number of MHC genes: the bank vole (*Myodes glareolus*). I will create specific molecular reagents for this species and employ advanced, high-throughput sequencing techniques. Result of my project will be crucial for an assessment of the generality of the TCR depletion hypothesis. Also, deepened knowledge of the evolutionary limitations imposed on the MHC gene numbers will result in a better understanding of dependencies and interactions among specific components of the immune system.