Current projects (last update 01.10.2016)

Molecular signature of non-permissive T cell alloreactivity to HLA-DPB1 in hematopoietic stem cell transplantation

Human leukocyte antigen (HLA)-DPB1 mismatches are frequent in unrelated hematopoietic stem cell transplantation (HSCT). HLA-DPB1 is known to play an important role in both graft-versus-leukemia and graft-versus-host effects. Previous research from our group has shown that HLA-DPB1 alleles can be classified into at least 3 T cell epitope (TCE) groups according to the median impact of individual amino acid polymorphism on T cell alloreactivity. The TCE model provides a unique system to study T cell alloreactivity since it allows for the investigation of "permissive" (i.e. moderate and clinically well tolerated) alloresponses to HLA-DPB1 alloantigens from self TCE groups, compared to "non-permissive" (i.e. strong and clinically less well tolerated) responses to HLA-DPB1 alloantigens from non-self TCE groups. The underlying hypothesis is that subjects are tolerant to self TCE but not to non-self TCE. In order to test this hypothesis, we are currently studying the role of (1) differences in the diversity of T cell receptor repertoires responding to permissive vs non-permissive mismatches at the protein and molecular level in HLA-DP allospecific T cell populations, (2) the relative origin of the T cells responding to these mismatches in terms of naïve and memory compartments, and (3) the differences in peptide repertoires presented by HLA-DPB1 molecules from different TCE groups as well as the effect of HLA-DM on the editing of these peptide repertoires. We draw on cellular models of alloreactivity and molecular techniques including next-generation TCR sequencing in order to achieve these goals. With these efforts we aim at dissecting the molecular and cellular signature of non-permissive HLA-DPB1 mismatches. This will not only be of clinical relevance for new cell therapy approaches for the treatment of blood cancers, but will shed new light onto the determinants of T cell alloreactivity to HLA molecules in general, which are currently poorly understood yet of critical relevance in different areas including transplantation and cancer immunotherapy.

HLA population genetics

HLA frequencies show widespread variation across human populations. Demographic factors as well as selection are thought to have shaped HLA variation across continents. HLA population genetic data is of interest not only for anthropological reasons, but also for its relevance in medical field such as transplantation and genetic epidemiology. In order to further characterize this variation, a worldwide comparison of HLA class I and class II diversity is being carried out. We draw data from online databases (e.g. allelefrequencies.net) and scientific papers to put together a large database of HLA allele frequencies from populations from all over the world. These data are being analysed using multidimensional scaling and clustering techniques using first field HLA-A, HLA-B and HLA-DRB1 frequency data. Our database currently includes 63 allele group data for 186 non-recently admixed populations and 30 recently admixed populations (mainly from the Americas) adding up to more than one million chromosomes. Our analyses show strong effect of geography on the distribution of HLA allele groups in non-admixed populations, and complex patterns of admixture in populations from the Americas. In addition, HLA data from populations in Central America is also being analysed in order to study their genetic diversity and admixture patterns.