The autoimmunome: Similarities and differences among genetic susceptibility to common immune-related diseases

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Autoimmune disorders arise when physiological tolerance to “self” antigens is lost. Although several mechanisms may be involved in this pathogenic process, dysregulation of T-cell and B-cell activation and of pathways leading to inflammation are logical candidates. Susceptibility to autoimmune diseases has been associated with multiple factors including genetics, epigenetics, and the environment. While the modest concordance rate in monozygotic twins suggests that environmental factors are major players in most autoimmune diseases, increased heritability within families and the decrease in risk with the degree of relatedness all argue in favor of genetic factors. With the advent of high-throughput genomics, massive amounts of genetic data are being produced and reported on a monthly basis. Although considerable insight has been gained from each of these individual studies, a detailed comparative analysis will likely identify both unique and common pathways operating in autoimmunity.

More than 40 genome-wide association studies (GWAS) have been published to date in several autoimmune diseases (AID) and hundreds of common variants have been identified that confer risk or protection. While statistical adjustments are essential to refine the list of potential associations with each disease, valuable information can be extracted by the systematic collection of moderately significant variants present in more than one trait. While involvement of the MHC region in chromosome 6p21 is not in question for most AID, the complex genetic architecture of this locus poses a significant analytical challenge. On the other hand, by considering the contribution of non-MHC-related genes, similarities and differences among AID can be readily computed thus gaining insights into possible pathogenic mechanisms. For example, statistically significant excess sharing of non-MHC genes was found between type I diabetes (T1D) and all other AID studied, a result also seen for RA. A smaller but significant degree of sharing was observed for multiple sclerosis (MS), Celiac disease (CeD) and Crohn’s disease (CD).

We have developed a bioinformatics tool called iCTNet (integrated Complex Traits networks), that enables downloading and visualization of large volumes of data and the relationships among the different data types, information that is not typically available for the general user. The most recent version of iCNet (scheduled to be released in Spring 2014) includes data from genome-wide association studies, OMIM, protein interactions, tissue expression, drug targets, drug side effects, and miRNA targets among other data types. During my presentation I will describe practical examples of how this tools may facilitate the biological interpretation of large throughput data in human immune-related diseases and how this can help to generate new hypotheses for drug repositioning strategies.

Using this class of approaches the unique genetic landscape for each autoimmune disease can start to be defined. Furthermore, this kind of analysis may set the basis for more targeted and rational therapeutic approaches.