The onset and development of autoimmune diseases in humans is based on several factors which include both a strong genetic background as well as environmental factors. The latter act on the genetically predisposed host triggering the immune mechanism that produces the immunopathological diseases known as organ specific or non-organ specific 1.

A large bulk of evidences 2-4 indicate that major histocompatibility complex genes play a pivotal role; these determinants act in association with several non major histocompatibility complex genes mostly involved in antigen processing and presentation and in the process of cell-to-cell cooperation. Nevertheless, although such a large documentation suggests that autoimmune diseases have strong genetic bases, the precise definition of the genes involved in such a process is still lacking. Clinical cases characterized by a multiorgan involvement raise intriguing questions about the fine mechanism involved in the tolerance to self components and about the abnormalities that allow for autoimmune reactivity.

The paper by Ghiringhelli et al. 5 published in the present issue of Annali describes the clinical observations on a case of autoimmune disease involving different organs. The patient was affected by autoimmune thyroiditis, myasthenia gravis, polymyositis and alopecia and presented with this clinical picture following thymus removal because of a thymoma. The different organs (thyroid, muscle and skin) involved in the autoimmune pathology during a long-time interval, might lead to interpret in a unified manner all the conditions as a complex association of multiorgan autoimmunity, rather than as distinct situations. It may be hypothesized that the removal of the thymus compromised, in a patient already prone to autoimmunity, the capacity to avoid self reactivity.

This observation acquires great importance in the light of the recent discovery of a gene located on chromosome 21 that can go through several and different mutation processes that correlate with a rare autosomal recessively inherited disease: autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) also known as autoimmune polyglandular syndrome (APS) type I.

Endocrine APS is generally divided into two major subgroups: type I and type II. Type II APS is usually characterized by the occurrence, in a given patient, of at least two of the three major autoimmune endocrine diseases (adrenal, thyroid and diabetes mellitus type 1). This syndrome occurs more commonly in women and is associated with other non-endocrine organ specific autoimmune diseases such as vitiligo, pernicious anemia and alopecia. APECED or type I APS is clinically characterized by the presence of Addison’s disease and hypoparathyroidism along with the susceptibility to mucocutaneous candidal infections. In addition to these primary disorders, these patients have a high incidence of many other organ specific autoimmune diseases such as thyroid disease, diabetes mellitus type 1, autoimmune hepatitis, vitiligo and alopecia 6.

The first symptom of APECED is usually mucocutaneous candidiasis which manifests in early childhood. The autoimmune destruction of the endocrine organs leads to a variable combination of autoimmune diseases such as Addison’s disease, hypoparathyroidism, diabetes mellitus type 1 and gonad dysfunction. Some patients also have autoimmune hepatitis and intestinal malab-
sorption along with alopecia and vitiligo. APECED is more common in Finnish, Sardinian, and Iranian Jewish populations among whom the incidence is approximately 1:25 000, 1:14 500, and 1:9000 respectively. However, several isolated cases have been reported worldwide. Furthermore, these mutations have been found in association with the autoimmune form of alopecia areata, widening the range of diseases possibly correlated with this genetic defect.

The APECED disease locus was assigned to chromosome 21q22.3 at linkage analysis by the Finnish group of Peltonen. In 1997, a specific gene correlated with APECED disease was identified in that region of the chromosome. The gene, identified on chromosome 21q at positional cloning by two independent groups is the autoimmune regulator gene (AIRE).

AIRE is expressed in lymph nodes, the fetal liver, in the peripheral monocytes/dendritic cell lineage and in epithelial cells within the medulla of the thymus. AIRE codifies for a protein that contains motifs suggestive of a transcription regulator.

It is well known that to avoid the potential pathological state of autoimmunity, it is necessary to purge the self-reactive lymphocytes from the repertoire, either by removal or silencing. The thymus is the structure responsible for purging of autoreactive cells (negative selection) soon after their generation. Since the thymic negative selection implies that the cells to be selected interact within the thymus with the specific peptides, the question “how determinants synthesized in peripheral tissues may reach the thymus in order to be presented to lymphocytes” has been debated. Surprisingly, it has been recently shown that the RNA transcripts encoding a multiplicity of proteins previously considered to be synthesized only in particular peripheral tissues can be detected in the thymus, specifically in the very rare epithelial cells in the medulla. AIRE partially drives the education of T cell clones in the thymus by regulating the ectopic expression of peripheral tissue restricted antigens in the medulla of the thymus. This occurs to variable degrees depending on the gene controlling the possible onset of autoimmunity. Thus, in the absence of the functional AIRE protein, the aberrant process of maturation would allow the emergence of autoreactive clones able to react against self antigens and hence possibly leading to immune-mediated damage of self tissues.

On the basis of these findings it can be proposed that the association of autoimmune diseases involving different organs (especially endocrine) in the same patient is likely to be correlated with a genetic defect at the level of transcription regulation of central tolerance in the thymus controlled by the AIRE. Indeed, autoimmune manifestations similar to APECED occur in neonatal thymectomized mice, highlighting the important role of the thymus in central tolerance.

Of note, the triggering factor of the autoimmune manifestations in the clinical case described by Ghiringhelli et al. has been thymus removal. It can be argued that the possible weak immunological equilibrium of the patient, due to a genetic predisposition (HLA, AIRE, others) has been overwhelmed by the sudden absence of the regulatory suppressive activity of the thymus. Thereafter, the previously latent autoimmune status became clinically evident and involved various organs.

Even if in the case of APECED the correlation between mutation and pathology is well described and corroborated, many other genes and factors may be involved in the process of the generation of autoimmunity. These include the histocompatibility molecules, cytokine receptors and CTLA-4. A complex mixture of elements can explain the occurrence of autoimmunity. Among these, genetic predisposition seems, to date, to play a key role.

In conclusion, the report by Ghiringhelli et al. might open a new window for medical doctors who, having to face an autoimmune pathological condition so widely distributed in many different organs in the same patient, have to consider a possible unified interpretation of all the manifestations. To this end, analyzing the genomic level and checking the correlation, if any, with histocompatibility molecules and with non-histocompatibility molecules such as the AIRE polymorphisms and different mutations might be necessary. Thus, it seems likely that in the future gene analysis would help to understand and perhaps even explain the onset of the patient’s clinical problems.

References


