

## THESIS OVERVIEW

The past decade has seen tremendous progress in biomolecular research on autoimmune diseases and most of the involved antigens in these diseases have been traced. There are, however, equivocal conclusions regarding the etiology of these diseases. The prevailing concept is that these diseases stem from a combination of endogenous and exogenous factors in genetically susceptible individuals. The exogenic factors are numerous and include pesticides, drugs, hormones, infections, UV radiation, stress, and others. There is a growing concern about the association between autoimmune diseases and certain environmental and occupational risk factors, including, among others, exposures to pesticides. That infections could trigger autoimmune diseases is also well established in the literature. Several studies have provided information linking infectious agents to a number of autoimmune diseases, but a direct association is still missing. Microbial products could synergize with environmental factors, predisposing to autoimmunity development. Not much information exists on the etiology of autoimmune diseases with extensive cutaneous manifestations like pemphigus, scleroderma and systemic lupus erythematosus. The remarkable complexity of their pathogenesis suggests that no single gene or environmental trigger is by itself likely to be responsible for the development of autoimmunity in these diseases.

This thesis details the work undertaken to study the immune response to common microbial superantigens and recall antigens, and xenobiotic compounds in common autoimmune skin diseases namely pemphigus, scleroderma and systemic lupus erythematosus. Also contained in the thesis is the genotypic analysis of twenty-two single nucleotide polymorphisms in thirteen cytokine genes in these diseases.

The immunological alterations in T cells and Th1 (IL-2 and IFN- $\gamma$ ) and Th2 (IL-4 and IL-10) cytokine expression caused by *in-vitro* exposure of peripheral blood mononuclear cells to various microbial antigens and xenobiotics compounds, including study of polymorphism in thirteen cytokine genes, in three different autoimmune skin diseases is detailed in separate chapters of the thesis.

**Chapter I** discusses the observations with pemphigus patients.

**Chapter II** details the results obtained with scleroderma (systemic sclerosis) patients.

**Chapter III** describes the outcome of the study with systemic lupus erythematosus patients.

Experimental approach in each of the diseases explored has been identical and includes the following:

- 1) Estimation of organochlorine pesticide levels in the blood of treatment-naïve patients and its comparison with healthy controls.
- 2) Quantitation of T cells in peripheral blood mononuclear cells of treatment-naïve patients and its comparison with healthy controls.
- 3) Quantitative (T cell response) and functional (cytokine secretion) response of peripheral blood mononuclear cells to the following stimuli:
  - a) Bacterial superantigens - SPEA & SEB
  - b) Cytomegalovirus antigen
  - c) Recall antigens - Candida antigen & PPD
  - d) Organochlorine pesticides - HCH & DDT
  - e) Mitogen (PHA-M) with and without prior HCH or DDT exposure
- 4) Re-examination of all the above parameters after clinical remission by standard prescribed immunosuppressive/steroid therapy.
- 5) Study of twenty-two single nucleotide polymorphisms in 13 cytokine genes of patients and healthy controls.