Novel approaches to pathogenesis, diagnosis and treatment of autoimmune diseases based on new insights into thymus-dependent self-tolerance

Abstract:

Autoimmune diseases are a significant burden for the quality of life and health care cost. Despite intense research efforts, the mechanisms underlying the development of autoimmune diseases are still largely obscure. This obvious ignorance explains why the current treatment of these chronic diseases remains inadequate and is associated with severe side effects. Here we propose an original and new approach to tackle this problem. Our approach is mainly based on the major biological function of the thymus, i.e. to ensure the generation of a diverse repertoire of T cell receptors that are self-tolerant. The thymus achieves this goal by using two complementary mechanisms: a) apoptotic deletion and developmental arrest of T cells bearing a receptor (TCR) with high affinity for self-antigens presented by major histocompatibility complex (MHC) proteins expressed by thymic epithelial and dendritic cells, and b) generation of self-antigen specific regulatory T cells. The escape from central self-tolerance now appears to play a prominent role in the development of autoimmune diseases.

Six workpackages will achieve the objectives of this proposal:
1. Intrathymic promiscuous gene expression and self-peptide tolerogenic therapy.
2. Preclinical studies of the autoimmune regulator (AIRE) in gene therapy.
3. Interest of anti-Coxsackievirus B4 vaccination for prevention of type 1 diabetes.
4. Exploration of a new T cell pathway governing autoimmunity and allergy.
5. Development, function and therapeutic utility of regulatory T cells in autoimmune diseases and asthma.

This ambitious research project will lead to new insights into disease mechanisms, and will concurrently provide a unique platform for innovative diagnostics and for disease-specific therapy aimed at a cure and prevention of autoimmune diseases, such as type 1 diabetes as a prototypic target of this proposal.

Coordinator:

UNIVERSITY OF LIEGE
Center of Immunology Liege Medical School Neuroimmune Endocrinology and Development Biology
B - Liege
Belgium