

Visit of Vincent Geenen – 24 March 2016

1. Course for the students (9h – 11h)

“Voyage[s] through the thymus, the small ‘brain’ of the adaptive immune system”

Structure and summary of the lesson:

- Evolution of the concepts about thymus physiology.
- T-cell differentiation in the thymus.
- Intrathymic programming of central immunological self-tolerance.
- A primary thymus defect in the development of organ-specific autoimmunity.
- Clinical evaluation of thymopoiesis.
- Thymus involvement in immunosenescence.

Reference

The Development and Survival of Lymphocytes.

In: *Janeway's Immunobiology*, 7th edition (2008), Garland Science, pp. 257-320.

2. Seminar (11h30 – 12h30)

“Thymus and Type 1 diabetes: Where are we now?”

Our studies have demonstrated that the thymus programs central self-tolerance to neuroendocrine functions through transcription of neuroendocrine-related genes in thymic epithelial cells (TECs). However, thymic neuroendocrine precursors are not secreted but processed as the source of *neuroendocrine self-antigens* that are presented by thymic proteins of the major histocompatibility complex (MHC). This process, highly specific of the thymus, has allowed an integrated and harmonious coevolution of the neuroendocrine and immune systems when recombination-activating genes and the subsequent adaptive immune response have emerged in cartilaginous fishes some 450 millions years ago.

All the members of the insulin gene family are expressed in murine TECs under the control of AutoImmune Regulator (AIRE) according a precise hierarchy: *Igf2 > Igf1 > Ins2 > Ins1*. *Igf2* transcription is defective in TECs of autoimmune diabetes-prone BB rats, and tolerance to insulin is severely impaired in *Igf2*^{-/-} mice as well as in *Igf2-loxP/Foxn1-cre* mice with *Igf2* deletion targeted in TECs. In addition, the diabetogenic coxsackievirus B4 (CV-B4) is able to persistently infect human and murine TECs and to inhibit *Igf2* transcription and IGF-2 synthesis in a murine medullary TEC line (collaboration with D. Hober, Laboratory of Virology, CHRU and University of Lille 2, France).

These studies show that: 1° IGF-2 is the dominant tolerogenic precursor of the family and mediates cross-tolerance to insulin; 2° A thymus dysfunction plays a crucial role in the development of the diabetogenic autoimmune response; and 3° Thymic infection by CV-B4 is implicated in type 1 diabetes (T1D) pathogenesis. Most probably due to its very low level of expression in the thymus, the protein insulin is highly immunogenic and is the primary autoantigen tackled in T1D. On the basis of the tolerogenic properties of IGF-2, we are currently working on the development of a negative/tolerogenic self-vaccine against T1D.

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References

1. Geenen V, Bodart G, Goffinet L, Michaux H, Henry S, Renard C, Martens H & Hober D
Programming of neuroendocrine self in the thymus and its defect in the development of neuroendocrine autoimmunity.
Frontiers in Neuroscience 7: article 187, doi: 10.3389/fnins.2013.00187, 2013
2. Jaidane H, Caloone D, Lobert PE, Sane F, Dardenne O, Naquet P, Gharbi J, Aouni M, Geenen V & Hober D
Persistant infection of thymic epithelial cells with coxsackievirus B4 results in decreased expression of type 2 insulin-like growth factor.
Journal of Virology 86: 11151-11162, 2012
3. Morrhaye G*, Kermani H*, Baron F, Beguin Y, Moutschen, Martens H & Geenen V
Impact of growth hormone (GH) deficiency and GH replacement upon thymic function in adult patients.
PLoS One 4: e5668, 2009