# T CELL RESPONSES IN NEUROLOGICAL DISORDERS

**PhD Thesis**


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**Pécs**

**2012**


# 1. INTRODUCTION

The major function of the immune system is to recognize colonizing microbes, infected cells and tumors and professionally extinguishes them, while maintains the body's integrity. The immune response provides defense against infectious agents, i.e. bacteria, parasites, fungi and viruses; against non-infectious foreign substances, macromolecules, such as proteins and polysaccharides that are recognized as foreign and also against tumor cells. The two functional parts of the immune system – the innate and adaptive immunity – mediate the protection against foreign cells and substances. The innate immune system defends the host by a non-specific, early, rapid, first line of protection and the adaptive immune system provides a later, specific immune responses.

NK cell is a type of cytotoxic lymphocyte that constitutes a major component of the innate immune system, able to lyse target cells through the different mechanisms of cytotoxicity and produce rapidly abundant cytokines, mainly interferon-gamma (IFN-γ). They express the surface marker CD56 in humans. Perforin and Fas/FasL pathways are the two major mechanisms of cellular cytotoxicity. Upon degranulation, the cytotoxic granules contain Perforin cause cell lysis by forming pores in cell membranes of target cells. FasL produced by effector cells induces apoptosis through Fas, its receptor on target cell surfaces.

T and B lymphocytes are the most important cellular components of the adaptive immune system. The function of these cells is to recognize specific "non-self" antigens by antigen-specific receptors. T cell receptor (TCR) is a heterodimer consisting of an α and a β transmembrane protein chains, each consist of one variable (V) domain and one constant (C) domain. The V domain has three hypervariable or complementarity determining regions (CDRs), which are responsible for the versatility of TCRs and antigen recognition. This diversity is a result of the rearrangement of antigen receptor coding genes. The TCR α-chain is generated by the recombination of V and J (joining) gene segments, whereas the β-chain is generated by the recombination of V, D (diversity) and J gene segments. The three CDRs in the α- and β-chains form the part of the TCR that specifically recognizes peptide-MHC complexes. Cytotoxic, $CD8^+$ T cells are able to induce the death of the target cells. $CD4^+$ T cells are commonly divided into two distinct lineages: conventional T helper (Th) and regulatory T (Treg) cells. Th cells control adaptive immunity by activating other effector cells. Treg cells are able to suppress activation of potentially deleterious autoreactive Th cells. Upon activation, all T cells express the late activation marker CD25. Among $CD4^+CD25^+$ T cells, only those with high fluorescence intensity of CD25 exert regulatory functions, while expression of low levels of CD25 may indicate T cell activation. Cytokines are small cell-signaling protein molecules secreted by the cells of innate and adaptive immunity. Th1 cells produce pro-inflammatory cytokines, such as IFN-γ, TNF-α, that improve cellular immune responses: maximize the killing efficacy of the macrophages and the proliferation of cytotoxic $CD8^+$ T cells. Anti-inflammatory cytokines, such as interleukin (IL)-4, IL-5, IL-6, IL-10, IL-13, produced by Th2 cells trigger humoral immune response: stimulate B-cells into proliferation, induce B-cell

antibody class switching and increase their neutralizing antibody production. Recently, the Th17 cells producing other pro-inflammatory cytokines, IL-23 and IL-17, have been suggested to participate in the induction of several organ-specific autoimmune diseases.

A small subset of T cells, called γδT cells, express a TCR consisting of one γ- and one δ-chain. γδT cells are suggested to bridge the innate and adaptive immune responses, quickly expand after infection and are able to produce great amounts of IFN-γ. The Vδ2 subset, expressing a δ2TCR variable chain, represents the majority of adult γδT cells mainly with a cytotoxic property.

Natural killer T (NKT) cells are a small subset of T cells that co-express αβTCR, but also express molecules specific to NK cells, such as CD56. This population, similarly to the γδT cells, is proposed to serve as a bridge between the innate and the adaptive immune systems, and have an important role in the regulation of the protection against autoimmunity and tumors. NKT cells are categorized into several distinct subsets based on their TCR repertoire. Type I NKT cells are characterized by limited repertoire diversity, also called invariant NKT (iNKT), and expresses an invariant Vα24-JαQ TCR α-chain. Besides iNKT cells, the $CD3^+CD56^+$ T cell subset contains large granular lymphocytes with conventional, diverse αβTCR. Recently, these cells have been termed NKT-like cells. The role of NKT-like cells has been suggested in the response to infectious agents, tumor rejection and autoimmunity. Like iNKT cells, mucosal-associated invariant T (MAIT) cells are also characterized by the expression of an invariant TCR rearrangement (Vα7.2-Jα33). In humans, the invariant TCR of MAIT cells was shown to be expressed in autoimmune lesions of CNS and PNS, which correlated with the expression of IL-4, suggesting an anti-inflammatory role and regulating autoimmune response.

Late-onset Pompe disease is a metabolic myopathy caused by abnormal lysosomal glycogen storage due to the deficiency of the lysosomal enzyme, acid α-glucosidase (GAA). At present, ultra-orphan Pompe disease is the only inherited muscle disorder which can be treated by the regular infusions of the recombinant enzyme (rhGAA). Enzyme replacement therapy (ERT) generates anti-rhGAA IgG-antibodies, which may interfere with efficacy. In humans, the effect of anti-rhGAA antibodies on the efficacy of ERT is controversial. In Pompe disease caused by complete absence of GAA, antibody production against rhGAA is increased due to lack of immune tolerance and the therapeutic response is worse. In contrast, no such antibody-related changes in efficacy were observed in several other human studies and antibody titer may decrease during the course of ERT similar to other lysosomal storage disorders treated by ERT.

The traditional definition of stroke, devised by the World Health Organization is „a focal (or at times global) neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours". Stroke is currently the second leading cause of death in the Western world, ranking after heart disease and before cancer. The mortality of patients with stroke is also extremely high in Central-Eastern European countries. Stroke is associated with high mortality and morbidity, and stroke survivors often remain permanently disabled. While direct neurological deficits cause early deaths, infectious complications prevail in the postacute phase of stroke contributing to the poor

outcome. Patients with stroke suffer from increased rates of infection, especially urinary tract infections and pneumonia. Such an increased susceptibility to infections after stroke may suggest early alteration of immune responses. Impaired T and NK cell responses, particularly a reduced IFN-γ production were described in a mouse model of focal cerebral ischemia, where the animals were susceptible to spontaneous pneumonia. This pulmonary infection was related to a massive apoptosis of lymphocytes in spleen and thymus. Recently, dramatic loss of T cells in the peripheral blood of patients with acute ischemic stroke, within 12 hours from onset of symptoms, has been indicated. IL-6 serum levels were increased on admission and continued to rise throughout the observation period (14 days), whereas IL-10 did not differ from control subjects.

Cancer is one of the three leading causes of death in industrialized nations. Cancers are caused by the progressive growth of the progeny of a single transformed cell. Malignant tumors are able to aggressively infiltrate the surrounding healthy tissues and to compose metastasis. Renal cell carcinoma (RCC) accounts for approximately 3% of all cancer diagnoses in the USA each year. The 82% of malignant neoplasms of RCCs are clear cell renal carcinomas. Gliomas are the most frequently occurring primary malignancies in the central nervous system, and glioblastoma multiforme is the most common and most aggressive of these tumors. Meningiomas are the most frequently diagnosed primary brain tumors. Atypical and malignant meningiomas comprise a small fraction of the total (~5%). The tumors express antigenic peptides (tumor-associated or tumor-specific antigens) that can become targets of tumor-specific immune responses (especially T cell mediated processes). It is necessary for the activation of effectory mechanisms of anti-tumor response that the antigen is first presented to the T cells on antigen presenting cells (APCs). Beside the cytotoxic T cells, the NK cells also have an important role in the defense against tumor cells. Humoral immune response may be also induced by particular tumor antigens.

## 2. AIMS OF THE STUDIES

Here, we investigated the role of T cells in immune responses in different neurological disorders.

### 2.1 Enzyme replacement therapy induces T cell responses in late-onset Pompe disease

At present, Pompe disease is the only inherited muscle disorder which can be treated by enzyme replacement therapy in the form of regular infusions of recombinant human acid α-glucosidase. ERT induces an IgG antibody response against rhGAA in most patients, which may interfere with the efficacy of treatment, therefore, we examined if ERT also induces rhGAA-specific T cell responses:

1. Are there any differences in lymphocyte frequencies, expression of activation and cytotoxic molecules in peripheral blood of patients with Pompe disease treated with rhGAA?
2. Does the treatment with rhGAA induce specific anti- or pro-inflammatory cytokine production in patients with Pompe disease treated with rhGAA?

**2.2 Impaired function of innate T lymphocytes and NK cells in the acute phase of ischemic stroke**

Acute-onset cerebrovascular diseases are connected to a number of immunological changes. Few human studies all addressed the rapid changes in the adaptive arm of the immune system, mainly T cells. Cells of the other part of the immune system, innate lymphocyte subsets have not been thoroughly examined in the acute phase of ischemic stroke. We may suspect that early changes in innate immune responses may be related to post-stroke infections resulting in poor outcome and high mortality of stroke. Therefore, we examined innate T cells and NKT-like cells in the early phase of acute ischemic stroke:

3. Are the frequencies of the innate T cells affected by acute ischemic events?
4. Are the anti- or pro-inflammatory cytokine productions and cytotoxicity of the innate lymphocyte subsets affected in the acute phase of ischemic stroke?

**2.3 Invariant Vα7.2-Jα33 TCR is expressed in human kidney and brain tumors indicating infiltration by mucosal-associated invariant T (MAIT) cells**

Recently, phenotypically and functionally similar iNKT and MAIT cells have been suggested to participate in immunoregulation of autoimmunity and immune surveillance of tumors.

The selective absence of the invariant Vα24-JαQ TCR of iNKT cells in central nervous system plaques of patients with multiple sclerosis was previously observed, while conventional Vα24 TCRs and invariant TCR of MAIT cells were present. To partly examine whether absence of iNKT cells in CNS plaques might be related to the CNS compartment or is specific to MS, here we examined tumors inside and outside the CNS, i.e. malignant brain tumors and kidney cancers. Therefore, we addressed:

5. Do iNKT cells infiltrate tumors within the CNS similarly to tumors outside the CNS?
6. Can we detect other invariant T cells in tumors with a special emphasis on MAIT cells, which may possess similar functions to iNKT cells?
7. If MAIT cells are present in tumors, what is the inflammatory environment? MAIT cells have been suggested to produce Th2 cytokines, but the similarity to iNKT cells and recent murine data suggested that the MAIT subset may be functionally heterogeneous as well.
8. What is the relation of MAIT and NKT-like cells in tumors?

9. Do MAIT cells express CD56? Do $CD56^+$ MAIT cells participate in anti-tumor immune responses?

# 3. EXPERIMENTS

## 3.1 Enzyme replacement therapy induces T cell responses in late-onset Pompe disease

Enzyme replacement therapy in ultra-orphan Pompe disease generates anti-rhGAA antibodies, which may interfere with efficacy.

7 Hungarian patients with late-onset Pompe disease (6 with ERT, 1 untreated) and 5 healthy controls were examined at different time points. The *ex vivo* frequency, intracellular perforin, surface FasL, CD25, CTLA-4 expression of T cells subsets, Tregs and NK cells were examined by flow cytometry. Peripheral blood mononuclear cells (PBMC) and isolated $CD4^+$ and $CD8^+$ T cells in the presence of antigen presenting cells were stimulated with rhGAA (1 and 10 μg/ml) for 48 hours *in vitro*. Intracellular IFN-γ expression and Th1, Th2, Th17 cytokine production of such cultures were measured by cytometric bead array (CBA). Activation markers were also examined.

All treated patients had an IgG antibody response against rhGAA. The *ex vivo* percentage of activated T cells was increased in the treated patients. rhGAA stimulation *in vitro* generated a dose-dependent increase in pro-inflammatory intracellular IFN-gamma expression in $CD4^+$ and $CD8^+$ T cells. Isolated $CD4^+$ and $CD8^+$ T cells produced increased amount of IFN-γ and TNF-α in half of the patients compared to controls after in vitro stimulation with rhGAA, while IL-4, IL-6, IL-17 levels were not different. Expression of cytotoxic FasL and perforin molecules by NK, NKT-like and $CD8^+$ T cells were not increased *ex vivo*.

In addition to the antibody response, ERT also induced cytotoxic and inflammatory T-cell responses, which may also influence treatment efficacy.

## 3.2 Impaired function of innate T lymphocytes and NK cells in the acute phase of ischemic stroke

Patients with stroke suffer from increased rates of infection, and this increased susceptibility to infections after stroke may suggest early change of immune responses. Functional alterations of innate lymphocytes, which can amount rapid immune responses and shape subsequent T cell reactions, were examined in the acute phase of ischemic stroke.

Frequencies, intracellular Perforin and IFN-γ expression of Vδ2 T cells, $CD3^+CD56^+$ NKT-like and $CD3^-CD56^+$ NK cells were examined sequentially in the peripheral blood of 20 healthy controls and 28 patients within 6 hours of the onset of acute ischemic stroke and after 72 hours by flow cytometry. Pro- and anti-inflammatory cytokine

production of isolated NKT-like and NK cells following in vitro activation was measured by cytometric bead array. NK cytotoxicity was examined in the peripheral blood mononuclear cells by a nonradioactive, colorimetric cytotoxicity assay.

Percentage of Vδ2, NKT-like and NK cells at 6 and 72 hours after stroke were constant and similar to percentages in healthy subjects. In contrast, pro-inflammatory intracellular IFN-γ expression by Vδ2 T cells, NKT-like cells and NK cells and IFN-γ production by isolated NK cells in culture was low at 6 hours and reached the level of healthy subjects by 72 hours after stroke. Anti-inflammatory IL-4, IL-5 and IL-10 productions of NKT-like and NK cells were not altered. Intracellular Perforin expression by Vδ2 T cells, NKT-like cells and NK cells, and NK cytotoxicity was low at 6 hours and reached the level of healthy subjects by 72 hours.

Pro-inflammatory and cytotoxic responses of NK, NKT-like and Vδ2 T cells become acutely deficient in ischemic stroke, which may contribute to an increased susceptibility to infections.

### 3.3 Invariant Vα7.2-Jα33 TCR is expressed in human kidney and brain tumors indicating infiltration by mucosal-associated invariant T (MAIT) cells

The anti-tumor response of human iNKT cells is well established. A novel T cell subset, mucosal-associated invariant T (MAIT) cells, possesses similar regulatory properties to NKT cells in autoimmune models and disease. Deficiency of human iNKT cells has been described in multiple sclerosis (MS) indicated by a decreased frequency in the peripheral blood and absence of the invariant Vα24-JαQ TCR in central nervous system (CNS) plaques of patients with MS despite the presence of conventional Vα24 TCR. Such deficiencies are not characteristic to the chronic autoimmune demyelinating disease of the peripheral nervous system (PNS), chronic inflammatory demyelinating polyneuropathy (CIDP). To examine whether absence of iNKT cells in CNS plaques might be related to the CNS compartment or is specific to MS, here we examined the clonality of four T cell subsets expressing invariant αTCR, including Vα24-JαQ (iNKT), Vα7.2-Jα33 (MAIT), Vα4-Jα29 and Vα19-Jα48 TCRs, in 19 tumors inside and outside the CNS by using RT-PCR SSCP (single strand conformation polymorphism) clonality assay, identifying the amplified and electrophoretically separated particular sequences by hybridization with specific probes.

The MAIT clonotype was identified and co-expressed with NKT clonotype in half of the tumors. In contrast, two other invariant T cell clonotypes (Vα4 and Vα19) were not present in tumors. Such tumors also expressed Vβ2 and Vβ13, the restricted TCRβ chain of MAIT cells and the antigen-presenting molecule MR1. A high percentage of infiltrating T cells was $CD8^+$ and expressed HLA-DR suggesting activation. Although the MAIT αTCR was identified in both peripheral $CD56^+$ and $CD56^-$ subsets, infiltrating lymphocytes were CD56 negative. The clonal presence of MAIT cells in tumors correlated

with the expression of pro-inflammatory cytokines but no IL-4, IL-5 and IL-10, suggesting that a pro-inflammatory subset of human MAIT cells may exist.

Our data imply that a $CD56^-$ subset of MAIT cells may participate in tumor immune responses similarly to NKT cells.

## 4. SUMMARY OF THESES

1. The *ex vivo* and *in vitro* frequencies of lymphocyte subsets in the treated patients with Pompe disease were not different from the untreated patient with Pompe disease and healthy controls. The *ex vivo* percentage of activated $CD4^+CD25^{low}$ T cells was significantly elevated in the treated patients with Pompe disease. Expression of cytotoxic FasL and perforin molecules by NK, NKT-like and $CD8^+$ T cells were not increased *ex vivo*.
2. rhGAA stimulation *in vitro* generated a dose-dependent increase in intracellular IFN-γ expression in $CD4^+$ and $CD8^+$ T cells in the treated patients with Pompe disease. Isolated $CD4^+$ and $CD8^+$ T cells produced increased amounts of IFN-γ and TNF-α in half of the treated patients after *in vitro* stimulation with rhGAA, while IL-4, IL-6, and IL-17A levels were not elevated. We show that enzyme replacement therapy induces pro-inflammatory T cell responses besides an antibody response in Pompe disease.
3. The percentages of particular innate lymphocytes, Vδ2, NKT-like and NK cells do not change in the acute phase of ischemic stroke in contrast to the reported decrease of adaptive T cells.
4. In contrast to unaltered frequency, an acute functional deficiency of innate lymphocytes occurs in the acute phase of ischemic stroke, within 6 hours: pro-inflammatory IFN-γ production, expression of perforin and NK cytotoxicity are decreased, while there is no change in production of Th2 cytokines and Th2-related ICOS expression. We may hypothesize that such early deficiency or its disregulated normalization may substantially influence susceptibility to infections similarly to animal models of cerebral ischemia.
5. MAIT and iNKT cells are the only known invariant T cells infiltrating brain and kidney tumors.
6. Since iNKT cells are present in CNS tumors, their absence in MS plaques is disease-specific and not related to the CNS environment.
7. MAIT cells may have a pro-inflammatory subset, which infiltrates tumors.
8. Brain and kidney tumors differ in infiltrating T cell and MAIT cell subsets: brain tumor infiltrating MAIT cells may express additional TCRβ to Vβ2 and Vβ13.
9. MAIT and iNKT cells in tumors do not express CD56 although both $CD56^+$ and $CD56^-$ subsets are present in the peripheral blood even in patients with cancer.

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***Cumulative impact factor of articles related to Theses:*** ***9.25***
***Cumulative impact factor of articles not related to Theses:*** ***10.37***

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## 6. ACKNOWLEDGEMENTS

First of all, I would like to thank my mentor and supervisor Prof. Zsolt Illés for his generous support and guidance in research. I am also grateful to Prof. Sámuel Komoly, the head of the Department of Neurology, and Prof. Júlia Szekeres-Barthó, the head of the Department of Medical Microbiology and Immunology for the support of my research.

I am grateful to László Szereday, whom I consider my honorary tutor, for all the help he has given me, for teaching and supporting me.

I also thank collaborators and stuff at the Department of Neurology, at the Department of Medical Microbiology and Immunology, at the Department of Immunology and Biotechnology, at the Department of Central Electron Microscope Laboratory and at the Department of Biochemistry and Medical Chemistry in the University of Pécs, who contributed to my work with her/his help, support, teaching or advices.

Finally, I express my warmest thanks to my parents, my whole family and my girlfriend for their love and encouraging support.