Modulation of human antigen-specific T cell response - therapeutic implications for multiple sclerosis

Institute of Neuroimmunology
CHARITÉ CAMPUS MITTE - UNIVERSITÄTSMEDIZIN BERLIN

1. Outpatient clinic (Clinicians, Study nurses, Data bank)
2. MRI area
3. Laboratory/Animal Facility (PhD, PhD students and Technicians)

An interaction between the specialized areas exists such that the data is efficiently transferable. In particular experimental immunoregulatory agents are directly passed on to the Clinic in early Phase II studies.

Research areas:
- Neurology
  - Imaging Techniques
- Patient Clinical Trials
- Biochemistry
  - Cell Signaling, Lipid Raft Signaling, Proteomics, Post-translational modifications
- Animal models
  - Experimental Autoimmune Encephalitis
- Immunology
  - Tolerance in Allergy, Autoimmunity and Transplantation; Infectious Immunology
- Genetics & Molecular Biology
  - Genetic Analysis of Multiple sclerosis in Europeans

Funding:
- German Research Council (DFG) through grants allocated to collaborative research centres „Sonderforschungsbereich“ (SFB) in Medicine
  - SFB507: Mechanisms of immune-mediated chronic CNS damage
  - SFB625: Mechanisms of T cell response by statins - a new therapeutic strategy in MS
- Federal Ministry for Research and Education "Bundesministerium für Bildung und Forschung" (BMBF)
- Joint German-Israeli Research Program (intergovernmental agreement concluded between the Israeli Ministry of Science and Technology (MOST) and the BMBF)

Outlook:
- TARGET-SPECIFIC STRATEGIES
  - In vivo analyses
    - EAE model
  - Ex vivo analyses
    - M S patients
      - Gene expression
      - T cell response
- CLINICALLY BENEFICIAL AGENT X
MULTIPLE SCLEROSIS (MS)
- inflammation
- demyelination
- axonal damage
- autoimmune nature
- APOPTOSIS dysregulation

CNS

CNS damage

Cytotoxic factors

activation

Bcl-X<sub>L</sub>

myelin specific

MS patients
Regulation of activated T cells by apoptosis

Therapeutic options for MS:

Antigen-specific T cell lines

Primary culture
14 days incubation with antigen

Expanded further
weekly restimulation with specific antigen

Therapeutic options for MS:

Regulation of activated T cells by apoptosis

J Neuroimmunol. 2002

MS patients

Healthy Controls

Bcl-XL

ß-actin

Caspase 3-like activity
DNA fragmentation

J Neuroimmunol. 2002

Antigen-specific T cell lines

Therapeutic options for MS:

Antigen-specific T cell lines

Therapeutic options for MS:

Regulation of activated T cells by apoptosis

Therapeutic options for MS:

Antigen-specific T cell lines
**therapeutic options for MS:**

**TRAIL**
- Activation
- Myelin specific
- Apoptosis

**Apoptotic ligand TRAIL**
downregulates Ca^{2+} influx through CRAC channels of antigen-specific T cells

**Apoptotic ligand TRAIL**
inhibits proliferation and cell cycle progression of human (auto)antigen-specific T cells

**TRAIL and its receptors**
- TR1 (DR4)
- TR2 (DR5)
- Amplifying intrinsic loop
- Executioner caspases
- Death domain

**TRAIL receptors in human brain**
- GFAP
- MAP
- PLP
- R3
- R4
- R2
- R1
- R0
- R5
- R6

**Charité J Immunol. 2002**

**Charité J Neurosci. 2002**
TRAIL is not expressed in normal human brain

Induction of TRAIL-mediated glioma cell death by human T cells

Inhibition of T cell proliferation and cell cycle progression by HMG-CoA reductase inhibitor atorvastatin
No modulation of early T cell activation (Ca²⁺ influx) by atorvastatin

Beneficial effect of atorvastatin in EAE

Induction of T cell anergy by atorvastatin

Induction of T cell anergy necessitates IL-10 signaling
Atorvastatin induces a subset of cells with a regulatory phenotype

**Suppressive capacity of atorvastatin-treated cells**
- Inhibitory cytokines/direct cell-cell contact

**Rapid phosphorylation of extracellular signal-related kinase 1**
- MAPK Erk1
  - Rapid phosphorylation following atorvastatin
  - Sustained expression (>24h)

**Phosphorylation of Erks is necessary for anergy induction**
- MEK inhibition
  - Restores normal T cell response

**Robust phosphorylation of Erk 1 mediated via MEK**
- MEK inhibition by U0126
  - Delays Erk 1 phosphorylation by atorvastatin
Transwell migration assay

Chemotaxis of human lymphocytes after atorvastatin exposure

Chemotaxis of human MBP-specific lymphocytes towards CCL19

Chemotaxis of human lymphocytes after atorvastatin exposure

Chemotaxis of human MBP-specific lymphocytes towards CCL19
ROCK ‘n’ Rho expression in human PBMCs (ROCK cleavage)

Atorvastatin inhibits ROCK cleavage (induction of Rho A)
Atorvastatin inhibits ROCK cleavage (induction of Rho A)

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ROCK cleavage is restored following mevalonate

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**TAKE HOME MESSAGE**

1. immunomodulatory activities of TRAIL and atorvastatin – potential in treating autoimmune disease; therapeutic activity of atorvastatin
2. multi-faceted atorvastatin - imp. mechanism for EAE/ME
   
   ▶ selective targets for inducing tolerance in autoimmune disease or protecting vs. CNS damage in MS

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