Seminar UMONS/ Dpt of Neuroscience

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invitation by Prof. Laurence RIS

Unbiased identification of peptide ligands to neuroinflammation pathology of Multiple sclerosis

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Multiple Sclerosis (MS) neuroinflammation pathology is characterized by molecular and cellular alterations at the blood-brain barrier (BBB) that becomes permissive to the extravasation of blood derived immune cells and blood compounds. To define the plethora of protein compounds that bind to the lesion sites entangled by non-affected CNS tissue we developed a double strategy combining molecular biology and bioinformatics approaches in adaptation to phage displayed peptide ligands reacting with the inflammatory BBB.
We performed *in vivo* screening of short (12aa) peptides in CNS neuroinflammation of the experimental autoimmune encephalomyelitis (EAE) rat model of MS and healthy controls. To extract the specific peptide ligands from both generated massive phage repertoires we developed a physical molecular DNA subtraction of both phage repertoires and generated a new subtraction phage repertoire of EAE specific peptides and confirmed them experimentally.
Next Generation Sequencing (NGS) can be used to provide a high-resolution view of the contents of selected phage displayed peptides. The comparative data analysis of the three generated phage repertoires (9.4 mio sequences) confirmed the biological data evaluation of specific peptide ligands to the altered neuroinflammatory CNS.
With the hypothesis that (some of) these peptides mimic protein domains interacting with the same targets, we developed a bioinformatics analysis method allowing, in three steps, the identification of the potential mimicked proteins and subsequent analysis of the encoding set of genes: i) mapping of the peptides against

the proteome of interest, ii) subtraction of random noise and the matches of a control repertoire, iii) retention of proteins with statistically significant scores.
Experimentally, among the most high score mimicked proteins, the derived synthesized peptides (20aa) of mimicked domains were tested for labeling of BBB alterations in CNS sections of MS and other chronic neurodegenerative diseases. *In vitro* studies and *in vivo* monitoring by MRI, confirmed their main target specificity to human endothelial cells under proinflammatory stimulation.
The strategy of combining the developed molecular biology and bioinformatics approaches adapted to phage display is applicable to (m)any disease models to streamline biomarker discovery and to identify functional proteins and domains. The generated gene lists linked to a series of tools for functional analyses provides furthermore new insights into the interactive proteins at the inflammatory BBB.

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Neuroinflammation, imagerie et thérapie de la sclérose en plaques

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