Prion-like protein spread in neurodegenerative diseases of the CNS and development of therapeutic approaches

Project description:
Huntington's Disease (HD) is an incurable, autosomal dominant neurodegenerative disorder of the CNS that is defined by a CAG expansion in exon 1 of the huntingtin gene leading to the production of mutant huntingtin (mHtt). Over time, this protein accumulates in neurons causing dysfunction and death which leads to a progressive disorder of movement and cognition along with psychiatric problems. To date, the disease has been considered to be cell autonomous, with a secondary inflammatory response as the cells die. However, our recent *post mortem* analysis of brains from HD patients who received fetal neural grafts has revealed the presence of mHtt aggregates within the genetically unrelated grafted tissue. Additionally, we have shown in these same patients that mHtt can be found in perivascular macrophages, and that in animal models of HD the blood-brain barrier (BBB) is leaky. These unique findings coupled to our work, and that of others, showing that mHtt is expressed in peripherally circulating monocytes raise questions as to whether mHtt is capable of passing from cell to cell, and as such the disease pathogenesis involves a non-cell autonomous component.

We propose that mHtt is capable of being transferred between cells through transynaptic and immune cell mediated processes and thereafter cause pathology. In other words, while HD is initiated by the aberrant expression of mHtt in critical populations of neurons, the disease process also involves non-autonomous mechanisms of protein transfer. In the years to come, we wish to:
1) determine whether there is a transynaptic transfer of mHtt.
2) determine whether mHtt can spread into the CNS via immune cells.

If reached, these two milestones will radically change our concepts on the pathogenesis of Mendelian neurodegenerative disorders of the CNS and with this the prospect of novel disease modifying therapies.

The purpose of this project is thus to study various mechanisms of transmission of pathological mHtt protein using a multidisciplinary approach which include the use of transgenic animals, immunohistochemistry/immunofluorescence, confocal microscopy and two-photon real time intravital imaging, flow cytometry, cell culture, and various molecular biology techniques and biochemical analyses.

Requirements and conditions:
Seeking:
- Highly motivated student
- Fluent in French and English (spoken and written)
- Highly adaptable. Efficient and respectful of deadlines. Capable of teamwork.
- For master students: must have completed a bachelor degree in a relevant discipline with a grade point average superior to B +
- For PhD students: must have completed a master degree with laboratory experience in a related field
- For post-doctoral fellows: relevant experience in neurodegenerative diseases of the CNS and related technical training is requested. Candidates with expertise in any additional imaging, cell culture and molecular biology training are encouraged to apply.
- The student must be admitted to one of the following programs:
Master's with thesis in neurobiology/PhD in neurobiology
- Funding has been secured to carry out the proposed project and insure salary support

Profile sought:
-Health-related fields
-Biochemistry and Microbiology
-Biology
-Medical Research

Documents required:
-Curriculum Vitae
-Transcripts

-Cover letter
-Letters of references (at least 2)

Deadline to apply:
Review of application will begin immediately and continue until the position is filled.
Appointed as soon as possible

Contact information:

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