Significance and research objectives

Chronic pain is a condition in which the pain goes from acute to chronic, persisting even after the tissues have healed. Each of us probably knows someone who suffers from chronic pain: the prevalence in our population is estimated at 30%. With limited treatment options, many patients have long since given up and suffer silently with no hope of respite. The productivity they lose as a result turn their private tragedy into a public burden, costing the US government alone an estimated $250 billion a year. In addition, chronic pain is a strong factor supporting the development of depression in patients and is responsible for the high increase in the number of suicides in society.

A great deal is known about the neurobiological mechanisms associated with the development and maintenance of chronic pain. Still we are not able to point our finger one those which while inhibited can lead to decrease in chronic pain symptoms development. Currently the role of autoimmune response in nervous system in pain chronicity is gaining a lot of interest. This response is connected with pathological activation of antigen presenting cells, that in nervous system can be microglia, dendritic cells or even neurons. Therefore **in presented project we will assess spatial (in different parts of brain) and temporal (at different time points after injury) changes in activation of immunological and neuronal cells with the use of Imaging Mass Cytometry (Hyperion Imagining System).** We will optimize this technology for the use in neuroimaging, which may contribute to the introduction of new standards in neuroscience research. Experiments will be performed in animal model of pain that is characterized by the presence of two phases of pain – acute and chronic, that will allow us to monitor aforementioned changes at different stages of the disease.

Although chronic pain is one of the most important medical problems (especially in the face of aging societies in developed countries), there has been little progress in developing improved therapeutics for this condition. Especially in the aspect of preventing the transition from acute to chronic stage of the disease. Therefore in second part of our project we will focus on assessing pain response after treatment with selective inhibitors of immunoproteasome. Immunoproteasome is a enzymatic complex with three catalytic subunits (LMP2, LMP7 and MELC-1), involved in antigen presentation that next lead to production of autoantibodies that can lead to changes in neuronal processing of pain. Studies on first generation of immunoproteasome inhibitors showed their potential in pain reduction, although due to lack of specificity and severe side effects their use in clinics is limited. **In presented project we will test novel compounds that were proved to be selective towards i20s subunits, to determine if this treatment will lead to decrease in chronic pain development and persistence.** To select proper compound for our studies we will check levels of expression of LMP2, LMP7 and MELC-1 throughout transition from acute to chronic pain state. Also we will measure activity of those subunits, as the amount of enzyme in the cell not always strictly corresponds with its activity.

Expected project results

We will determine changes in the crosstalk between neuronal and immunological cells in brain structures responsible for pain processing during the transition from acute to chronic state. We will also describe the level of expression and activation of i20s subunits, that due to its involvement in autoimmune response is thought to be novel target in the prevention and treatment of chronic pain. **Our results may provide a foundation for the development of a new disease-modifying therapeutic approach in this condition.**