ABSTRACT

Huntington´s disease (HD) is an inherited monogenic neuropsychiatric degenerative, progressive, and fatal condition. The disease onset is in middle age of the patient. The most prominent clinical features are motor impairment, progressive decline in cognitive functions, and personality changes. Any preventive or disease-modifying therapies are not available so far. Therapeutic interventions can only target symptoms. It is believed that the primary pathology of HD results from massive degeneration of neurons in the basal ganglia. However, the expression of mutant huntingtin was detected in all tissues. Thus the mutation in non-neuronal cells of the brain and in peripheral tissues contributes to the pathology of HD. Neuroinflammation, especially microglia activation, is involved in the pathogenesis of HD. Given evidence that mutated huntingtin is expressed in peripheral immune cells, it is possible that inflammatory changes detected in peripheral tissues may reflect the inflammatory process in central nervous system (CNS). Several recent studies indicated that the immune system could act as a modifier of HD neuropathology. In order to monitor the success of any disease-modifying drugs in the pre-manifest stage of HD it is important to identify robust biomarkers of the onset and disease progression. Cerebrospinal fluid and peripheral blood may provide insight into pathology of HD, new prospective biomarkers and potential therapeutic targets. Using the transgenic porcine HD model and quantitative proteomic approach (Luminex xMAP technology), we monitored the immune system dysfunction in HD and searched for candidate biomarkers of disease onset and progression. Our findings identify proteins significantly affected in HD in transgenic minipigs. Using the quantitative multiplex immunoassay techniques and detailed data analysis allowed us to show the involvement of innate immune system as well as lack of adaptive immune anti-inflammatory response in CNS in transgenic minipigs. We identified IFNα and IL-10 proteins as promising biomarkers in CNS and IL-8 in blood serum from transgenic minipigs. Using the concentration measurement of cytokine levels, we will continue to monitor the disease progression in pre-manifest stage in transgenic minipigs. Furthermore, this methodology will be used in a pre-clinical study for reducing the level of mutant huntingtin using AAV5 vector in minipig model for HCH in the near future.