ABSTRACT

Neurological disorders affect more than 14% of the population worldwide and together with traumatic brain and spinal cord injuries represent major health, public and economic burden of the society. Incidence of inherited and idiopathic neurodegenerative disorders and acute CNS injuries is growing globally while neuroscience society is being challenged by numerous unanswered questions. Therefore, research of the CNS disorders is essential. Since animal models of the CNS diseases and injuries represent the key step in the conversion of the basic research to the clinics, we focused our work on generation of new animal models and on their use in pre-clinical research. We generated and characterized transgenic minipig model of Huntington's disease (HD) which represents the only successful establishment of a transgenic model of HD in minipig which should be valuable for testing of long term safety of HD therapeutics. Next, we crossed the well characterized R6/2 mouse HD model with the *gad* mouse model which lacks the expression of UCHL1 which led to results that support the theory of "protective" role of mutant huntingtin aggregates and suggest that UCHL1 function(s) may be affected in HD disturbing certain branches of Ubiquitin Proteasome System. Traumatic spinal cord injury and Amyotrophic Lateral Sclerosis (ALS) are the two most severe and common disorders of the spinal cord in humans. Thus, the two animal models we used in our human neural stem cells (HSSC) grafting experiments were: i) mutant $SOD1^{G93A}$ transgenic rat model of ALS (SOD1 rat) and ii) the rat model of acute lumbar (L3) compression injury developed in our lab. Intraspinal grafting of clinical grade HSSC used in our experiments led to local protection of α-motoneurons residing in the close proximity of the grafted cells in immunosuppressed SOD1 rats and demonstrated progressive and significant improvement in motor and sensory function in immunosuppressed rats with previous L3 contusion injury. Our numerous xenogeneic grafting experiments led us to the development of new immunosuppressive tacrolimus-loaded pellets which are now commercially available and provide steady drug release for up to 3 months, making delivery labor efficient, minimally invasive, and producing stabilized blood concentration levels. Our work resulted in generation of one of the first large animal models of Huntington's disease, revealed the possible role of UCHL1 in HD and demonstrated the therapeutic potential of neural stem cell therapy in spinal cord disorders. These results were already successfully applied in experimental and human clinical settings and we believe that will further stimulate and accelerate translational research of CNS disorders.