Phenotypic evaluation of mice carrying a point mutation of the alpha-II spectrin gene as an animal model for the syndrome of ataxic neuronal spectrinopathy

Summary

Recently, an increasing number of cases of α-II spectrin-dependent neuropathies have been identified. Initially, mutations in the *SPTAN1* gene encoding α-II spectrin were associated with severe infantile spasms disorders, including early infantile epileptic encephalopathies and West syndrome. Currently, hereditary motor neuropathies (spastic paraplegias or ataxias) have also been added to these disorders. In the vast majority of cases, spectrinopathies remain resistant to pharmacological treatment. The pathomechanisms associated with spectrin mutations underlying infantile spasms are still poorly understood due to the lack of animal research models.

Since the identification of spectrin proteins over half a century ago, it has been discovered that they play a role not only in the canonical function of cytoskeletal structure but also in processes such as the development of the nervous system (myelination, axon and dendrite shaping, synaptogenesis), signal transmission across the cell's external membrane, intracellular transport of proteins and vesicles, phagocytosis, shaping of the immune response, cell cycle regulation, and angiogenesis.

So far, only a few animal models useful for studying the function of α-II spectrin have been obtained, but only in two of these models, which have α-II spectrin gene knockout in the peripheral or central nervous system, have generalized seizures and spastic seizures been observed. These animals, due to their short lifespan of less than one month, do not allow for the assessment of the role of α-II spectrin in mature individuals.

The aim of the doctoral thesis was to provide a phenotypic description of Spna2R1098Q mice, which carry a point mutation in the α-II spectrin gene. These mice serve as a model for various spectrin-dependent cerebellar ataxias and could be used to study the mechanisms responsible for spectrin-dependent neuropathies throughout an individual's lifespan. Additionally, this model allows for testing new therapies for these disorders. Interestingly, Spna2R1098Q mice are the only animal model that exhibits a phenotype of spasms and motor and memory impairments, which are part of the clinical spectrum observed in patients suffering from spectrin-dependent neuropathies. Research conducted as part of the doctoral project allowed for the characterization of the

mouse model and demonstrated the presence of motor and memory deficits. It was confirmed that disruptions in α-II spectrin lead to the secondary loss of β-III spectrin. Negative effects of the Spna2R1098Q α-II spectrin mutation on morphometric characteristics, including spleen size, were also observed. No differences were observed in the function of the innate and acquired immune systems in Spna2R1098Q mice, despite a decrease in the number of leukocytes and lymphocytes in peripheral blood.