Abstract

DISP3 protein, also known as PTCHD2, belongs to the PTCHD family of proteins, which contain a sterol-sensing domain in their structure. The expression of the *Disp3* gene is high in neural tissues and is regulated by thyroid hormone. The *DISP3* gene is associated with development and progression of certain types of tumors, as well as with development of some neural pathologies. Neural stem cells also display high expression of the *Disp3* gene.

Neural stem cells are defined by their capability to self-renewal and capacity to differentiate into the basic types of neural cells - neurons, astrocytes, and oligodendrocytes. Precise regulation of the balance between proliferation and differentiation of neural stem cells is crucial for development of the central nervous system and its subsequent proper functioning, and disruption of this balance may lead to development of various pathologies.

In this work we mainly focused on describing the function of the DISP3 protein in neural cells and tissues. We have shown that during differentiation of neural stem cells, the expression of the *Disp3* gene is significant decreased. Furthermore, we have found that in neural stem and progenitor cells, the increased expression of the *Disp3* gene promotes their proliferation. Moreover, when *Disp3* expression was disrupted, the "stemness" of the cells was suppressed, leading to increased spontaneous neuronal differentiation. Differentiation of cells into astrocytes, neurons, and oligodendrocytes was affected by changes in the expression of the *Disp3* gene. In the population of differentiated cells with the mutated *Disp3* gene, there were more highly differentiated astrocytes, the number of differentiated neurons increased, and the cells were also able to better differentiate into oligodendrocytes. In contrast, elevated *Disp3* expression resulted in impaired cell differentiation. These results indicate that in neural cells, DISP3 affects the balance between proliferation and differentiation.

We also found high levels of the *DISP3* gene expression in some types of primary brain tumors, particulary in subtype 4 medulloblastomas. Subsequent *in vitro* analysis has shown that tumor cell proliferation can also be affected by modulated *DISP3* expression. For further experiments, we have prepared lines of transgenic mice with increased expression of the *Disp3* gene. In these mice, elevated cell proliferation was found in the cerebellum, from which meduloblastomas are expected to originate. Taken together, our results support the hypothesis that DISP3, due to its influence on the proliferation and differentiation of neural cells, may be involved in the oncogenesis of brain tumors.