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Dynamic Properties of Microtubules: Investigation for Huntington's Disease Terranostics

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Huntington's disease (HD) develops as a result of a polyglutamine mutation (encoded by the CAG triplet) in the huntingtin protein gene (HTT). The juvenile form of the disease evolves with more than 50 number of CAG repeats in htt. HD belongs to the group of neurodegenerative, as it leads to the death of the striatum neurons, and later in the cerebral cortex. HTT has been shown to be involved in a variety of cellular processes, including cellular transport of both individual vesicles and organelles. Microtubules (MT) are involved in these processes. MT polymerize from tubulin, have polarity and dynamic properties. One of their functions is to be "rails" for intracellular transport mediated by motor proteins. There is ample evidence to indicate that the MT dynamics disorders and the MT network intracellular architecture desorganization accompany many diseases, including neurodegenerative ones, which motivated us to investigate changes in their dynamics in patients with HD.

As model systems, we used: (1) fibroblasts isolated from skin biopsies of HD patients with different polyglutamine fragment lengths and healthy donors; cultured (2) neurons and (3) glial cells obtained by directional differentiation from iPSCs of HD patients and healthy donors. The dynamics of the MT network restoration after its disassembly in the cold in skin fibroblasts was analyzed. It turned out that the number of MT growing from the centrosome in the early stages does not differ in the cells of patients with HD and healthy donors (which indicates the absence of the centrosome-located MT organizing centers activation), however the average length of MT increases faster in the cells of patients. To study the dynamic properties of MT, the method of transfection with fluorescently labeled plus-terminal protein EB3-GFP was used, which made it possible to observe the growth and disassembly of the plus-ends of MT in real time. Next, the dynamics of MT were analyzed in the ImageJ program using automatic plugins and manual tracing. The dynamics of MT was studied in various regions of the cell: in the central part (region of the nucleus and centrosome), on the leading edge and in the tail of fibroblasts; in axons, bodies and dendrites of neurons. Interestingly, the dynamic properties of MT at the leading edge and in the tail of skin fibroblasts depended on the CAG repeats number in the HTT gene: with an increase in the repeats number there was an increase in dynamic parameters at the leading edge, whereas in the tail part - on the contrary. In the central part of the cells the tendency to increase growth rates was observed in all cases. Similarly, we observed an increase in growth rates in the bodies and axons of cultured neurons of HD patients, while in dendrites the growth rates did not differ from those in neurons obtained from healthy donors.

The results obtained made it possible for the first time to evaluate in vitro differences in the dynamic properties of MT of cultured fibroblasts and neurons of HD patients and healthy donors, which makes it possible to describe the effect of mutant HTT on the MT dynamics properties as well as to approach the study of MT as targets for HD patients diagnostics and possible therapy.

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