Construction of CNF1 autoassembling variants endowed with blood-brain barrier crossing ability: an innovative therapeutic approach for RTT

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Several pieces of evidence suggest that fine-tuning of brain Rho GTPases activation by the bacterial toxin CNF1 rescues the neurobehavioral phenotype in MeCP2-308 mice, as model of Rett syndrome (RTT). Indeed, a single intracerebroventricular CNF1 injection in symptomatic RTT mice of both sexes has been proved to revert motor and cognitive impairments and the main deficits in the brain (such as atrophy in astrocytes population, abnormal IL-6 cytokine levels, bioenergetics and mitochondria dysfunctions, amongst others), thus suggesting the use of CNF1 as a totally innovative therapeutic approach for RTT. However, one of the main translational issues concerning the use of CNF1 toxin as a drug is that such protein is not able to penetrate the blood-brain barrier (BBB) by itself and intracerebroventricular injections are thus needed to reach the brain district.
Here we describe an innovative approach to the construction of highly specific and effective drug delivery system represented by protein-only entities, in which the therapeutic protein agent itself is fused to selected protein sequences, which promote protein-protein interactions in absence of unspecific aggregation. The resulting CNF1 nanoparticles are expected to be better suitable for blood administration than the monomeric form. Furthermore, CNF1 nanoparticles may be enriched with BBB crossing peptides, thus addressing the brain region and retaining the original therapeutic/activity profile of the wild type protein agent. This highly attractive nanotechnological application is made possible thanks to the availability of many microbial organisms successfully used as cell factories. Recent results from our research network will be presented and discussed.

Selected references

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