The Cytotoxic Necrotizing Factor 1 (CNF1) increases brain energy level, counteracts neuroinflammatory markers and rescues cognitive deficits in a murine model of Alzheimer's disease

S. Loizzo[1], R. Rimondini[2], S. Travaglione[1], A. Fabbri[1], M. Guidotti[3], A. Ferri[4], G. Campana[5], C. Fiorentini[1]
[1]Dept. of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità, Rome, Italy, [2]Dept. of Medical and Clinical Sciences DIMEC, University of Bologna, Bologna, Italy,[3]Dept. of Veterinary Public Health and Food Safety, Istituto Superiore di Sanità, Rome, Italy, [4]Institute of Cellular Biology and Neurobiology, CNR, [5]Dept. of Pharmacy and Biotecnology FaBiT, University of Bologna

Overexpression of pro-inflammatory cytokines and cellular energy failure are associated with neuroinflammatory disorders, such as Alzheimer's disease. Transgenic mice homozygous for human ApoE4 gene, a well known AD and atherosclerosis animal model, show decreased levels of ATP, increased inflammatory cytokines level and accumulation of beta amyloid in the brain. All these findings are considered responsible for triggering cognitive decline. Recently, we have demonstrated that an *Escherichia coli* protein toxin, named Cytotoxic Necrotizing Factor 1 (CNF1), improves the mitochondrial activity and regulates pro-inflammatory cytokines levels in a mouse model of Rett's syndrome. These effects, accompanied by a long-lasting amelioration of cognitive performances, were strictly Rho GTPases-dependent. The Rho GTPases, ubiquitously expressed molecular switches that cycle between a GDP-bound inactive and a GTP-bound active state in eukaryotic cells, encompass the three subfamilies Rho, Rac and Cdc42 that control different signalling pathways. All of them are constitutively activated by CNF1 through deamidation of a critical glutamine residue that lock them in their activated, GTP-bound state. In the present work, we have demonstrated that a a single dose of intracerebroventricular (icv) administration of CNF1 to aged apoE4 mice, beside inducing a strong amelioration of both spatial and emotional memory deficits, favored the cell energy restore through an increment of ATP content. This was accompanied by a modulation of cerebral Rho and Rac1 activity. Furthermore, CNF1 decreased the levels of beta amyloid accumulation and interleukin-1ß expression in the hippocampus. It is noteworthy that all these aspects are connected with Rho GTPases' activity and considered crucial markers in AD mouse models. Altogether, these data suggest that the pharmacological modulation of Rho GTPases by CNF1 can improve memory performances in an animal model of Alzheimer's disease *via* a control of neuroinflammation and a rescue of systemic energy homeostasis.