TARGETING BRAIN RHO GTPASES IN RETT SYNDROME: PRECLINICAL EVIDENCE OF THERAPEUTIC EFFECTS

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Rho GTPases are a group of proteins with a well-established role as regulators of actin cytoskeleton dynamics in response to extracellular stimuli. Consistent with their involvement in neurobiological processes related to cognition and synaptic plasticity, mutations in genes encoding for several regulators and effectors of the Rho GTPases underlie various forms of intellectual disabilities (ID). Based on this evidence, in the last few years we have investigated whether the activation of brain Rho GTPases rescues the neurobehavioral phenotype in a mouse model of Rett syndrome (RTT). Our first approach consisted of a single intracerebroventricular injection of CNF1, a bacterial protein produced by several strains of *Escherichia coli*, able to enter cells and to specifically activate the Rho GTPases Rho, Rac, and Cdc42 (De Filippis et al., 2012). We found that RTT-related phenotypic and molecular alterations as well as brain mitochondrial dysfunction can be rescued by modulation of Rho GTPases by CNF1. Recently, we have extended these findings by demonstrating the activation of Rho GTPases in mouse brain by intraperitoneal administration of LP-211, a selective and brain penetrant serotonin receptor 7 agonist. This treatment restores behavioural and synaptic plasticity deficits and rescues molecular alterations in the brain of a RTT mouse model (De Filippis et al., 2014). These results pave the way to innovative therapeutic approaches for RTT targeting brain RhoGTPases.

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