Translational Medicine @ UniSa - ISSN 2239-9747 2019, Special Issue 1(14): 14

OC.10-NEUROPROTECTIVE ROLE OF HRP-2/SYNCRIP IN A C.ELEGANS MODEL OF SPINAL MUSCULAR ATROPHY

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SMN1 is the gene responsible for Spinal Muscular Atrophy (SMA), a devastating neuromuscular disease characterized by progressive and selective degeneration of lower motor neurons (MNs), leading to muscle atrophy and death of patients. SMA has been extensively studied, but the molecular mechanisms leading to MNs degeneration are still unknown. Therefore, animal SMA models are crucial to understand the pathogenesis of the disease and the functions played by SMN. In C.elegans, as in all models, SMN ortholog (smn-1) full depletion causes strong larval lethality and impaired locomotion. We overcame smn-1 KO pleiotropic effects by silencing smn-1 only in 19 MNs (Gallotta et al., HMG 2016) and we observed an age-dependent degeneration and neuronal death that mimic the key features of SMA pathology. Hence, we used our SMA model as a tool to identify new neuroprotective modifiers, genetically interacting with smn-1 in the MNs. By RNA sequencing of SMA patients-derived iPSC we identified SYNCRIP, a heterogeneous nuclear ribonucleoprotein, as a new modifier of SMN function. SYNCRIP, similarly to SMN1, is part of the spliceosome and is involved in pre-mRNA processing and transport. SYNCRIP homolog in C. elegans is hrp-2, a gene expressed in all tissues, including MNs. We demonstrated that HRP-2/SYNCRIP overexpression in neurons is able to partially rescue, in vivo, the neurodegeneration, the neuronal death and the defects in locomotion observed in our model (Rizzo et al., Brain under revision). Our results strongly suggest SYNCRIP as a new potential target for innovative combinatorial therapeutic approaches for SMA.