Study of neuron-astrocyte interaction using multi-modal integrated bioinformatics workflow identifies a new potential therapeutic target for ALS

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A new therapeutic target for **Amyotrophic Lateral Sclerosis (ALS)** has recently been identified, the Tumor Necrosis Factor Receptor Superfamily member 21 (TNFRSF21), also known as death receptor-6 (**DR6**). This study was conducted by researchers from the **Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center and University of Milan** in collaboration with **Columbia University (New York)**, and was published in the November issue of eminent **Nature Communications** journal.

Neurodegenerative diseases such as ALS are characterized by the selective death of motor neurons in the Central Nervous System. These cells control the activity of skeletal muscles and the death of motor neurons result in the loss of voluntary movement. Therefore, this disease leads to muscular weakness, atrophy, dysphagia, dysarthria and dyspnea with premature death. To date, there is no therapy available for ALS.

Currently the mechanisms underlying the selective degeneration of motor neurons are not completely understood, but an important role could be played by cell-cell interactions. In this study an analytical pipeline (SEARCHIN) was used for the identification of ligand-receptor candidates, which through the use of analytical and proteomics data is able to provide the most likely ligand-receptor interactions that mediate the pathophysiological phenotype.

For this study we also used the co-cultures technique between astrocytes from ALS mouse model, which express mutant superoxide dismutase-1 (mutSOD1) and exert a toxic effect on motor neurons through an unknown mechanism. Through the use of proteomics and regulatory network analysis, it was possible to identify a candidate ligand-receptor responsible for motor neuronal degeneration, the amyloid precursor protein (APP)

released by astrocytes and DR6 present on motor neurons surface. This thesis was further confirmed by *in vivo* experiments. Indeed, the silencing of DR6 in the motor neurons of mutSOD1 transgenic mouse models leads to an amelioration of the pathological phenotype.

Although these results are promising, a deeper knowledge of the molecular mechanisms underlying the effects of DR6 is required in order to translate its therapeutic modulation to patients. These results have shown how an integrative approach can provide important information on neurodegenerative diseases. Therefore, the SERCHIN strategy should be taken into consideration, for the identification of new therapeutic targets for ALS.

Prof. Corti, M.D., Ph.D., PI of the Neural Stem Cell Laboratory in the Neuroscience Division, at the Department of Pathophysiology and Transplantation (UNIMI), is co-author of the research. The research group included **Dr. Nizzardo**, PhD, and **Dr. Rinchetti**, PhD, members of Corti lab and researchers of the **Foundation IRCCS Ca' Granda, Ospedale Maggiore Policlinico**, Centro Dino Ferrari, University of Milan. This study was supervised by **Prof. Przedborski** at the Motor Neuron Center, Columbia University, a long-time collaborator of Corti's group.

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