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Transplanted ALDHhiSSClo Neural Stem Cells Generate Motor Neurons and Delay Disease Progression of nmd Mice, an Animal Model of SMARD1.

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Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is an infantile autosomal recessive motor neuron disease, caused by mutations in the Immunoglobulin micro-binding protein 2 (IGHMBP2). We investigated the potential of a spinal cord neural stem cell population isolated on the basis of aldehyde dehydrogenase activity (ALDH) to modify disease progression of nmd mice, an animal model of SMARD1. ALDH(hi)SSC(lo) stem cells are self-renewing and multipotent and when intratechally transplanted in nmd mice generate motor neurons properly localized in the spinal cord ventral horns. Transplanted nmd animals presented delayed disease progression, sparing of motor neurons and ventral root axons and increased life-span. To further investigate the molecular events responsible for these differences, microarray and Real time RT-PCR analysis of wild-type, mutated and transplanted nmd spinal cord were undertaken. We demonstrated a down-regulation of genes involved in excitatory amino acid toxicity and oxidative stress handling, as well as an up-regulation of genes related to the chromatin organization in nmd compared to wild-type mice, suggesting that they may play a role in SMARD1 pathogenesis. Spinal cord of nmd transplanted mice expressed high transcript levels for genes related to neurogenesis such as Doublecortin (DCX), LIS1 and drebrin. The presence of DCX-expressing cells in adult nmd spinal cord suggests that both exogenous and endogenous neurogenesis may contribute to the observed nmd phenotype amelioration.

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