P-33

In Vivo Reprogramming Using SOX2 in the CNS

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INTRODUCTION

Central nervous system diseases, particularly neurodegenerative disorders, pose significant challenges in medicine. These conditions, characterized by progressive neuronal loss, have remained largely incurable, exacting a heavy toll on individuals and society. In recent years, in vivo reprogramming using SOX2 has emerged as a promising approach for central nervous system regeneration.

METHODS

We conducted an extensive search of published scientific literature in databases including MEDLINE, EMBASE, Web of Science, and SCOPUS using the following search strategy until 1 November 2023: [((in vivo) OR (in situ)) AND (reprogramming) AND ((brain) OR (spinal cord)] AND ((sox2))]. Only the titles, abstracts, or keywords were searched in SCOPUS. We applied no language restrictions in our search. To identify duplicate entries, we considered factors such as the author, publication year, article title, and the source's volume, issue, and page numbers. Our search included studies of all types, including descriptive studies and case reports. Additionally, we manually reviewed the bibliographies of selected articles.

RESULTS AND CONCLUSIONS

In vivo studies have demonstrated the potential of Sox2 to reprogram non-neuronal cells into neurons in the brain and spinal cord. Sox2 alone can induce the transformation of astrocytes and NG2 glial cells into DCX+ neuroblasts and neural progenitors, showing proliferative activity and the ability to progress towards neuronal maturation with the addition of factors like BDNF, Noggin, and VPA. However, Sox2 by itself is insufficient for complete neuronal maturation into Neun+ neurons. Further enhancement of neuronal integration and functionality has been observed with additional treatments, indicating the importance of supplementary factors for full differentiation and integration into neural circuits. Studies also show that Sox2 reprogramming can reduce scar formation and improve functional recovery in spinal cord injury models, with potential implications for treating neurodegenerative diseases and injuries. Safety studies up to 50 weeks post-Sox2 injection have not observed tumor formation, highlighting its potential safety for therapeutic applications.

Reprogramming Factors	Expression Location	Animal Model /Lesion Model	Animal Age (Time of Reprogramming *)	Delivery Methods		Target Cell (Markers)	Functional Outcome
Sox-induced in vivo brain reprogramming							
Sox2 + BNDF/noggin or VPA	Striatum	C57BL/6J and ICR mice hGFAP–Cre, mGfap–Cre line 77.6, Nes–CreERTM, NG2–Cre, PrP–CreERT, Rosa–YFP, Rosa–tdTomato (Ai14)	Between 6 weeks and 24 months	Lentivirus	Stereotactic injection	Neuron (NeuN)	Functional electrophysiology
Sox2	Striatum	C57BL/6 and ICR mice Tlxflox/flox mice transgenic pGFAP-Cre mice	Not mentioned	Lentivirus	Stereotactic injection	Neuron (DCX)	
Sox2/VPA	Striatum	Cst3-CreERT2, Nes-CreERTM, Ascl1-CreERT2, Ascl1neoflox/neoflox, Rosa-YFP, and Rosa-tdTomato	2–6 months of age	Lentivirus	Stereotactic injection	Neuron (NeuN, Calretrin)	
Sox2 + Nurr1 + Lmx1a + Foxa2 + VPA	Striatum	C57BL/6J mice mGfap-Cre line 77.6, PrP-CreERT, Pdgfra-CreERT, Dat-Cre, and Rosa-tdTomato (Ai14)	6 weeks to 24 months	Lentivirus	Stereotactic injection	Dopaminergic neuron	Electrophysiological Properties and firing patterns, network connectivity
Sox2 ± ASCL1	Cerebral cortex	C57BL/6J mice Sox10-iCreERT2/GFP or GLASTCreERT2/GFP mice / Stab Wound Lesion	8–10 weeks old (3 days after stab wound injury)	Retrovirus Lentivirus	Stereotactic injection	Neuron (DCX, NeuN)	
Sox2	Corpus callosum(left)	C57BL/6J mice / Demyelination induced by 0.2% Cuprizone in diet chow	12 weeks old	Lentivirus	Stereotactic injection	Oligodendrocyte precursor cells (PDGFRα+) oligodendrocytes	

Reprogramming Factors	Expression Location	Animal Model /Lesion Model	Animal Age (Time of Reprogramming *)	Delivery Methods		Target Cell (Markers)	Functional Outcome
Sox-induced in vivo spinal cord reprogramming							
Sox2/VPA	Spinal cord	C57BL/6J and the immunodeficient NSG mice / hemisection at the T8 level	2–3 months of age ((immediately after hemisection)	Lentivirus	Manual injection (into the spinal cord parenchyma at each of the two locations 3 mm apart at the T8)	Neuron (NeuN, MAP2), Synapse-forming GABAergic interneurons	
Sox2	Spinal cord	C57BL/6J mice Ptenflox, p53flox, p21 KO, mGfap-Cre line 77.6, Thy1-STOP-YFP, Rosa-tdT / contusion injury at the T7–9 level	8 weeks and older	Lentivirus	Manual injection (into the spinal parenchyma at each of the two locations 2 mm apart at the T8 level)	Neuron (NeuN, MAP2)	
Sox2	Spinal cord	ICR mice / Completely compression for 5 s at T10 level	8 weeks old (1 week after SCI)	Adenovirus	Manual injection (1.0 mm caudal and rostral to the lesion site)	Neuron (Nissl and βIII-tubulin)	Behavioral test (BMS score, Running wheel test, Swimming test, Inclined plate test, Mechanical allodynia test)
Sox2	Spinal cord	C57BL/6J mice Rosa-YFP, Rosa-tdT, Sox2f/f, Pdgfra-CreER™, Ascl1-CreERT2, Nes-CreERT2, Foxj1-CreERT2, Rosa-TVAg mouse line / dorsal hemisection at the C5 level	2 months of age and older	Lentivirus	Manual injection (0.5 mm rostral and caudal to the incision, bilaterally)	Neuron (NeuN, VGLUT2, GAD6, VGAT)	Behavioral test (Grid-walking test)