Expression of FGF-2 in neural progenitor cells enhances their potential for cellular brain repair in the rodent cortex

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INTRODUCTION

Neural progenitor cells (NPC) transplanted in vivo into the cerebral cortex have shown to have a limited migration potential. This is a major drawback in using NPC for structural brain repair strategies. Fibroblast growth factor-2 (FGF-2) plays a critical role to maintain NPC in an immature state and this is required for the directed migration of these cells towards VEGF in vitro. Here, we tested the hypothesis that over-expression of FGF-2 in NPC could be an effecient approach to increase the invasive properties of these cells in the normal as well as in the ischemic rat brain cortex.

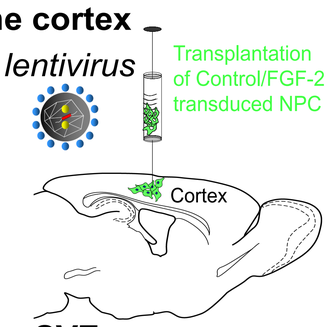
METHODS

NPC isolated from the SVZ of PO pups are transduced with a lentiviral vector carrying FGF-2 and GFP:

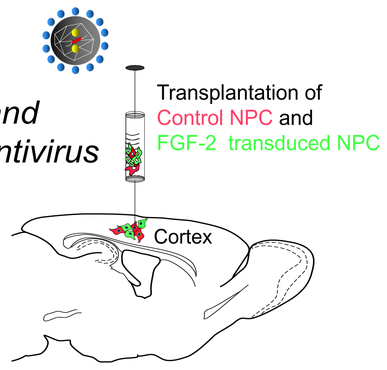
In vivo transplantation of NPC at P3 :

(1) In the cortex

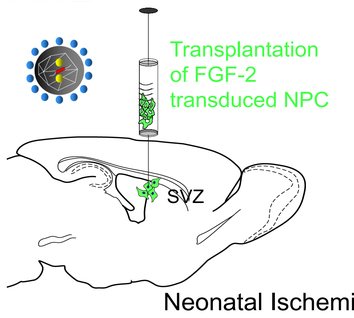
(I) GFP lentivirus



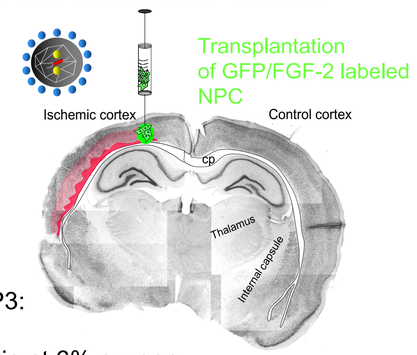
(II) GFP and tomato lentivirus



(2) In the SVZ



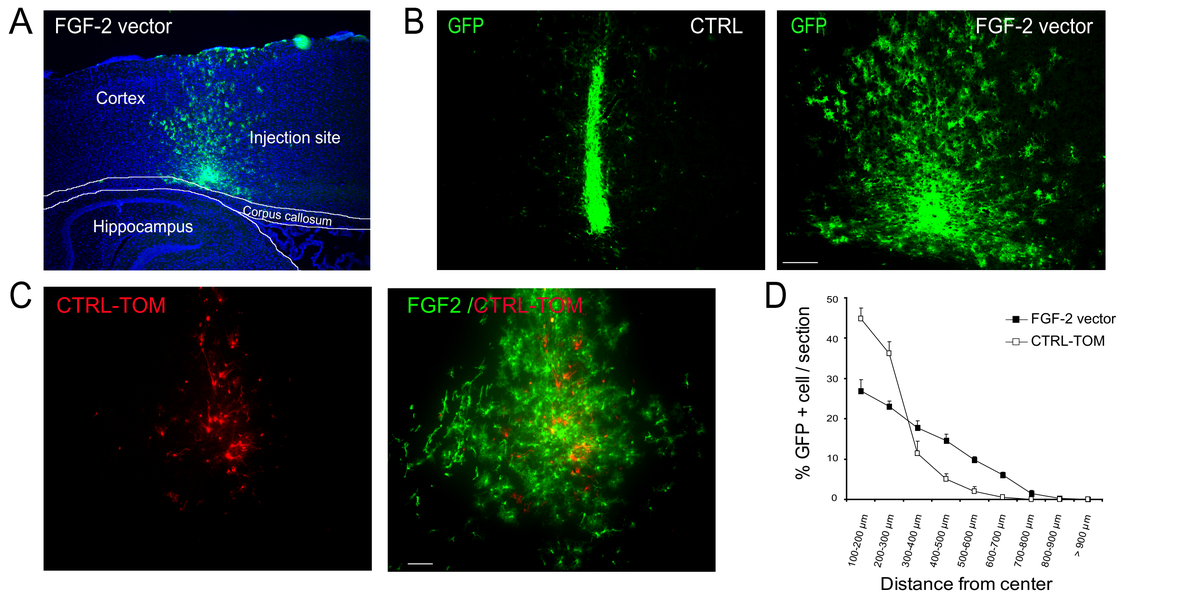
(3) In the ischemic cortex



Neonatal Ischemic model at P3:
Right carotid artey ligation
followed by 30 min of hyopoxia at 6% oxygen

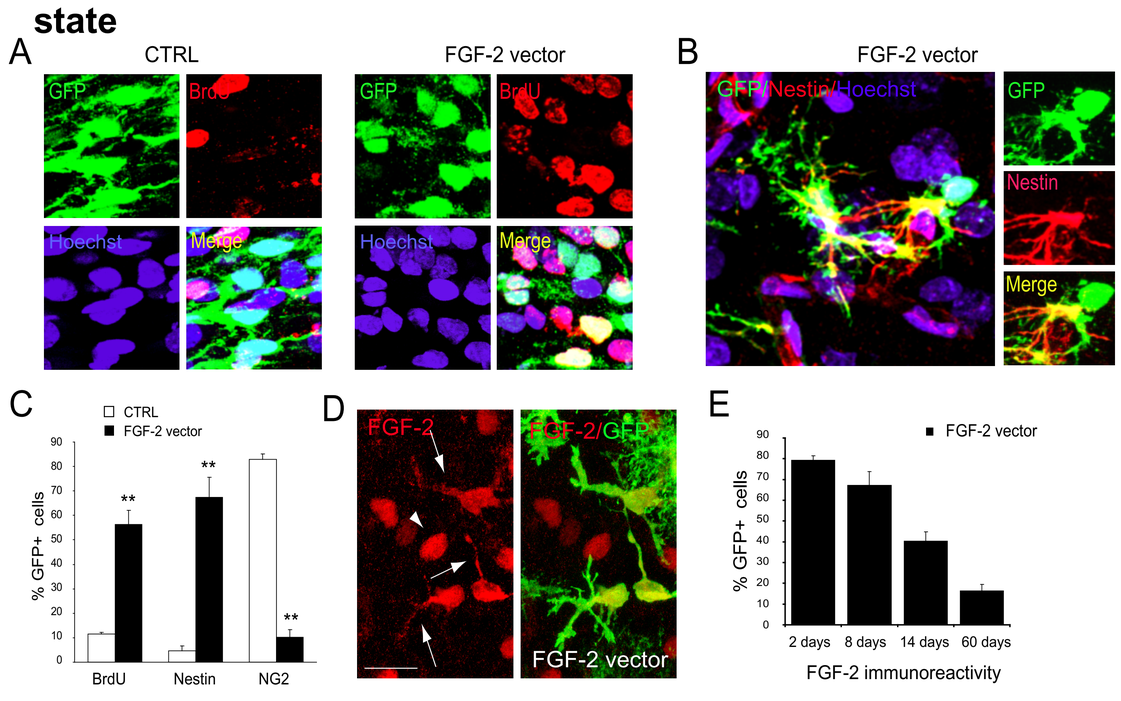
Rats are perfused after 1 week for BrdU analysis or after 2 weeks.

1. In the cortex FGF-2 transduced NPC disperse better



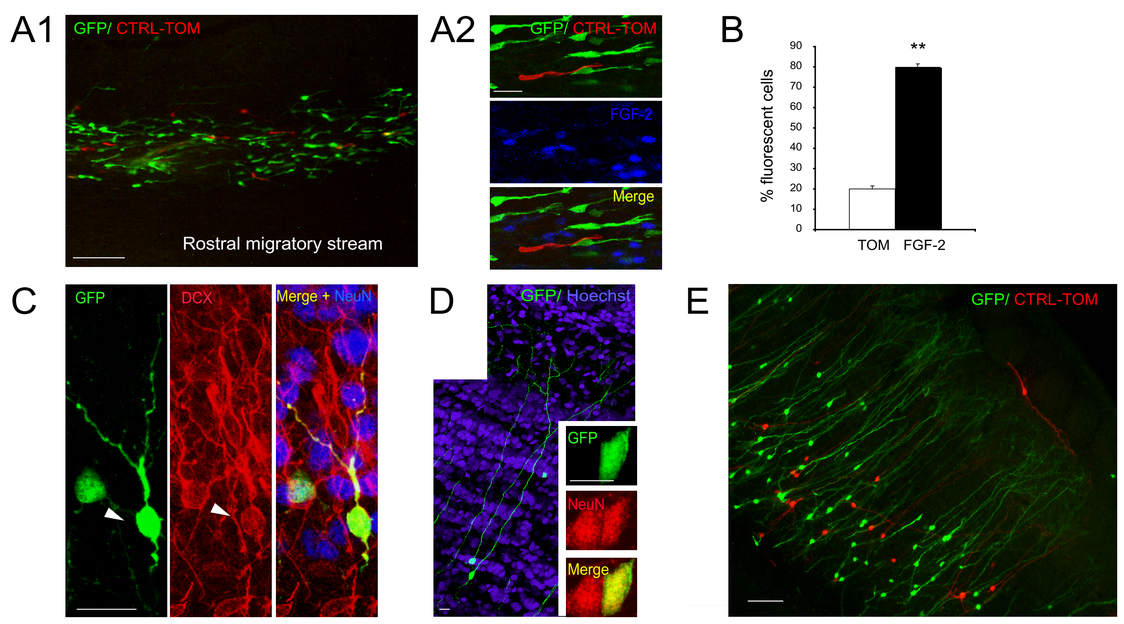
(A) Site of transplantation. (B) Dispersion of NPC 2 weeks after transplantion. (C) Increased dispersion of (green) FGF-2 NPC compared to (red) control tomato labeled NPC. (D) Graph showing increased dispersion of FGF-2 NPC 8 days after transplantation *(P<0.001).*

2 . Increased migration of FGF-2 NPC is associated with an immature state



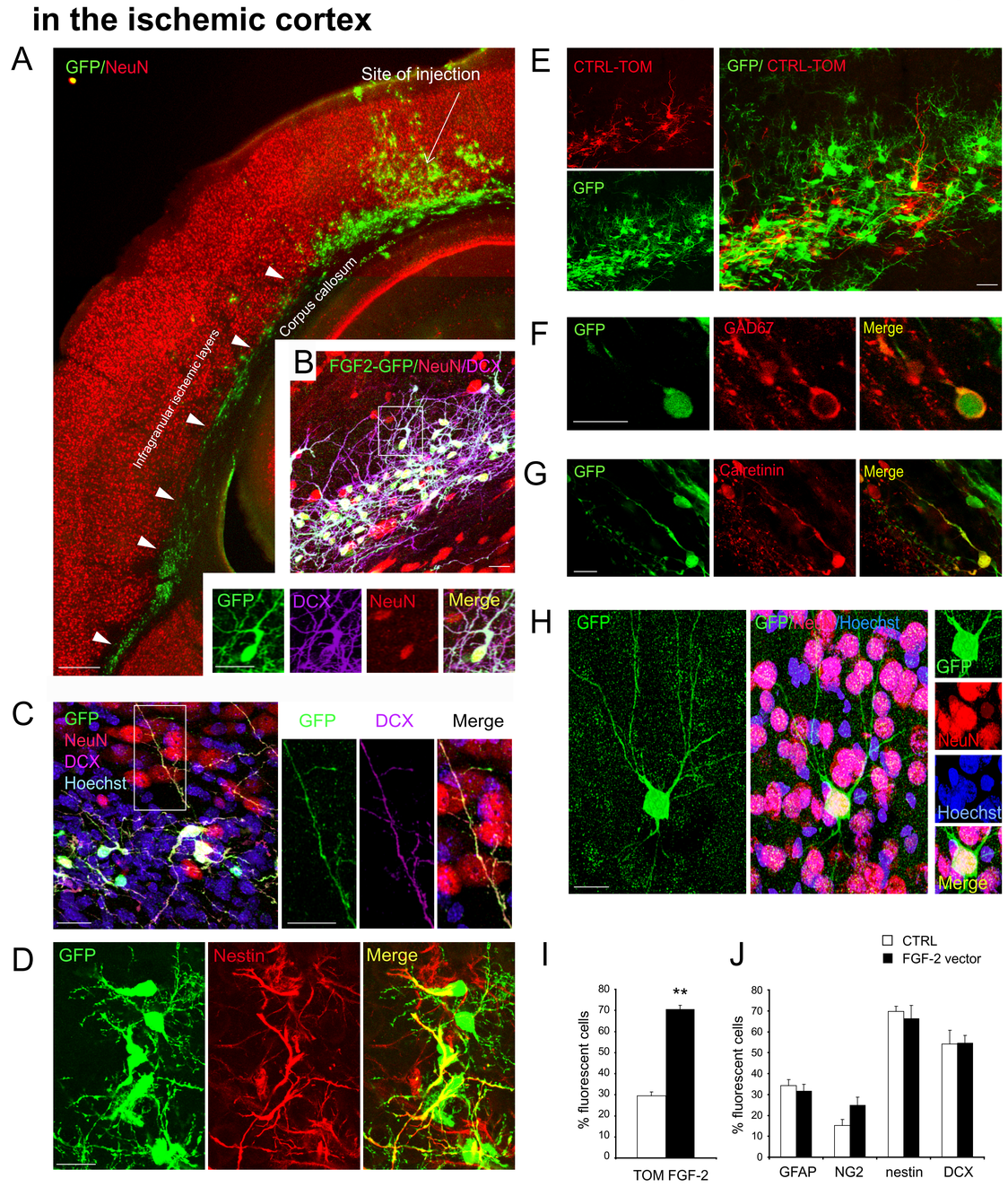
Higher fraction of (A) BrdU positive and (B) nestin positive FGF-2 NPC, showed on the graph (C) two weeks after transplantation *(**P<0.005, t-test).* (D) Nuclear and cytoplasmic FGF-2 immunoreactivity of FGF-2 transduced NPC, with time dependent regulation (I).

3. FGF-2 transduction increases the pool of grafted neurons in the olfactory bulb



(A1 and A2) Green FGF-2 and red control tomato FGF-2 NPC migrate inthe RMS and become neurons in the olfactory bulb (C and D). (B and E) The proportion of FGF-2 neurons is isgnificantly increased compared to control neurons *(** P<0.001, t-test).*

4. FGF-2 transduction increases the pool of grafted neural progenitors in the ischemic cortex



(A) One month after transplantation FGF-2 NPC have migrated in the ischemic infra-granular layer (white arrow), become new neurons (B) with DCX positive processes (C). (D) FGF-2 NPC still express nestin. (E) The pool of FGF-2 NPC is significantly higher than red control NPC. FGF-2 NPC express GAD67 (F), Calretinin (H) and NeuN with more mature morphology (H). (I) The proportion of FGF-2 NPC is higher than control NPC *(**P<0.001, t-test)* and both differentiate into GFAP, NG2, nestin and DCX positive cells.

CONCLUSION

These results reveal an important role for FGF-2 in regulating NPCs function when interacting with the host tissue after transplantion and offer a potential strategy to generate a robust source of migratory and immature progenitors for repairing a neonatal iscemic cortex.