# The effects of SDF-CXCR4 signaling on tumor growth: the involvement of neural progenitor cells

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## Introduction

Neural progenitor cells (NPCs) tend to migrate specifically to sites of CNS injuries. Such behavior is mediated by the signaling of the chemokine SDF-1 and its receptor CXCR4 **[1]**. Glioma releases high levels of SDF-1, which may attract the migration of NPCs, which express CXCR4 intrinsically **[2]**. The migration of NPCs toward gliomas may change the growth pattern of a tumor.

To test the possibility, the present study examined whether NPCs migration facilitated by the SDF-1/CXCR4 signaling affected the growth of tumors. NPCs were transplanted into the lateral ventricle while an injection of SDF-1 was made near the tumor site. T2-weighted imaging (T2WI) was repeatedly acquired to monitor the growth of tumors before, and after the treatment. Our investigations directly provide evidence regarding the role of NPCs in tumor expansion.

## Material and Methods

Pregnant Sprague–Dawley rats (National Laboratory Animal Center, Taiwan) were injected intraperitoneally with 50 mg/kg ethylnitrosourea (ENU) (Sigma) at 18–19 days of gestation. The offspring generated brain tumors spontaneously as early as 3 month old. NPCs were prepared from primary subventricular zone (SVZ) cells as described in the below. The brain of SD neonatal rat was taken off and the tissues nearby SVZ were collected. The tissues were mechanically dissociated, filtered, and seeded in the serum free medium. The cell density was $1.5*10^6$ cells/ml and cultured condition was controlled at 37℃, 5% $CO_2$ with humidity. The NPCs gradually developed to neurospheres and were then passaged to single cells when the average diameter reached 150um. NPCs were transplanted to the lateral ventricle (Bregma = -0.5 mm; Lateral = 1.5 mm; Depth 3.5 mm.) ipsilateral to the tumor location and SDF-1 was injected near the tumor site. The injected NPCs were $1*10^6$ cells at 1 ul and the SDF-1 concentration was 10 $\mu$g/ml. The rats were scanned for tumors by a 7-T MRI system. Rats were fitted in a custom designed headholder and anesthetized with isoflurane flowed in oxygen (isoflurane at 5% for induction and 2% for maintenance). T2WIs were acquired using a fast spin echo sequence, with a field of view of 3 cm, slice thickness of 1 mm, 28 slices with no gap to cover the entire brain, a TR of 5100 msec, a TE of 70 msec, echo train length of 8, number of excitations being 6, and a matrix size of 256*256. Rats detected with tumors by T2WI were subject to the transplantation of NPCs combined with SDF or vehicles of both. The scan time points were Day0 (before the injection), Day7, Day14, Day28, and Day42. Because tumors are readily distinguishable from surrounding tissues owing to the hyper/hypo signal intensities, the measurement of tumor volume was based upon the summation of these pixels using MR Vision (MR Vision Co.). The doubling time (Td) of the tumor was calculated by customized Matlab codes.

## Results and discussion

The combinative treatment of NPCs and SDF altered the growth pattern of the tumor significantly (n=4). Fig.1 shows a representative example of a rat transplanted with NPC and SDF, and monitored for 6 weeks. The upper, middle and bottom rows correspond to three slices along the anterior-posterior axis. Arrows indicate the tumor location. As seen in Fig.1, the tumor was only detected as a small area of hyperintensity at baseline in the middle slice. With time, the tumor gradually expanded, and extended to the more frontal and posterior slices. The volume of the tumors was plotted against time, and displayed in Fig. 2. The transplanted and sham rats showed very different tumor growing patterns. The Td was 15.30 ± 0.16 days for the SDF-NPC group and 59.61 ± 11.69 days for the sham group. Our finding supports a view that, when the migration of transplanted cells is promoted via the SDF-1/CXCR4 signaling, it may lead to rapid growth of tumors.

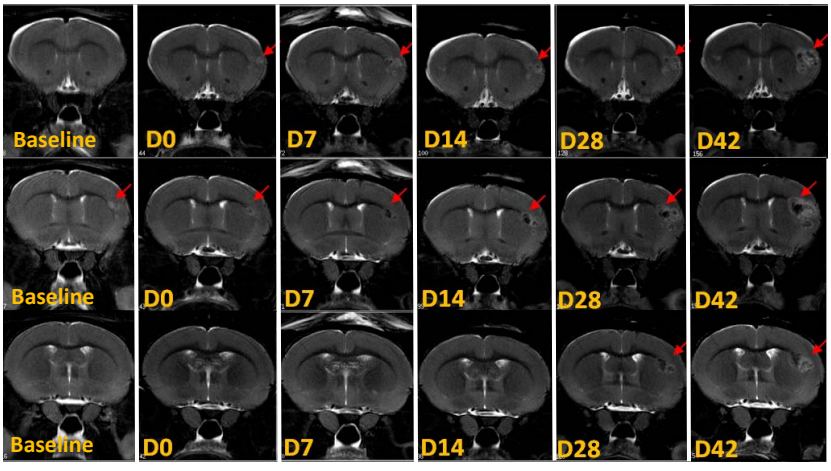


Fig. 1

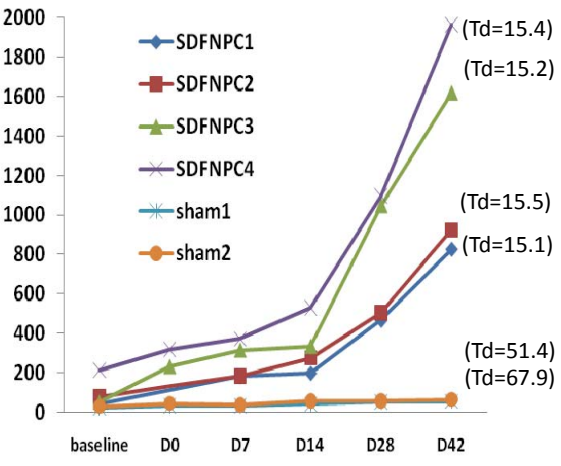


Fig. 2

**Reference:[1]** Imitola J et al., *Proc. Natl. Acad. Sci.*,101;18117–18122, 2004. **[2]** Zhao D et al., *Mol Cancer Res*.,6;1819-1829, 2008.