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1: [PLoS ONE](#). 2009;4(2):e4434. Epub 2009 Feb 11.



## **Tumorigenic potential of olfactory bulb-derived human adult neural stem cells associates with activation of TERT and NOTCH1.**

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**BACKGROUND:** Multipotent neural stem cells (NSCs) have been isolated from neurogenic regions of the adult brain. Reportedly, these cells can be expanded in vitro under prolonged mitogen stimulation without propensity to transform. However, the constitutive activation of the cellular machinery required to bypass apoptosis and senescence places these cells at risk for malignant transformation. **METHODOLOGY/PRINCIPAL FINDINGS:** Using serum-free medium supplemented with epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF), we established clonally derived NS/progenitor cell (NS/PC) cultures from the olfactory bulb (OB) of five adult patients. The NS/PC cultures obtained from one OB specimen lost growth factor dependence and neuronal differentiation at early passage. These cells developed glioblastoma tumors upon xenografting in immunosuppressed mice. The remaining NS/PC cultures were propagated either as floating neurospheres or as adherent monolayers with maintenance of growth factor dependence and multipotentiality at late passage. These cells were engrafted onto the CNS of immunosuppressed rodents. Overall, the grafted NS/PCs homed in the host parenchyma showing ramified morphology and neuronal marker expression. However, a group of animals transplanted with NS/PCs obtained from an adherent culture developed fast growing tumors histologically resembling neuroesthesioblastoma. Cytogenetic and molecular analyses showed that the NS/PC undergo chromosomal changes with repeated in vitro passages under mitogen stimulation, and that up-regulation of hTERT and NOTCH1 associates with in vivo tumorigenicity. **CONCLUSIONS/SIGNIFICANCE:** Using culturing techniques described in current literature, NS/PCs arise from the OB of adult patients which in vivo either integrate in the CNS parenchyma showing neuron-like features or initiate tumor formation. Extensive xenografting studies on each human derived NS cell line appear mandatory before any use of these cells in the clinical setting.

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