Biomaterial microenvironments to support the generation of new neurons in the adult brain.

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Public Summary:
Neural stem cells (NSC) in two regions of the adult mammalian brain continuously generate new neurons throughout human life, and they can potentially be harnessed for neurogeneration. Their behavior is regulated by a complex repertoire of signals that precisely regulate the activation, proliferation, differentiation, and integration of the newborn cells. We have explored whether implantation of engineered biomaterials can stimulate the generation of new neurons in normally quiescent regions of the brain. In this engineered biomaterial microenvironment, new neuron formation was observed in normally non-neurogenic regions of the brain. Additionally, the decreased neurogenesis in the hippocampus of aged rodents was partially rescued toward levels of young animals. We thus demonstrate for the first time de novo neurogenesis stimulated solely by delivery of synthetic biomaterial forms of proteins naturally found within adult neurogenic regions, offering the potential to replace neurons lost in neurodegenerative disease or injury as an alternative to cell implantation.

Scientific Abstract:
Neural stem cells (NSC) in two regions of the adult mammalian brain-the subventricular zone (SVZ) and hippocampus-continuously generate new neurons, enabled by a complex repertoire of factors that precisely regulate the activation, proliferation, differentiation, and integration of the newborn cells. A growing number of studies also report low-level neurogenesis in regions of the adult brain outside these established neurogenic niches-potentially via NSC recruitment or activation of local, quiescent NSCs-under perturbations such as ischemia, cell death, or viral gene delivery of proneural growth factors. We have explored whether implantation of engineered biomaterials can stimulate neurogenesis in normally quiescent regions of the brain. Specifically, recombinant versions of factors found within the NSC microenvironment, Sonic hedgehog, and ephrin-B2 were conjugated to long polymers, thereby creating highly bioactive, multivalent ligands that begin to emulate components of the neurogenic niche. In this engineered biomaterial microenvironment, new neuron formation was observed in normally non-neurogenic regions of the brain, the striatum, and the cortex, and combining these multivalent biomaterials with stromal cell-derived factor-1alpha increased neuronal commitment of newly divided cells seven- to eightfold in these regions. Additionally, the decreased hippocampal neurogenesis of geriatric rodents was partially rescued toward levels of young animals. We thus demonstrate for the first time de novo neurogenesis in both the cortex and striatum of adult rodents stimulated solely by delivery of synthetic biomaterial forms of proteins naturally found within adult neurogenic niches, offering the potential to replace neurons lost in neurodegenerative disease or injury as an alternative to cell implantation. Stem Cells 2014;32:1220-1229.