Molecules that Enhance Axonal Sprouting and Recovery after Stroke

Stroke induces a process of axonal sprouting. Studies indicate that the cell bodies of neurons that give rise to axonal sprouting after stroke are located in two places: neurons in cortex near the stroke site and neurons in cortex in the hemisphere opposite to the stroke (Zhang and Chopp., '09; Murphy and Corbett, '09; Benowitz and Carmichael, '10; Overman et al., '12). Axonal sprouting from both cortical sites establishes new patterns of connections (Carmichael et al., '01; Zhang and Chopp, '09; Murphy and Corbett, '09; Brown et al., '09; Benowitz and Carmichael, '10; Overman et al., '12). Axonal sprouting from cortex contralateral to the stroke is correlated with functional recovery in rodent stroke models and the study of contralateral axonal sprouting is a valid research approach. This talk will focus on axonal sprouting and neuroplasticity in peri-infarct cortex for three reasons. First, in human stroke it is plasticity in sensory, motor and language maps in cortex ipsilateral to the stroke that is most closely correlated with improved functional recovery (Carmichael, '06; Ward and Frackowiack, '06; Kantak et al., 12; Rehme et al., '12). Transfer of brain mapping functions to the contralateral hemisphere is associated with poor recovery in humans and in fact inactivating the output of contralateral cortical areas with transcranial magnetic or direct current stimulation has been proposed as a therapy for stroke recovery (Wittenberg, '10; Rehme et al., '12). Second, this same phenomenon is seen in rodent stroke models, where transfer of sensory maps to the contralateral hemisphere occurs with large strokes and is not associated with as much functional recovery as when sensory maps reorganize in cortex on the same side as the stroke (Dijkhuizen et al., '01; van Meer et al., '12). Third, we have recently produced detailed and quantitative maps of axonal sprouting in two mouse stroke models and shown that axonal sprouting occurs in motor, premotor and somatosensory peri-infarct areas after stroke and that a specific subset of these newly formed connections causally mediates behavioral recovery (Overman et al., '12).

A process of axonal sprouting in the adult cortex means that a fully differentiated neuron must receive a signal to sprout, activate a molecular growth program, and extend an axon. In vivo imaging of cortical indicates that these processes do not normally occur in adult cortex (Zuo et al., '05; Holtmaat et al., '06), so this is a novel molecular growth program that is activated in stroke. This talk will focus on the molecular control of axonal sprouting after stroke, how these molecules relate to motor recovery, and how these principles might lead to new pharmacological therapies for neural repair.

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