MOTOR CRC 1451

Motor Control Science Club, March 27, 2023, 5:00 PM CET

The lecture is open to everybody

New strategies to promote recovery after CNS injury

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Neurons of the adult mammalian central nervous system (CNS) do not normally regenerate injured axons causing severe and permanent disabilities, for example, after spinal cord injury. The lack of CNS regeneration is mainly attributed to a developmental decline in the neuron-intrinsic growth capacity of axons. Despite numerous efforts to facilitate axon regeneration, such as delivering neurotrophic factors or neutralizing inhibitory cues, success has remained very limited. In the optic nerve, activating the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathway stimulates the regeneration of CNS axons. JAK/STAT3 activation is achieved via the delivery of IL-6- type cytokines such as CNTF, LIF, IL-6, and/or the genetic depletion of the intrinsic STAT3 feedback inhibitor: suppressor of cytokine signaling 3 (SOCS3). However, the low and restricted expression of the cytokine-specific α-receptor subunits in CNS neurons required for signaling induction generally limits these pro-regenerative effects of native cytokines.
For this reason, we developed a gene therapeutic approach using the designer cytokine hyper-interleukine-6 (hIL-6), which consists of the bioactive part of the IL-6 protein covalently linked to the soluble IL-6 receptor α subunit. In contrast to native cytokines, hIL-6 can directly bind to the signal-transducing receptor subunit glycoprotein 130 (GP130), abundantly expressed by almost all neurons, thereby circumventing natural cytokines' limitations. We found that hIL-6 is reportedly as potent as CNTF but activates cytokine-dependent signaling pathways significantly stronger in different types of neurons because of its higher efficacy. In the visual system, virus-assisted gene therapy with hIL-6, even when applied only once post-injury, induces more robust optic nerve regeneration than previous approaches. Strikingly, a single unilateral injection of AAV-hIL-6 after SCC into the sensorimotor cortex promoted the regeneration of spinal cord axons and remarkably enabled locomotion recovery of both hindlimbs. Thus, transneuronal stimulation of neurons located deep in the brain stem using highly potent molecules might be a promising strategy to achieve functional repair in the injured or diseased human CNS.

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