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Treatment of nerve demyelinating diseases and remyelination: actions of interferon-β and of an interleukin-6 chimera

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Current therapy of Multiple Sclerosis

Loss of the myelin sheath around neurons in the brain and spinal cord underlies the pathology of Multiple Sclerosis (MS). Therapies aimed at reducing demyelination, which in MS results from an autoimmune process, have demonstrated clinical efficacy. Among such therapies, recombinant Interferon (IFN)-beta significantly slows down the progression of MS and decreases the number of relapses in both the relapsing-remitting phase of the disease and its more advanced secondary-progressive phase. Magnetic resonance imaging (MRI) demonstrates that IFN-beta strongly suppresses appearance of demyelinating lesions and the resulting cerebral atrophy. Nowadays over 100,000 MS patients are treated with IFN-beta (Rebil) or with Copaxone to slow down the disease.

Research is now directed at stimulating re-myelination, which could allow recovery of neurological functions in demyelinating diseases of the central (CNS) and peripheral (PNS) nervous systems. During the relapsing-remitting early stage of MS, remyelination is observed with good regression of neurological symptoms after attacks. In later stages, the ability to remyelinate is severely reduced, causing the irreversible neurological disabilities.

Switching-on differentiation of myelinating cells

Myelination is a function of differentiated glial cells: oligodendrocytes in the CNS and Schwann cells in the PNS. During embryonic development, these glial cells originate from neural crest cells (NCC), which migrate and become myelinating cells in the CNS and PNS. But NCC differentiate also in other directions, into melanocytes that pigment the skin and pigmented cells of the retina and the inner ear. The human genetic Waardenburg syndrome type 2 (WS2) is characterized by deafness with a defect in pigmented cells and the affected gene is the microphtalmia transcription factor MITF. This factor is crucial for the formation of melanocytes and pigmented cells without which the eye does not develop in the mouse embryo. MITF is overexpressed in malignant melanoma, a skin cancer resulting from abnormal melanocyte differentiation.

We recently discovered a molecular switch that converts a melanoma cell, producing skin melanin, into a glial cell producing myelin proteins. This trans-differentiation was achieved by a IL6RIL6 chimera formed by fusing Interleukin-6 (IL-6) and the soluble IL-6 receptor. IL6RIL6 is very efficient to trigger the cell surface gp130 receptor, and this causes repression of the MITF gene leading to a loss of tyrosinase and the other enzymes producing melanin pigments. The MITF gene promoter is positively regulated by cAMP and by Pax-3, a paired-homeodomain transcription factor active during embryogenesis. IL6RIL6 acts at least in part by reducing Pax-3. In humans, Pax-3 mutations also cause forms of the Waardenburg syndrome. Hence, the signals induced by IL6RIL6 act on genes that control the differentiation of embryonic neural crest cells, and switch this differentiation toward the myelinating glial function.

In normal dorsal root ganglia explants from mouse E14-E18 embryos (containing both neurons and glial cells but not yet myelinating), IL6RIL6 addition induces synthesis of myelin gene products such as the myelin basic protein (MBP), the Po and CNPase proteins, and promotes myelination of neuronal axons sprouting from the explants. On isolated Schwann cells cultures, IL6RIL6 induces myelin gene products and enhances attachment of these cells along axons when they are added to purified ganglionic neurons.

Remyelination after neural lesions

In vivo, the embryonic glial cells undergo a final maturation immediately after birth and then begin to actively myelinate the nerves. This maturation is reversible and, upon nerve damage, the glial cells cease to synthesize myelin while existing myelin sheaths are destroyed as a prerequisite for repair of nerve fibers. In sciatic nerve lesions, Schwann cells revert to an embryonic precursor state with expression of Pax-3 acting as a repressor of MBP gene expression. Since IL6RIL6 represses Pax-3 while inducing myelin genes, we are studying the effect of in vivo IL6RIL6 injections to rats with sciatic nerve sections. Preliminary electron microscopic results indicates increased remyelination in the distal sciatic nerve segment following traumatic demyelination (Fig. 1).

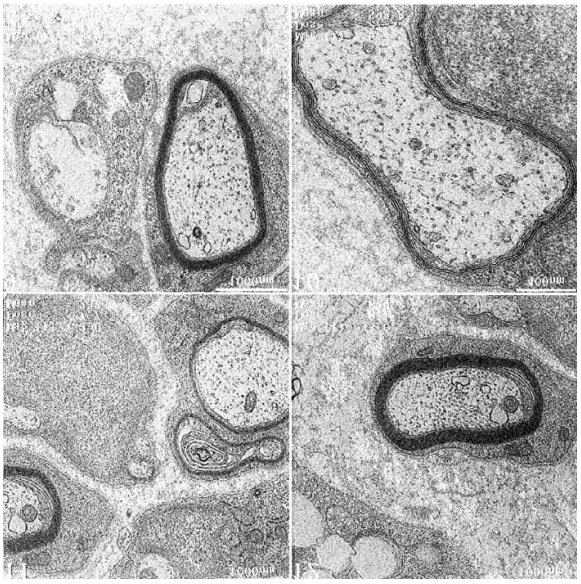

Fig. 1. *Remyelinating axons in sectioned rat sciatic nerve.*

A number of growth factors (such as neuregulins) and cytokines (such as ciliary neurotrophic factor, which also uses gp130 as part of its receptor system) control the proliferation and differentiation of Schwann cells and oligodendrocytes. The activity of the IL-6 chimera appears to be on the late transition from non-myelinating to myelinating phenotype. This new recombinant molecule may find applications, alone or in combination with other factors, for promoting remyelination of nervous tissues in demyelinating diseases and following nerve traumatisms. The IL-6 chimera has also neuroprotective action, which may contribute to nerve regeneration. It may also be used for ex-vivo culture of myelinating glial cells that could be transplanted into the brain or peripheral nerves as a mean to achieve remyelination in neurological diseases, including progressive MS.

Other applications of the IL-6 Chimera: Hematopoiesis and Liver cell protection

All types of blood cells in our body derive from a small pool of stem cells in the bone marrow stroma. Bone marrow transplantation (BMT) allows to reconstitute hematopoiesis in patients with leukemias or undergoing cancer chemotherapy. Since stem cells are rare, their expansion without loss of their pluripotential hematopoietic ability, would increase the efficacy of BMT.

Studies in collaboration with Dr Tsvee Lapidot's group (Department of Immunology) have shown that the IL6RIL6 chimera has a marked effect on the ability of human stem cells to engraft into NOD/SCID mice, whose immunodeficiency allows the engraftment of foreign human cells. Adding IL6RIL6 to ex-vivo cell cultures prior to transplantation, increased the efficacy of engraftment over that obtained with Stem cell factor and Flt-3 ligand (two major growth factors of stem cells). IL6RIL6 is particularly active on the most purified stem cell, allowing expansion without loss of engraftment potential. Applications of IL6RIL6 in clinical BMT and gene therapy are being studied.

IL-6 chimera also activates liver stem cells and exerts hepato-protection in mice poisoned with carbon tetrachloride. Applications of this effect in liver pathologies are under study (with Dr S. Brill and I. Zvibel, Ichilov Hospital, Tel Aviv and Prof. D. Shafritz, Albert Einstein College of Medicine, New York).

Recent Publications

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