Gene Therapy Approaches in Spinal Cord Injury

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Spinal Cord Injury

Primary damage

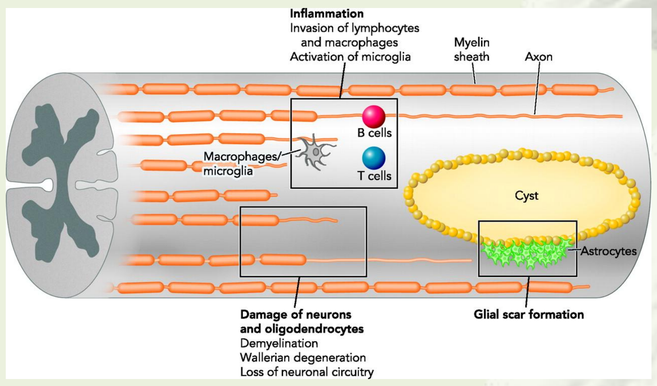
- A hit breaks the vertebrae
- Bone fragments tear spinal cord tissue

Secondary wave of damage

- Changes in blood flux
- Leakage of neurotransmitters (glutamate) and free radicals
- Invasion of immune cells
  - Increase in cytokine concentration
  - Fight against infection and clean waste

Scar formation

- Accumulation of astrocytes
- Pericytes
- Secretion of chondroitin sulphate proteoglycans (CSPG)



Gene Therapy for SCI

Nonviral vectors

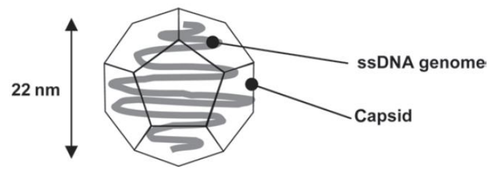
Plasmids:
- Low efficienct gene delivery and expression

Viral vectors

AAV

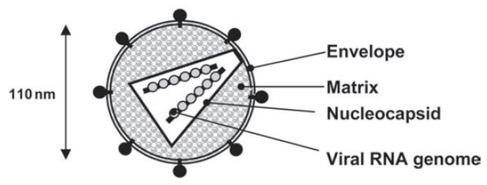
- Transgene insert capacity: 4.5kb
- Serotypes:
  - AAV2 → neurons
  - AAV5 → glial cells (few neurons)
  - AAV1 → glial cells (few neurons)
  - AAV9 → good motor neuron transfection

- **scAAV** → Double-stranded AAVs (self complementary AAV) more effective in retrograde motor neuron infection after i.m. administration.



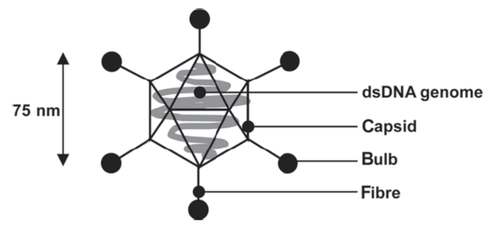
LV

- Transgene insert capacity: 6kb
- Good at targeting astroglia
- Risk of insertional mutagenesis
- Commonly pseudotyped with:
  - **VSV-G** to target spinal cord glial cells
  - **Rabies-G virus** to target distant spinal motor neurons by retrograde transport when injected intramuscularly.
- Integrase-deficient LVs (**IDLV**) → no insertional mutagenesis.



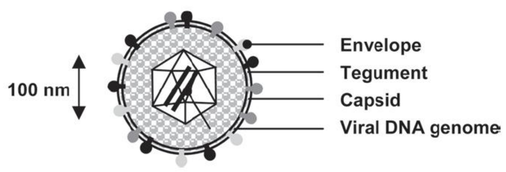
Ad

- Transgene insert capacity: 8-30kb
- They generate immune response.
- High transgene expression levels



HSV

- Transgene insert capacity: 30-40kb
- High capacity of *in vivo* transgene expression
- Completely pure vector stocks are difficult to obtain



Therapeutic Genes

Brain-Derived Neurotrophic Factor (BDNF)

Enhances integration of regenerated axons by promoting synapse formation or maybe an increase in the efficiency of signal transduction of the regenerated axons.

Glial cell-line Derived Neurotrophic Factor (GDNF)

Exerts tropic effects on adult spinal axons and Schwann cells that contribute to axon growth after injury.

Neurotrophin-3 (NT-3)

Induces growth of corticospinal axons.

Transforming Growth Factor-α (TFG-α)

Transforms astrocytes to a growth supportive phenotype after SCI.

Conclusions and Discussion

Gene therapy offers a hopeful strategy to treat spinal cord injury. Previously, systemic administration of Neurotrophic factors used to produce secondary effects and toxicity, since high doses were required to get to the CNS. Later, cell transplants showed a promising potential, although engraftment and survival of transplanted cells is not 100% efficient. Hence, gene therapy offers a way to locally administer a therapeutic gene at a clinical doses so that the minimum toxicity is caused.

However, viral vectors carry some risk associated. More efficient and less dangerous vehicles are required to pass from pre-clinical to clinical trials. A future approach would be combinational strategies, where genetically engineered cells could be obtained by ex vivo gene transfer and lately transplanted into the spinal cord. Biomaterials to serve as bridges between both parts of the glial scar are also being tested. Moreover, strategies where promoters could be induced to express or not the therapeutic gene would be of great clinical interest, and are already being tested.

To sum up, there is no one and only strategy that will cure SCI in short term, although great efforts are directed to find the combination that will be both efficient and safe enough for being tested in patients.

References

- Burton E.A., Glorioso J.C., Fink D.J., Gene Therapy Approaches in Neurology, In Waxman S.G., Molecular Neurology. Amsterdam: Elsevier Academic Press, 2007.
- Tenenbaum, L et al., Recombinant AAV-mediated gene delivery to the central nervous system. J GeneMed 2004; 6: S212-S222.
- Blesch A, Tuszynski MH. Cellular GDNF delivery promotes growth of motor and dorsal column sensory axons after partial and complete spinal cord transections and induces remyelination. J Comp Neurol. 2003 Dec 15;467(3):403-17.
- Blesch A, Tuszynski MH. Transient growth factor delivery sustains regenerated axons after spinal cord injury. J Neurosci. 2007 Sep 26;27(39):10535-45.