IJAE
Vol. 123, n. 1 (Supplement): 187, 2018
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Delayed peripheral nerve repair: description of degenerative and regenerative processes

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Nerve fiber regeneration and complete functional recovery after peripheral nerve injury do not always occur and can be influenced by patient age, gender, lesion site, injury severity, size of the gap between damaged nerve stumps and time interval that elapses before performing surgical repair.

The poor outcome occurring after a long delay can be due to loss of the neuron ability to regenerate, loss of the Schwann cell ability to support regeneration and, of course, progressive muscle atrophy.

The aim of this study was to investigate the degenerative processes of the denervated distal nerve stump in order to understand which role they can have during delayed nerve regeneration.

Morphological and biomolecular analyses carried out on degenerated nerves showed several collagen fibers and fibroblasts, atrophic Schwann cells and a significant reduction of soluble Neuregulin1 (NRG1, an important factor for the survival and activity of Schwann cells) already after 3 months of degeneration.

Moreover, functional, morphological, morphometrical and biomolecular analyses were carried out on regenerated distal nerve stumps 6 months after nerve repair (immediate or 3 and 6 months delayed). A rat surgical model of delayed nerve repair consisting of a cross suture between the chronically degenerated median nerve distal stump and the freshly axotomized ulnar proximal stump was used.

Functional recovery analysis shows that only the group repaired immediately and not the two delayed-repaired groups, recovered partially. Moreover, quantitative analysis shows that the delayed groups have fewer and smaller myelinated fibers compared to the immediate repair group. Finally, biomolecular analysis performed on the 6-months delayed group shows that soluble NRG1 maintains a low expression also after 6 months of regeneration.

These results demonstrate that, despite a delay of 3 or 6 months, the fibers are still able to regenerate, even if they are fewer and smaller than the immediate repaired group. Moreover, the analysis of the NRG1/ErbB system shows a significant decrease of soluble NRG1 in both degenerating and delayed-repaired nerves.

Our results suggest that NRG1 plays an important role in Schwann cell activity after denervation, therefore its manipulation could be a good strategy to improve the outcome after delayed nerve repair.