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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1612151> since 2017-02-06T13:33:17Z

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(Article begins on next page)

REGULATION OF THE NRG1/ERBB SYSTEM IN CMT1A PERIPHERAL NERVES

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Neuregulin1 (NRG1) is a growth factor playing a pivotal role in the development of the peripheral nerve through the activation of the transmembrane co-receptors ErbB2-ErbB3, mainly expressed by Schwann cells.

Several soluble and transmembrane NRG1 isoforms were identified; they play different and specific roles in the myelination during development and in the remyelination following nerve injury.

Transmembrane isoforms are mainly expressed by axons and are involved in both development and nerve repair: their down-regulation impairs - and their over-expression promotes - both myelination and remyelination. On the contrary, soluble NRG1 isoforms, which are mainly secreted by Schwann cells, seem to play a role only following nerve injury: their absence or over-expression do not affect myelination, while their down-regulation negatively affects remyelination.

We previously demonstrated that soluble NRG1 isoforms are strongly and transiently up-regulated after nerve injury, thus suggesting a role for these isoforms in the response to nerve damage.

Here we show that in the rat experimental model of the peripheral demyelinating neuropathy Charcot-Marie-Tooth 1A (CMT1A) the expression of the different NRG1 isoforms is finely regulated, as well as the expression of NRG1 co-receptors ErbB2 and ErbB3, thus showing that CMT1A nerves have a gene expression pattern highly reminiscent of injured nerves.

It has been recently demonstrated by others that treatment with soluble NRG1, restricted to early postnatal development, can have a positive effect on the outcome of the disease.

Nevertheless, it is known that soluble NRG1 has bifunctional, concentration-dependent effects on myelination *in vitro*.

Therefore, the expression analysis of the different endogenous NRG1 isoforms may contribute to understand the role played by the NRG1/ErbB system during the CMT1A neuropathy development. Further analyses will be necessary to understand whether endogenous expression of NRG1 isoforms plays a positive or a negative role in the disease pathogenesis.