Analysis of the biological role of angiogenin, mutated in ALS, as a paracrine*, stress-induced motoneuron survival factor

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Grant: 200 000 €

Amyotrophic Lateral Sclerosis (ALS) is a fatal condition where nerve cells controlling muscle functions die, resulting in paralysis and eventual death. Little is known about the causes of ALS, and there is no cure for this condition. We have recently been involved in a clinical study that has identified mutations in a gene encoding for the protein angiogenin in ALS patients.
Research in our laboratory demonstrated that angiogenin is found in these nerve cells and protects them against stress-induced cell death by promoting and sustaining cell survival signaling. Further experiments showed that in mouse models of ALS, angiogenin treatment, after onset of ALS-like symptoms, increased the lifespan and muscle function of the mice.

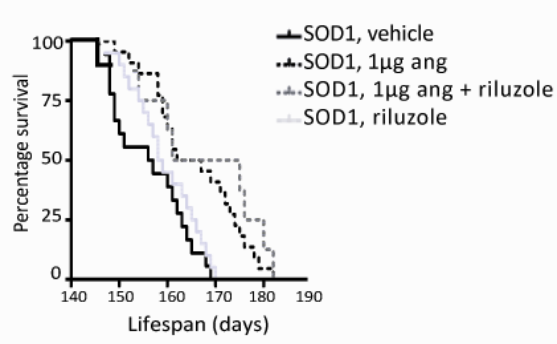

Figure 1. Angiogenin extends lifespan and activates survival pathways in the SODG93A mouse.
A. Kaplan–Meier analysis of survival following angiogenin (ang) treatment in the SOD1 mouse [n=24 per treatment]. Animals were sex-, age- and litter-matched and treated daily with ang (1µg), ang (1µg) and riluzole (22mg/kg), riluzole alone or vehicle (PBS). Ang alone increased lifespan (164.50 ± 3.82 days) when compared to vehicle-treated SOD1 mice ($p < 0.01$). Riluzole alone had no significant effect on lifespan. The combination of ang and riluzole extended lifespan when compared to riluzole only-treated SOD1 mice (168.75 ± 3.42 days; $p < 0.01$).

These results suggested that angiogenin delivery may be beneficial in treating patients with newly diagnosed ALS.
The present project aims to understand how angiogenin precisely works in the protection of nerve cells in ALS. We will explore whether angiogenin signals not only within nerve cells, but also impacts on the surrounding support cells and blood vessel cells, and indeed requires these support cells to exert any beneficial activities. Using a state-of-the-art molecular biology approach, we will also identify novel targets of angiogenin, and will test whether these represent new candidates for the treatment of ALS.
Increasing our understanding of the mechanism of action of angiogenin is important before angiogenin or angiogenin derivatives can be tested in humans. Moreover, by identifying new targets of angiogenin, this research can provide novel therapeutic strategies for the treatment of ALS. With this project we hope to accelerate the translation of our research findings into new treatment options for ALS patients, but we will also obtain new important insights into the causes of this fatal disease.

*Paracrine signalling means signalling from one cell type to a different cell type

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Call for projects 2011
Grant: 200 000 €
Project Duration: 3 years

Investigator: Jochen H.M. Prehn, Royal College of Surgeons, Dublin, Ireland

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Angiogenin – A 'Help me signal' that may become a new therapeutic
The group of Prof Jochen Prehn at the Royal College of Surgeons in Ireland investigates the importance of angiogenin, a gene mutated in familial and 'sporadic' ALS patients, in disease pathophysiology, and aims to develop Angiogenin as a new therapeutic target for the treatment of ALS.

The project funded by the Fondation Thierry Latran builds on previous work by the group that demonstrated Angiogenin is a 'neuroprotective' factor, and is released from stressed motoneurons as a 'Help me signal'. The project investigates how Angiogenin works, and which cells receive this 'Help me signal'. Specifically, the group investigates the ability of Angiogenin to regulate astroglia and endothelial cell function by targeting novel subsets of RNAs. The ongoing research identifies and characterizes these novel angiogenin substrates. In doping so, the group hopes to provide important new insights into the disease process, and to deliver Angiogenin or Angiogenin substrates as novel therapeutic targets for the treatment of ALS.

References:
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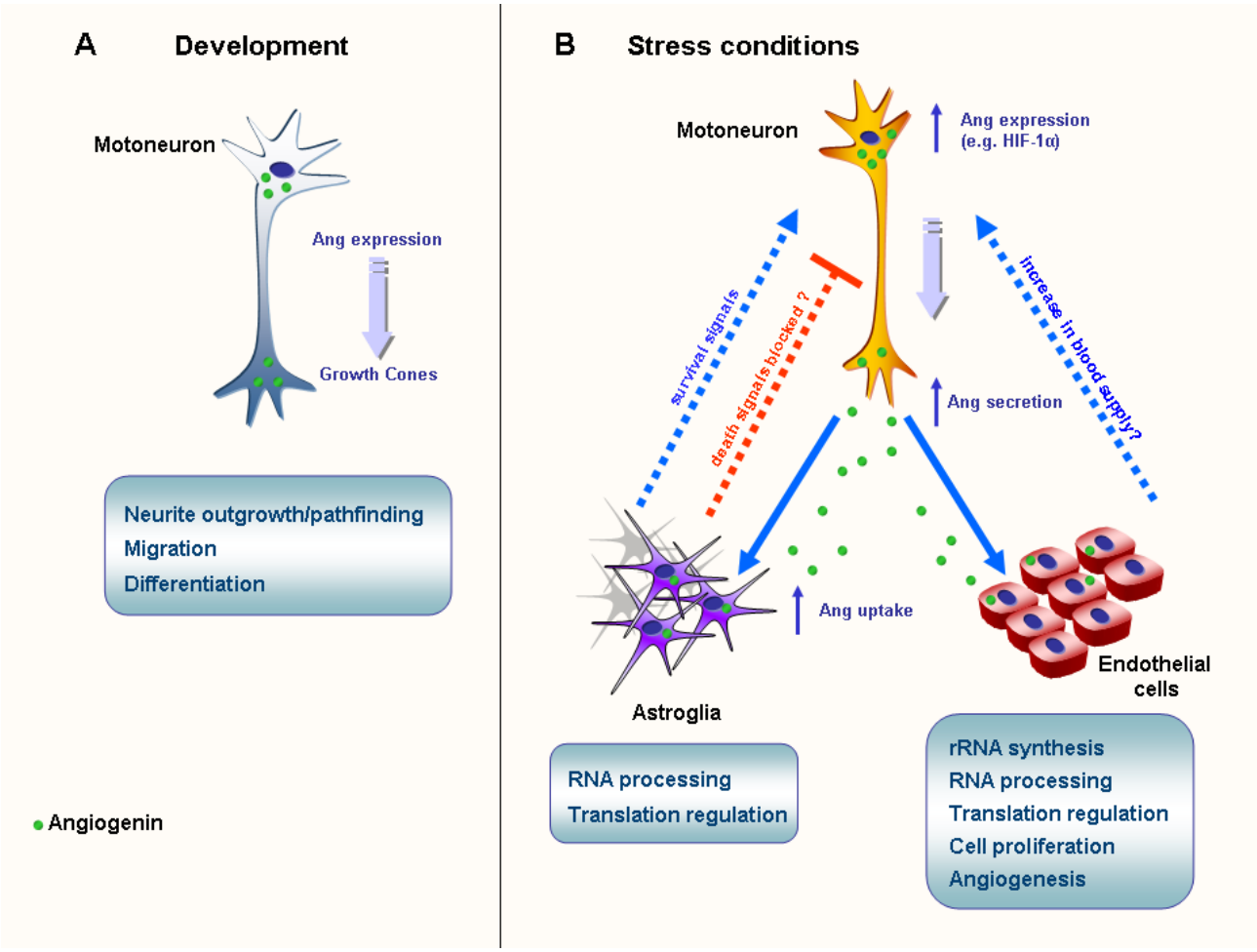

Schematic representation of the known and newly proposed functions of Angiogenin in motoneurons during normal development (A) or during stress conditions in the adult (B).