Curriculum in Neuroscience and Experimental Neurology - Final Course Programme

"The neuronal soma: a key functional component of the axon (paradox intended)"

San Raffaele Scientific Institute, Milan, Italy
14 and 15 June 2018

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Foreword

The axon is not a translationally inert territory

While the majority of neuronal proteins are manufactured in the endoplasmic reticulum and in cytosolic polysomes of the neuronal cell body, many proteins affecting synaptic plasticity are synthesized in dendrites. Conversely, the axon has long been viewed as a passive transmitter of information relying, for protein synthesis and homeostasis, on bidirectional vesicular traffic, to and from the soma. However, an average pyramidal neuron's axonal volume can reach 1000 times the volume of its cell body. More importantly, increasing evidence emphasizes the role of localized protein synthesis, translational control, and locally regulated metabolism in axons. Sustained local translation in distal axons is key to neuronal survival. Decreased translation of mRNAs trapped in pathological aggregates might damage distal axons, causing the death of postmitotic neurons. Local mRNA translation is required for presynaptic maturation and plasticity. Thus, it is likely that sustained local translation in the presynaptic terminal be required for synaptic maintenance in adult mice. In fact translational activity is enhanced by extrinsic cues (BDNF, netrins and semaphorins), by mTORC1-induced 4E-BP phosphorylation, or by decreasing eIF2a phosphorylation. In mammals, local translation has been observed in the axon of cultured embryonic neurons, in embryonic peripheral sensory axons, in the axonal initial segment of adult CNS neurons, and in mature PNS axons, with polysomes located close to the plasma membrane. Axons, including adult ones, contain noncoding RNAs, including miRNA, and transport RNAs. Moreover, several messenger RNAs are targeted to the axon: for example, the 3'UTR of the importin β1 mRNA contains an axon-targeting signal, and transcript localization to the axon is important for efficient regeneration.

The axon and motor neuron disorders

While all genes mutated in isolated or familial cases of amyotrophic lateral sclerosis (ALS) are ubiquitously expressed, neurodegeneration mainly affects long-range (sometimes meter-long) projection neurons – definitely the longest motor axons of the human body. The upper and lower motor neurons, which are prone to degeneration in ALS patients, might be particularly sensitive to pathological messenger ribonucleoprotein aggregates. In ALS, presynaptic and axonal damage precedes the demise of the neuronal cell body. A sudden decline in the level of synaptic proteins precedes defective synaptic function and neuronal loss, suggesting that defective maintenance of the synaptic proteome could be an underlying cause of neurodegeneration. Thus, it is likely that sustained local translation in the presynaptic terminal be required for synaptic maintenance in adult mice. Similar principles are predicted to apply to other neurodegenerative disorders affecting long range projection neurons.

In this course, we plan to discuss some aspects of axonal biology, metabolism and transport, and their potential relevance for neurodegenerative disorders.

Introductory material:
Review #1: https://doi.org/10.1016/j.cell.2014.03.005
Review #2: https://doi.org/10.1016/j.neuron.2017.10.015

Thursday, June 14

10:00-11:00 *RNA Control of Axonal Functions*
Prof Mike Fainzilber, Weizmann Institute of Science, IL
11:00-11:30 Discussion

11:30-12:30 *Endosomes: new players in axonal mRNA translation*
Dr. Jean-Michel Cioni, University of Cambridge, UK
12:30-13:00 Discussion

13:15 Lunch

15:00-17:30 **two journal clubs on topics discussed in the morning**

First paper: The RNA-binding protein SFPQ orchestrates an RNA regulon to promote axon viability. https://doi.org/10.1038/nn.4280

Second paper: Axonally synthesized ATF4 transmits a neurodegenerative signal across brain regions. https://doi.org/10.1016/j.cell.2014.07.001

attending: Jean-Michel Cioni, Gabriella Viero, Filippo Casoni and Giacomo Consalez

Friday, June 15

9:30-10:30 *Axonal transport in health and disease*
Giampietro Schiavo, University College of London, UK
10:30-11:00 Discussion

11:00-12:00 *microRNAs: gatekeepers of time and space in axonal development*
Marie-Laure Baudet, University of Trento, IT

12:00-12-30 Discussion

12:45 Lunch

14:00-16:30 **two journal clubs on topics discussed in the morning**

First paper: Activity-Dependent Exocytosis of Lysosomes Regulates the Structural Plasticity of Dendritic Spines. https://dx.doi.org/10.1016/j.neuron.2016.11.013
Please also read: Characterization of LAMP1-labeled nondegradative lysosomal and endocytic compartments in neurons https://doi.org/10.1083/jcb.201711083

Second paper: FMRP-mediated axonal delivery of mir-181d regulates axon elongation by locally targeting Map1b and Calm. https://doi.org/10.1016/j.celrep.2015.11.057

attending: Marie-Laure Baudet, Gabriella Viero, Filippo Casoni and Giacomo Consalez