Sorting Neuronal Survival Signals

Motor neurons control muscle contraction, and one of the early events in ALS is the loss of connections between these neurons and their target muscles. For many years, it has been known that growth factors secreted by the muscle control both neuron-muscle connections and the survival of the motor neuron. These growth factor molecules bind to receptors on the surface of the neuron and are transported, in membrane bound packets called "endosomes", to the neuronal cell body in the spinal cord, relaying a pro-survival signal (See Figure 1A).

Figure:1

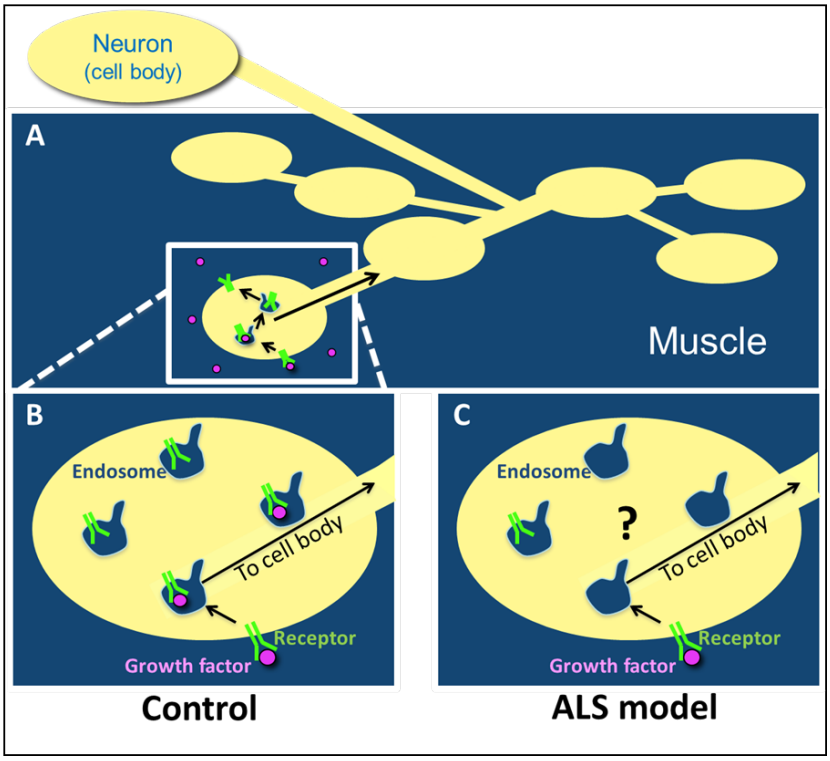


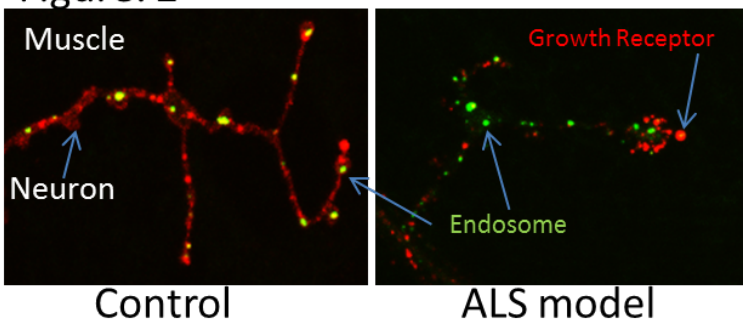
Figure 1: (A) This cartoon depicts the connection between the neuron and the muscle (enlarged in panel (B)) where growth factor molecules (pink) secreted by the muscle, bind to the receptors (green) on the neuron. Endosomes (blue) carrying these receptors are transported to the cell body of the neuron. (C) In the ALS model flies (see below), growth receptors are not located in the correct endosomes.

Dr. Mugdha Deshpande, the Blazeman Foundation Postdoctoral Fellow for ALS Research, has been working to understand how these processes may go awry in ALS, in Avital Rodal's lab at Brandeis University. She is using fruit flies as a model system to study these growth signals, since it is possible to rapidly manipulate fly genes and to visualize transport in their neurons. Previous studies in the lab have indicated that in ALS-model fruit flies, which express a human ALS gene and have neurodegeneration and reduced lifespan, pro-survival signaling from growth receptors is reduced. The main goal of the current project is to understand how these survival signals are sorted into endosomes and transported within the neuron, and how mutations causing ALS alter this process.

Dr. Deshpande compared the location of growth receptors with respect to other markers of the transport machinery inside the neuron. She found that in ALS model fly's neurons, the growth

Figure 2: Location of growth receptors in the fruit fly. In normal flies (left), growth receptors (red) coincide with the endosomal markers (green), appearing yellow in the merged image. This co-localization is reduced in neurons from ALS model fruit flies (right).

Figure: 2



receptors do not coincide with the appropriate endosome as often as in the healthy flies (Figure 1B and Figure 2A). Her current experiments are aimed at understanding why these growth receptors have been mis-sorted in the ALS model, and if correction of the sorting defects can suppress neurodegeneration and shortened lifespan in the flies. In parallel, Dr. Deshpande is working with Dr. Suzanne Paradis at Brandeis to develop a system to study growth receptor signaling in mammalian neurons expressing a human ALS gene, to test if there are defects comparable to those she saw in the fly model. She has found that growth of these neurons is severely affected when they are modified to express this ALS gene (Figure 3), and is now testing if these defects are related to problems with specific growth factor signaling and endosome sorting. By understanding how growth and survival signals are being diverted from their normal itinerary in diseased neurons, it will be possible to develop new therapies to return these signals to the appropriate location.

Figure: 3

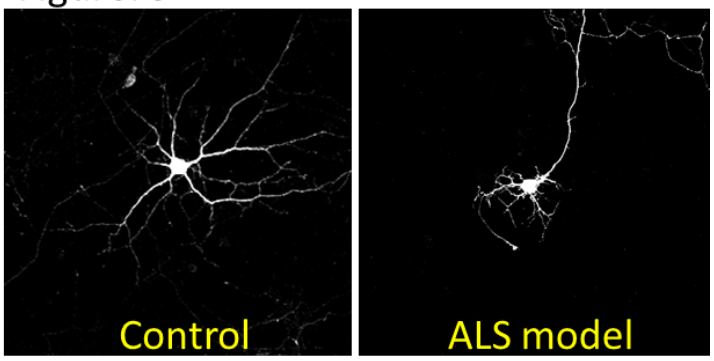


Figure 3: Branching pattern of healthy rat neurons (left). This branching pattern depends on normal growth factor signaling. Expression of human ALS gene in these neurons causes defects in this branching pattern (right).