Version en anglais

To keep neuronal polarity, endocytosis at the base of the axon is necessary

Neurons are made up of two very different parts: the axon, and 'the rest'. To maintain these differences, two cellular mechanisms were known. By combining genetics on an identified neuron from the worm C elegans, and the detection of endocytosis in rodent neurons or differentiated human neurons in culture, scientists have revealed a new mechanism, endocytosis in the initial segment of the axon. These results are published in the journal *Nature*.

Neurons, the main cells of the brain, are highly polarized cells, i.e. they consist of two very different parts: on the one hand, the axon, a very thin tubular compartment (less than 1 µm in diameter) that can reach a length of several cm or even nearly a meter for some neurons. The axon allows the transmission of electrical signals to target neurons via synapses. On the other hand, the cell body and the dendrites make up the "receptor" part of the neuron, where many synapses are formed with other neurons. The electrical signals from the synapses are combined and then, if large enough, will cause the generation of an action potential at an intermediate compartment between the axon and the soma called the axon initial segment (AIS). In addition to its role in action potential generation, the AIS plays a very important role in maintaining the polarization of neurons. This is because the components of the axon or dendrites/soma, especially the proteins, are very different. Neurons have mechanisms in the AIS that allow the sorting of cellular elements to ensure this polarity. So far, scientists have been able to identify two cellular mechanisms that preserve polarity. Firstly, intracellular transport vesicles are sorted at the AIS: those carrying axonal proteins pass a filter in the AIS, while vesicles carrying dendritic proteins enter the AIS but cannot pass the filter and turn back. Secondly, proteins on the plasma membrane on the surface of neurons diffuse within the membrane, but the AIS also has a diffusion barrier that slows down the diffusion and prevents the entry of dendritic surface proteins into the axonal membrane.

In a collaboration with Stanford University in California, the scientists identified a third mechanism for preserving neuronal polarity: the internalisation of dendritic surface proteins by endocytosis and their degradation in the AIS. To reach this conclusion, they used three biological models. First, they studied some neurons from the nematode worm Caenorhabditis elegans, a one-millimetre long worm that is one of the most studied model systems by biologists. Focusing their study on one of the worm's 302 neurons, the scientists showed that this neuron possesses an AIS and that blocking endocytosis specifically in this neuron causes the redistribution of a dendritic surface protein called DMA-1 to the axon. Furthermore, this protein, which is responsible for the formation of dendritic branches, causes the ectopic formation of branches normally absent in the axon when present in the axon. They also showed that endocytosis plays the same role for dendritic surface proteins in human neurons, as well as in rodent neurons. The scientists also directly visualised AIS endocytosis using a fluorescence imaging method that detects endocytosis vesicle formation in real time (see Sposini et al. 2020) to show that dendritic surface proteins are indeed internalised in the AIS

of neurons, and that the frequency of endocytosis vesicle formation is the same as in dendrites.

These results represent an important advance in the understanding of the cellular mechanisms of neuronal polarity formation and preservation. They will also allow us to study this new form of endocytosis and to determine its specific mechanisms, which could lead to a better understanding of the functioning of the AIS, an essential compartment of neuronal function.

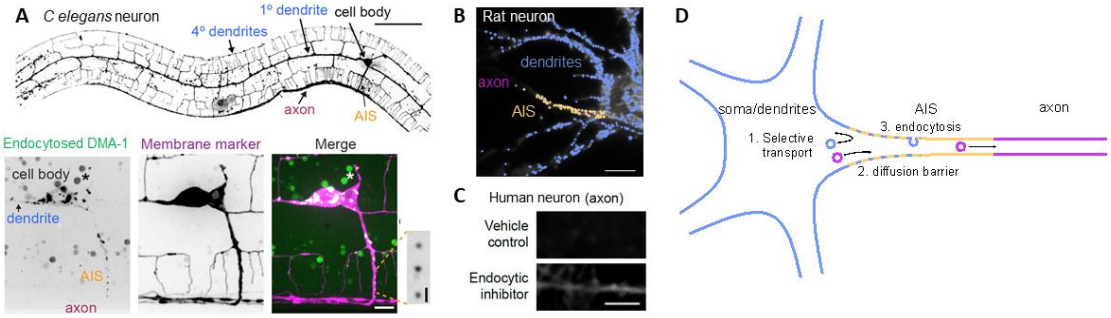

Figure: Endocytosis at the AIS is necessary for maintaining the polarity of dendritic proteins. **A**, Morphology of the PVD neuron in *C elegans*. Dendrites are very long and branched, while the axon does not branch. In the AIS, identified with various markers, dots mark endocytosed dendritic protein (GFP-FLPon-CLIC1). **B**, In a rat neuron, endocytic events containing a dendritic protein occur in the dendrites and soma (light blue crosses) and the AIS (yellow crosses) but very few in the axon. **C**, In human neurons, after blocking endocytosis dendritic proteins, normally not present in the axon, become detectable in the axon. **D**, Scheme of the three cellular mechanisms which maintain polarity in neurons. The third mechanism, endocytosis in the AIS, is revealed in the study by Eichel et al.