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Research Report

Axon ensheathment and metabolic supply by glial cells in Drosophila

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ABSTRACT

Neuronal function requires constant working conditions and a well-balanced supply of ions and metabolites. The metabolic homeostasis in the nervous system crucially depends on the presence of glial cells, which nurture and isolate neuronal cells. Here we review recent findings on how these tasks are performed by glial cells in the genetically amenable model organism *Drosophila melanogaster*. Despite the small size of its nervous system, which would allow diffusion of metabolites, a surprising division of labor between glial cells and neurons is evident. Glial cells are glycolytically active and transfer lactate and alanine to neurons. Neurons in turn do not require glycolysis but can use the glially provided compounds for their energy homeostasis. Besides feeding neurons, glial cells also insulate neuronal axons in a way similar to Remak fibers in the mammalian nervous system. The molecular mechanisms orchestrating this insulation require neuregulin signaling and resemble the mechanisms controlling glial differentiation in mammals surprisingly well. We hypothesize that metabolic cross talk and insulation of neurons by glial cells emerged early during evolution as two closely interlinked features in the nervous system.

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1. Introduction

The first living beings on earth were single-celled organisms. During evolution, multicellularity turned out to be an advantage and more and more complex organisms appeared on earth. In the most primitive animals, all cells were presumably equally well equipped to take up nutrients and to feed from the environment. Simple porifera might resemble these early stages of evolution (Leys, 2015; Nielsen, 2008). However, soon the first cells developed sensory skills helping to catch more and possibly bigger prey (Monk and Paulin, 2014). The evolution of such specialized cells occurred at the expense of being able to feed themselves, possibly similar as nematocysts of cnidaria or as light detecting photoreceptor cells. Thus, the epithelial cells flanking the newly forming sensory structures were equipped with supportive functions (Hartline, 2011). This can still be seen in the visual systems of today's animals where photoreceptor cells are always paired with pigment cells (Gehring and Ikeo, 1999). Moreover these two cell types stay in intensive metabolic cross talk

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(Kusakabe et al., 2009). Assuming that the sensory cell developed into the ur-neuron, its support cell developed into what we know today as glial cell.

During the evolution of the nervous system, the putative sensory ur-neuron had to connect to muscles to transduce signals far from the point where they were perceived. It is conceivable, that support cells developed protective and supportive functions for the thin cell processes that are formed now, the axons (Hartline, 2011). This way first blood–brain barrier functions evolved and neurons were not only nurtured but also protected from their environment. Only later in evolution, more and more interneurons emerged that allowed more and more complex computing of the sensory input, leading to the development of complex nervous systems. At this point glial cells could have adopted modulatory functions during synaptic transmission.

From an evolutionary perspective, it thus appears likely that glial cells were initially equipped with supportive metabolic functions nurturing the neuron, then acquired insulating properties allowing better conductance of neuronal signals and finally, glial cells gained neuromodulatory properties. To test whether such hypotheses have any rational basis, glial functions have to be analyzed in many divergent species. Our current knowledge on glial biology is largely influenced by the analysis of the mammalian nervous system. Here, metabolic coupling has been nicely demonstrated between astrocytes and synapses or myelinating oligodendrocytes and axons (Fünfschilling et al., 2012; Lee et al., 2012; Pellerin and Magistretti, 2012). Analysis of glial cell functions in the invertebrate nervous systems are scarce. In recent years, however, glial cells have been increasingly well analyzed in Drosophila (Freeman and Rowitch, 2013). Flies have been used as a genetically amenable model system for more than one century. During this time various developmental processes have been studied and many of them proved to rely on evolutionary conserved mechanisms. For example, axis determination, eye or heart development, but also metabolic control and innate immunity obey evolutionary conserved principles (Gonzalez, 2013; Kounatidis and Ligoxygakis, 2012; Nüsslein-Volhard and Wieschaus, 1980; Padmanabha and Baker, 2014; Qian and Bodmer, 2012; Rajan and Perrimon, 2013). Similarly, research on Drosophila helped to improve our understanding of the nervous system, where again both development and function appear to follow highly conserved molecular pathways. For example, in all species studied so far determination of the neuronal cell fate relies on proneural genes that encode proteins of the bHLH transcription factor family (Bertrand et al., 2002). And even the specification of more distinct neuronal cell fates appears regulated through the action of conserved transcription factors (Thor and Thomas, 2002). All organisms rely on the same neurotransmitters which induce related postsynaptic responses (Martin and Krantz, 2014). Even complex forms of neuronal computing such as learning and memory are established through evolutionary conserved molecular pathways (Mayford and Kandel, 1999). Here we review recent findings that demonstrate further evolutionary conservation of energy homeostasis and axon ensheathment in the brain.

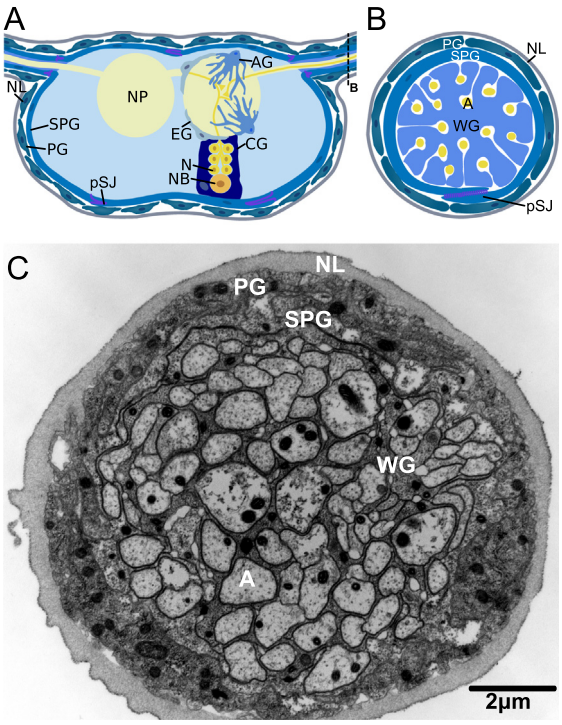

Fig. 1 – Structure of the Drosophila CNS. (A) The nervous system is surrounded by an extracellular matrix, the neural Lamella (NL), and two glial cell layers, the perineurial glia (PG) and the subperineurial glia (SPG). These two cell layers built the BBB, with the SPG forming the main diffusion barrier by establishing intra- (only in the PNS) and intercellular pleated septate junctions (pSJ). The neuroblasts (NB) and neuronal cell bodies (N) are ensheathed by the cortex glia (CG). The neurons project their axons into the neuropil (NP), which is covered by a layer of ensheathing glial cells (EG). Astrocyte-like glial cells (AG) send their processes into the neuropil to make close contact with axons and synapses. The dotted line indicates the position of the orthognoal section shown in (B). (B) The architecture of peripheral nerves. Nerves projecting into the periphery are surrounded by the neural lamella (NL). The outermost glial layer consists of perineurial glial cells (PG). Together with the subjacent pleated septate junction (pSJ)-forming subperineurial glia (SPG), these two glial layers form the blood–brain barrier. The third and innermost glial layer consists of wrapping glial cells, which ensheath the axons (A). The morphology of the wrapping glia strongly resembles that of non-myelinating Schwann cells forming Remak fibers in the mammalian PNS. (C) Transmission electron microscopy picture of a cross-section of a peripheral third instar larval nerve. The different glial cell types are indicated.

2. The Drosophila nervous system

As a holometabolic insect, Drosophila goes through four different stages during development: embryo, larva, pupa and the imago. During these stages major remodeling of the body, including the nervous system takes place. The larval nervous system develops from stem cells that are called