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The glia doctrine: Addressing the role of glial cells in healthy brain ageing☆

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ABSTRACT

Glial cells in their plurality pervade the human brain and impact on brain structure and function. A principal component of the emerging glial doctrine is the hypothesis that astrocytes, the most abundant type of glial cells, trigger major molecular processes leading to brain ageing. Astrocyte biology has been examined using molecular, biochemical and structural methods, as well as 3D brain imaging in live animals and humans. Exosomes are extracelluar membrane vesicles that facilitate communication between glia, and have significant potential for biomarker discovery and drug delivery. Polymorphisms in DNA repair genes may indirectly influence the structure and function of membrane proteins expressed in glial cells and predispose specific cell subgroups to degeneration. Physical exercise may reduce or retard age-related brain deterioration by a mechanism involving neuro-glial processes. It is most likely that additional information about the distribution, structure and function of glial cells will yield novel insight into human brain ageing. Systematic studies of glia and their functions are expected to eventually lead to earlier detection of ageing-related brain dysfunction and to interventions that could delay, reduce or prevent brain dysfunction.

1. Introduction

Cognitive frailty is emerging as one of the greatest health challenges of the twenty-first century. As life expectancy of the population increases, the prevalence of cognitive decline, Alzheimer's disease (AD) and other forms of dementia is also increasing. Nearly 50% of adults over the age of 85 living in industrialised countries are thought to suffer from some form of dementia. The most significant non-modifiable risk factor for cognitive decline and AD in older adults is age itself. In addition, even healthy ageing entails some cognitive impairment that may be modifiable. Therefore, it is critical to understand the basis of ageing-associated cognitive decline, at the molecular, functional and organismal levels, with focus on healthy brain ageing and the most prominent brain diseases.

In the large majority of cases, it is not known whether the primary factors leading to AD are environmental and/or genetic, and more research on brain ageing, AD and other dementias is urgently needed. Recently, research in this area has shifted from an emphasis on the role of neurons, *e.g.* loss of neurons and structural and functional disruptions, to a broader view including a focus on glial cells. An increasing body of evidence suggests that glial cells play a major role in brain ageing and in several disease processes of the brain. This article summarizes recent advances and emerging hypotheses related to functions of glial cells, with an emphasis on the role of astrocytes.

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2. Glial cells: characteristics and complementarity

Glial cells in the brain include astrocytes, oligodendrocytes and microglia. In the gray matter, astrocyte processes make intimate contacts with neurons through perisynaptic processes (Ventura and Harris, 1999), while astrocyte endfeet almost completely ensheathe the blood vessel endothelium (Mathiisen et al., 2010). In the white matter, bundles of myelinated axons are tightly packed, while astrocytes make contact with naked axons at the nodes of Ranvier, and oligodendrocytes generate the myelin sheath. Microglia mediate innate immunity in the brain (Kettenmann et al., 2011) and may play a role in synaptic communication and modulation (Tremblay, 2011).

2.1. Astrocytes

Astrocytes, the most numerous cell type in the human brain, fill most of the space between neurons and blood vessels (Fig. 1A). Recent studies from several laboratories including our own show that astrocytes have strong impact on neuronal function, neuronal development, and brain ageing. Astrocytes regulate extracellular ion concentration, water homeostasis and the acid-base balance in the brain (Amiry-Moghaddam and Ottersen, 2003; Chesler, 2003; Nagelhus and Ottersen, 2013; Papadopoulos and Verkman, 2013). They also actively modulate synaptic transmission by releasing neuroactive compounds. This arrangement with three elements – the presynaptic terminal, the postsynaptic dendrite and the perisynaptic astrocytic process – making a functional unit is referred to as the "tripartite" synapse (for excellent recent reviews see (De Pitta et al., 2011, 2012; Santello et al., 2012). There is bidirectional communication between the neuronal and astrocytic elements: (1) release of transmitters at the synapse can trigger G-protein coupled responses in astrocytes (*e.g.* through P2Y1 ATP receptors). This can lead to increase in the intra-astrocytic Ca^{2+} concentration, which in turn stimulates release of signal substances such as glutamate, D-Serine and ATP. (2) It has been shown that astrocytes can feed back to the synapse to control synaptic transmission, either through exocytotic release (Bezzi et al., 2004; Chen et al., 2013; Jourdain et al., 2007) or by channel-mediated release of transmitters (Han et al., 2013a; Lee et al., 2010). Gliotransmitter release from astrocytes can either increase synaptic transmitter release, or decrease it. Adding to the ability of astrocytes to regulate synaptic activity is that different synaptic stimuli could change the morphology of astrocyte perisynaptic processes. By morphologically adapting to changes in the external environment, astrocytes may influence dynamic synaptic plasticity (Oliet et al., 2001; Panatier et al., 2006). However, the role of "gliotransmitter" release in regulating synaptic plasticity is highly debated (Agulhon et al., 2010; Sun et al., 2013).

Astrocyte endfeet form a continuous sheath at the blood-brain barrier (BBB) (Mathiisen et al., 2010) and at interfaces with the cerebrospinal fluid (CSF) (Klika and Antalikova, 1969). Because of

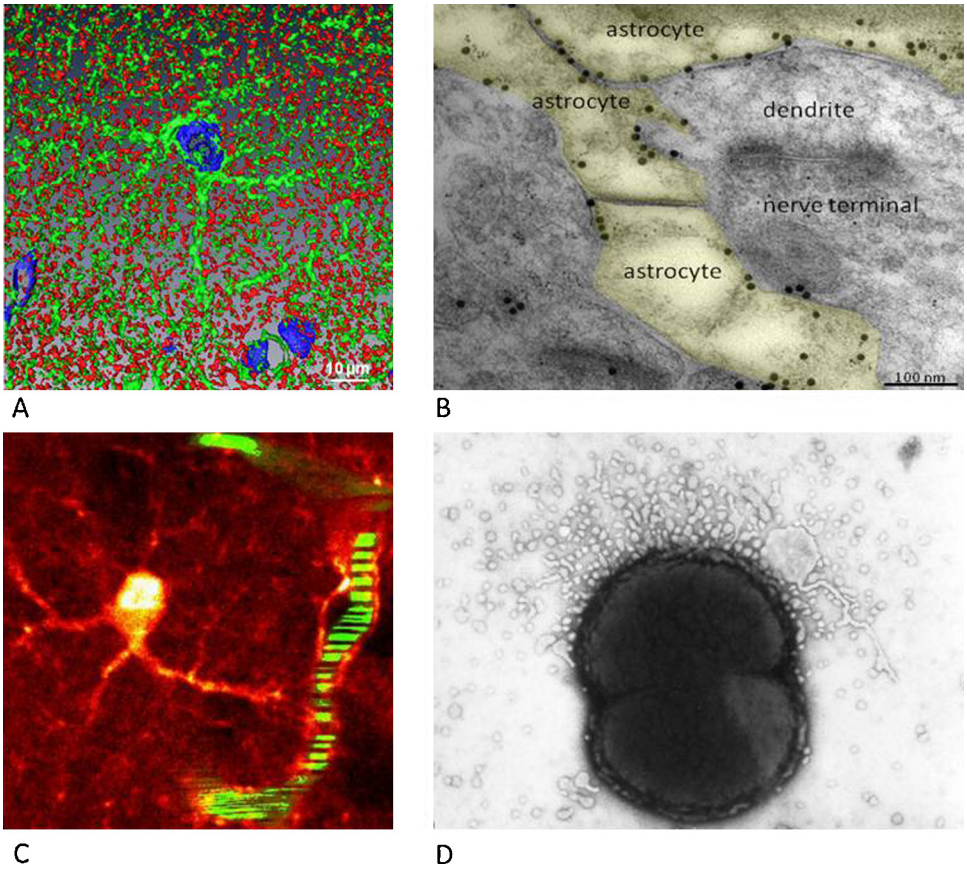

Fig. 1. Astrocytes and bacterial exosomes. (A) Confocal image showing an astrocytic cell body and processes (labelled for glutamine synthetase, green; nuclei, blue). The astrocytic processes make several contacts with VGLUT1 positive synapses (red). (B) Electron micrograph showing delicate astrocytic processes (yellow pseudocolour) labelled for the plasma membrane glutamate transporter GLT-1 (large gold particles). The astrocytic processes almost completely ensheathe a synapse consisting of a presynaptic nerve terminal and a postsynaptic dendrite. VGLUT1 (small gold particles) is localized both in the astrocytic processes and the nerve terminals. (C) Image from cortex of an anesthetized mouse obtained with two-photon laser scanning microscopy. An astrocyte is labelled by the red fluorescent dye sulforhodamine 101. A capillary is outlined by FITC-dextran (green). (D) Bacterial outer membrane vesicles released from a meningococcal *pilG* mutant (Tønjum et al., 1995, with permission).