# Significance of intercellular communication for neurodegenerative diseases

**Hilal Cihankaya, Carsten Theiss, Veronika Matschke***

The nervous system is a highly complex organization composed of its basic unit, the neuronal cells, and specialized supporting cells, the glial cells. The main glial cells in the central nervous system (CNS) are astrocytes, microglia and oligodendrocytes. Astrocytes are the most abundant glial cell type in the CNS, and they are mainly responsible for the maintenance of neurons. Microglial cells are the most important immune cells in the nervous system and are activated in response to damage and inflammation. Oligodendrocytes produce myelin sheaths wrapping the axons of neurons in the CNS, thus isolating them from the environment and allowing more efficient propagation of action potentials. Normally, neurons and glial cells work together in a balanced and controlled way to maintain a homeostasis. However, under pathological conditions of the nervous system, this coherence between neurons and glial cells can be destroyed, leading to impairments in its function.

Different neurodegenerative diseases involve different neuronal populations, nevertheless they all share common characteristics at their base in terms of cellular defects, such as protein aggregation, oxidative stress, mitochondrial dysfunction, impaired cellular trafficking and production of free radicals. While neurons are the focus of research on neurodegenerative diseases, the contribution of non-neuronal cells to neuronal cell death is undeniable. These non-neuronal cells regulate all of the aforementioned cellular pathways to maintain neural homeostasis. Any alterations in the physiological functions of these cells may affect intercellular signaling, leading to neurodegeneration in cell autonomous and/or non-cell autonomous pathways. Intercellular interactions between neurons and non-neuronal cells can occur through three main mechanisms: (i) secretion of molecules via autocrine and paracrine signaling, (ii) direct cell-to-cell contact mediated by receptors, and (iii) secretion of vesicles (Meyer and Kaspar, 2017). All in all, it is very important to unravel the distinct roles of each type of glial cell and their aberrant interactions with neurons in a diseased state to better understand the pathogenesis of neurodegenerative diseases and to develop potential therapies against them.

One of the main factors in the progression of neurodegenerative diseases is neuroinflammation. Microglia, the key players of the immune system in the CNS, take the role of sensing danger signals through their ramified branches. Once they are activated, microglia transform into amoeboid shape and play a dual role in secreting molecules, ranging from anti-inflammatory to proinflammatory functions. In some neurodegenerative diseases, the balance between beneficial and harmful elements of microglia is disturbed. In general, microglia prefer to produce and release neuroprotective agents at disease onset. However, during disease progression, a shift from neuroprotection to neurodegeneration is observed, and microglia start to release harmful molecules such as cytokines and chemokines (**Figure 1A**). These molecules, having both paracrine and autocrine functions, amplify the inflammatory response and ultimately exacerbate the neurological disease by causing neural cell death. Being a double-edged sword for neurons, microglia can have different effects in various animal models for amyotrophic lateral sclerosis (ALS), the most common motor neuron disease (Cihankaya et al., 2021). Besides the release of cytokines and neurotrophic factors, neurons can communicate with glial cells through direct cell-to-cell interactions. For example, C-X3-C motif chemokine ligand 1 (CX3CL1) is constitutively produced by neurons in the CNS, and surprisingly has only one receptor expressed by microglia, named CX3CR1. CX3CL1 has two different forms:

(i) the membrane-bound form, which acts as a cell adhesion molecule for inflammatory cells and (ii) the soluble form, which is cleaved from the membrane of neurons, and can bind to the CX3CR1 on the microglia (Chapman et al., 2000). Activation of CX3CL1/CX3CR1 signaling by both membrane-bound and soluble CX3CL1 in the case of a neurodegenerative disease controls microglial activation, and consequently the neuron-microglial communication (Mecca et al., 2018). Additionally, internalization of secreted exosomes containing mRNAs, microRNAs, and proteins by neighboring cells in the CNS is another way of intercellular interaction between CNS cells, as all cell types are able to secrete exosomes in the CNS (Meyer and Kaspar, 2017). Based on the content of the exosomes, it is possible to modify gene expression in the target cell and thus affect neuron-glia communication. In conclusion, targeting microglia and shifting the balance towards neuroprotection may be important to delay disease progression and open the way to finding new therapies for neurodegenerative disorders. Astrocytes, the most abundant glial cell type, perform several roles in the CNS, such as providing structural and metabolic support to neurons, maintaining nutrient and ion balance, regulating cerebral blood flow, and modulating transmitter uptake and release. The two most important glutamate transporters in humans, the excitatory amino acid transporter 1 and 2, are mainly localized on the membranes of astrocytes and play a role in glutamate uptake by transporting excess amount of extracellular glutamate (**Figure 1B**). In neurodegenerative diseases, these glutamate transporters have been shown to be downregulated, resulting in increased levels of synaptic glutamate and thus excitotoxicity in the brain parts associated with the respective diseases (Maragakis and Rothstein, 2006). Besides neurons, astrocytes are able to release glutamate by two different mechanisms: (i) via exocytosis and (ii) via hemichannels, which are activated upon low extracellular calcium levels. Once glutamate is released, its propagation through the astrocyte syncytium can proceed in two pathways. First, released glutamate by neurons can trigger metabotropic glutamate receptors on the astrocyte membrane, which in turn can activate inositol triphosphate ($IP_3$), causing release of calcium from intracellular stores within the astrocytes. This calcium can be transferred to neighboring astrocytes via gap junctions, resulting in formation of calcium waves. Second, increased amount of $IP_3$ may induce adenosine triphosphate release through gap junctions acting in a paracrine

manner, which in turn may activate purine receptors on the neighboring astrocytes. This event leads to activation of even more $IP_3$, and consequently triggers more adenosine triphosphate and calcium release through a positive feedback loop. In neurodegenerative diseases, this enormously involved cell-to-cell communication between astrocytes and neurons has been shown to be severely impaired. For example, increased calcium wave signaling among astrocytes during the Alzheimer's disease (AD) progression and impairment of astrocyte syncytium due to uncoupling of cell-to-cell interactions in Huntington's disease point to the importance of glial cells in the unhealthy state (Maragakis and Rothstein, 2006). In addition to their role in the glutamate metabolism, astrocytes, which in fact are not part of the immune system, may participate in the neuro-immunological response when neural damage is involved. This process is called reactive astrogliosis and is accompanied with upregulation of the intermediate filament, glial fibrillary acidic protein (GFAP). Colocalization of $GFAP^+$ astrocytes with amyloid-β42 in AD, mutant superoxide dismutase 1 in ALS, and mutant huntingtin in Huntington's disease has been demonstrated in different studies (Lian and Zheng, 2016). Astrocytes displaying these mutant protein aggregations, together with axonal degeneration, make neurons more susceptible to cell death in the above-mentioned diseases. Studies regarding nitric oxide (NO) have shown its role in both physiological as well as pathological processes and that it can be released by neuronal and glial cells (Contestabile et al., 2012). NO is an important cellular signaling molecule regulating neuronal function. Under physiological conditions, NO is synthesized by neuronal cells following increases in $Ca^{2+}$-concentration, thus controlling neuronal plasticity and neuronal mechanisms at the pre-synapse. Contrary to initial assumptions that astrocytes synthesize NO only after induced stress, the release of NO from astrocytes also has a modulatory function on neuronal activity under physiological condition (Buskila et al., 2007). However, pathologically elevated glial-derived NO levels are neurotoxic.

Thus, a balance of NO levels as well as a defined interaction between neuron and glia is important for physiological regulation of many neuronal functions. Overall, the dynamic interplay between abnormal astrocytes and neurons can affect healthy astrocytes present in close proximity and worsen a disease state.

Oligodendrocytes insulate the axons of neurons while providing metabolic and physical support. The proliferation and differentiation of oligodendrocytes, as well as myelination of neurons, are directed by oligodendrocyte-neuron signaling, and any dysfunction in this process results in motor, sensory and cognitive deficits, as seen in developmental disorders along with neurodegenerative diseases such as AD, ALS, multiple sclerosis and multiple system atrophy (Ettle et al., 2016; Tognatta and Miller, 2016). Downregulation of myelin-specific proteins in most of neurodegenerative diseases, morphological alterations of the myelin structure in ALS, accumulation of alpha-synuclein proteins in oligodendrocytes of multiple system atrophy patients, metabolic uncoupling of iron and lactate mechanisms in AD and ALS, are some of the events that eventually lead to axonal loss and neurodegeneration during disease progressions (**Figure 1C**; Tognatta and Miller, 2016).

In contrast to the prevailing idea of limiting neurodegenerative diseases to the CNS, the involvement of peripheral immune system in the progression of these diseases should be considered. Disruption of the blood brain barrier and blood spinal cord barrier in neurodegenerative diseases allows peripheral immune cells to infiltrate the CNS parenchyma, resulting in intimate contact of these cells with neurons (**Figure 1D**).

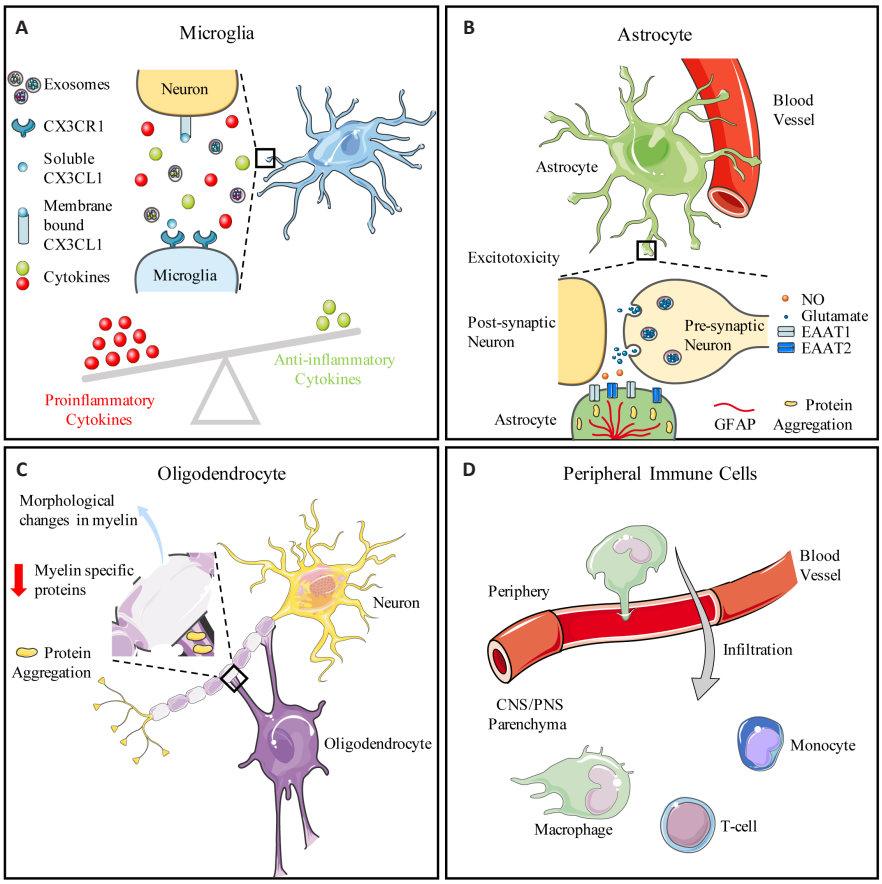


**Figure 1 | Changes in the intercellular communications between neurons and non-neuronal cells in case of neurodegenerative diseases.**
(A) The balance between proinflammatory and anti-inflammatory molecules is impaired during the course of the disease and proinflammatory response overweigh anti-inflammatory response, resulting in neuronal cell death. (B) Downregulated glutamate transporters on the astrocyte membranes cause excitotoxicity in the synaptic cleft accompanied by reactive astrogliosis and various types of protein aggregates in several neurodegenerative diseases. (C) Myelination of neurons by oligodendrocytes is impaired in diseased state, resulting in axonal loss and consequent neuronal cell death. (D) Disruption of the blood-brain/spinal cord barrier allows peripheral immune cells to invade the nervous system and disrupt neuronal activity. CNS: Central nervous system; CX3CL1: C-X3-C motif chemokine ligand 1; CX3CR1: C-X3-C motif chemokine receptor 1; EAAT1: excitatory amino acid transporter 1; EAAT2: excitatory amino acid transporter 2; GFAP: glial fibrillary acidic protein; NO: nitric oxide; PNS: peripheral nervous system.

The presence of infiltrating proinflammatory monocytes in CNS tissue has been demonstrated in some neurodegenerative diseases, suggesting the idea that peripheral immune cells can also contribute to neuroinflammation (Zhao et al., 2013). Additionally, the investigation of T-cell population in ALS revealed that a transformation of the immune response from protective Th2 and T-regulatory cells to toxic Th1 cells occurs during the course of the disease. On the other hand, B-cells were not detected in the spinal cord samples of ALS models and patients, suggesting that they do not play an essential role in ALS (Rodrigues et al., 2012). However, the presence of immunoglobulins in the sera of ALS patients suggests that peripheral immunoglobulins might either be directly cytotoxic to neurons or trigger microglia to participate in the non-cell autonomous death of neurons (Rodrigues et al., 2012). Due to the lack of a protective barrier in the PNS, macrophages, whose primary role is to remove debris remaining from axonal degeneration, can directly interact with the degenerating nerve fibers in response to neurodegeneration (Zhao et al., 2013). Macrophages are also physiologically capable of producing large, cytotoxic amounts of NO, which actually serves to defend against pathogens such as bacteria. In an infiltrated neuronal tissue, however, this has negative consequences, which is a reason why the involvement of NO in chronic inflammatory diseases is discussed. Some studies also suggest that infiltrating macrophages exert neuroprotective effects, therefore it is debatable whether macrophages are either beneficial or harmful. Considering these conditions, repair or reinforcement of endothelial cells, the fundamental components of barrier structures, can be a potential therapy against infiltration to prolong neurodegenerative disease progression and improve neuronal survival (Rodrigues et al., 2012). For example, replacement of defective non-neuronal cells by cell transplantation (such as astrocytes, microglia and T-lymphocytes) may be one way to alter the cellular environment surrounding the dying neurons (Rizzo et al., 2014).

In summary, the interactions between neurons and non-neuronal cells seem to play an important role in the pathophysiology of several neurodegenerative diseases (**Figure 1**). A better understanding of this aberrant interplay between neurons, microglia, astrocytes, oligodendrocytes, and peripheral immune cells may help to develop new targets and treatment strategies to delay the progression of neurodegenerative diseases.

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**Hilal Cihankaya, Carsten Theiss, Veronika Matschke***
Ruhr University Bochum, Medical Faculty, Institute of Anatomy, Department of Cytology, Bochum, Germany (Cihankaya H, Theiss C, Matschke V)
International Graduate School of Neuroscience (IGSN), Ruhr-University Bochum, Bochum, Germany (Cihankaya H, Theiss C)
***Correspondence to:** Veronika Matschke, Dr.rer.nat., Veronika.Matschke@rub.de.
https://orcid.org/0000-0001-9717-4485 (Veronika Matschke)
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