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Editorial

Neurodegenerative diseases: failures in brain connectivity?

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The human brain is the most complex structure encountered by natural science. This structure is made up of ~1 trillion neural cells that form an intricate web of innumerable connections, which form the substrate for information processing. These connections are of fundamental importance because brain function lies in communications that are shaped by the environment and experience. Neural tissue is intrinsically plastic, and neural circuitry is constantly rewired and remodelled. Plasticity of the brain is controlled at three interdependent levels: in subcellular compartments, at the level of single cells and at the level of cellular networks. At all levels, however, signalling imbalance may cause toxicity, damage and death of neural elements, which in turn compromise communication processes within the neural web, thus causing neurological disease. Evidence is accumulating that the disruption of connectivity within neural circuits, loss of synapses and deteriorated synaptic plasticity precede death of neurones, and that this is fundamental pathologically to our understanding of neurodegeneration is accumulating. The synaptic deficits precede plaque formation and brain atrophy in Alzheimer's disease, and in a rat glaucoma model loss of synaptic activity occurs before demise of retinal ganglion cells.[1–3]

The life and death of neural cells are closely associated. Indeed, development, function and maintenance of neural circuitry require neuro- and synaptogenesis, as well as neural extinction and synaptic pruning.[4–6] Therefore, it is not surprising that the very same intracellular signalling cascades are involved both in physiological regulation and in disruption of neural connectivity.[7] As long as both are kept in balance, the brain will function properly; the pathological deregulation of controlled death routines triggers neurodegeneration. In fact, death and survival represent one of the facets of overall brain homeostasis, and the fundamental question of what distinguishes homeostasis from dyshomeostasis and death at every level from the individual synapse to the brain as a whole represents the core of our understanding of brain physiology and brain diseases.

This concept of balance is also implicit in cell death pathways. Both apoptosis and autophagy, as well as cell death processes that do not have all the classic features of either, have been implicated in neurodegeneration.[8] In apoptosis, in particular, cells exist in a state of equilibrium between the pro- and anti-apoptotic proteins that constitute the programme, and death occurs when this equilibrium is disturbed. In addition, cells express natural cytoprotective factors, the activity of which must also be overcome for death to occur. Perhaps the existence of these equilibria is one reason why apoptosis has become such an active area of translational research, as there are common clinical situations, such as cancer, wherein we need to tip the balance towards pro-death factors, and others, such as neurodegeneration and cardiovascular diseases, wherein we need to boost anti-apoptotic activities.

Brain homeostasis is controlled at many levels. First, the CNS is homeostatically independent from the body, being separated by the blood–brain barrier.[9] Second, neurones have evolved very high degrees of specialisation, perfecting the electrical excitability and synaptic transmission that enable rapid information transfer in neuronal networks.[10–12] Third, the high specialisation of neurones renders them homeostatically vulnerable and encourages the development of neuroglia, which have attained unprecedented complexity in the human brain.[13–15] Several types of neuroglia (astrocytes, oligodendrocytes and microglia) control brain architecture, microenvironment and defence. This makes the brain an extremely resilient organ, and indeed, brain resists ageing substantially better than any other tissue. Furthermore, the exceptional plasticity of the neural circuitry allows the possibility of repair and regeneration after lesions. The failure of brain homeostasis, however, has grave cognitive consequences.

Neurodegenerative disorders, progression of which inevitably results in dementia, are the ultimate and unique scourge of mankind, being generally absent in every other animal species. These diseases are, arguably, the most fearful conditions that can be met by humans, because they destroy the main asset of *Homo sapiens*, the intellect, thus reducing man to a helpless mindless body. It is singularly important that neurodegeneration and dementia are specific human diseases, as no animal naturally suffers either from Alzheimer's disease or from Parkinson's. It may well be that the appearance of intellect, which provided *Homo sapiens* with an enormous evolutionary advantage, came at the price

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of neurodegenerative diseases, which specifically impair the very reason for the biological success of the human species.

The causes of neurodegenerative diseases are legion, being represented by traumatic assaults (physical, chemical or infectious), by genetic factors that predispose the nervous system to neurodegenerative developments, by the combination of the above and by other, yet unknown reasons. Conceptually, however, neurodegeneration can be regarded as a primary connective failure because it destroys the neural circuitry, thus affecting information processing. Our knowledge of the cellular and subcellular mechanisms of neurodegeneration is still rudimentary, yet it is safe to assume that it is the contacts between neural cells that suffer first.

Connections in neural circuitry are formed by synapses that exist in both chemical (formed mostly by neurones) and gap-junctional (formed mostly between neuroglia) varieties. The classical chemical synapse is determined by at least three cells, which cooperate to produce the synaptic structure. The presynaptic terminal makes the synaptic input, which is received by the postsynaptic neuronal membrane, while the surrounding glial membrane forms the synaptic microenvironment.[16,17] These three subcellular compartments, working in concert, determine the dynamic synaptic plasticity at both functional and structural levels. The gap junctions, which also form electrical synapses, provide direct signalling between neural cells, which involves the diffusion of second messengers, ions and metabolic substrates. However, the role of this signalling in information transfer in the brain remains generally unexplored, although potentially it can represent another powerful cognitive tool.

Neurodegeneration affects connectivity at all levels. Pathological Ca^{2+} signalling can affect pre- and postsynaptic compartments, while the failure of astrocytes can deprive the synapse of glial support, with its subsequent elimination.[18–20] The microglial cells, which constantly scan the brain parenchyma and surveil synaptic contacts, can also contribute to synaptic demise.[21,22] On a functional level, dysfunctional astrocytes cause an imbalance of neurotransmitters, which has begun to be seen as one of the main reasons for emotional and cognitive disorders.[19] All these pathological steps accumulate and determine the onset of the neurodegenerative process. Further accumulation of pathologically relevant cellular damage initiates neurotoxicity, which ultimately results in localised or more generalised brain atrophy.

Although the pathogenesis of neurodegenerative disease is clearly complex, it is tempting to see the pathological disruption of synaptic connectivity, as opposed to physiological synaptic remodelling, as having a fundamental role. Restoring order to the yin and yang between synapse formation and maintenance *versus* disruption may therefore be as important therapeutically as modulating the cell death–survival balance. Among the many unresolved issues, here is why some neurodegenerative diseases are so localised – what is so special about the dopaminergic neurones of the substantia nigra that makes them a target for Parkinson's disease? This issue of *Cell Death and Differentiation* presents a collection of reviews dedicated to various aspects of neurodegenerative diseases, which discuss our current and imperfect state of knowledge of these problems, and we hope that these will inspire the readers to broaden their interests to contribute to pathologies that challenge our very humanity.

Conflict of interest

The authors declare no conflict of interest.

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