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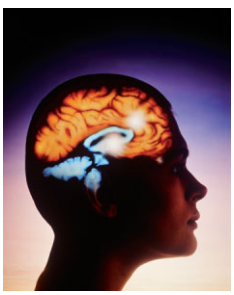
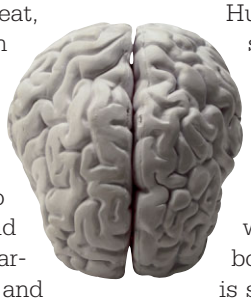
Editorial: Diseases of the brain – neuronal function and dysfunction

Nervous system disorders are among the most devastating human pathologies, affecting an ever increasing part of the population. It is indicative that within a decade the prevalence of neurodegenerative conditions such as stroke and Alzheimer's disease among the elderly in industrialized nations is predicted to rise above 50%. For this reason, developing effective strategies aiming to battle diseases that afflict the nervous system is becoming increasingly critical.

To attain the goal of countering neuronal dysfunction and loss, it is important to first understand neuronal function. Unless we have an understanding of the underlying cellular and molecular mechanisms, we cannot hope to successfully and efficiently intervene to neutralize brain pathologies. This is no simple task given the complexity and intricacies of the nervous system. Adding insult to injury, the number of nervous system diseases is large and expanding, while their origin and cause is just as diverse. Is there a limited set of common denominators in the form of core cellular processes and biochemical pathways that characterize brain diseases and are involved in their pathogenesis? Extensive studies in recent years have contributed to a more coherent and detailed picture of mechanisms involved in nervous system pathologies. In spite of the diversity of conditions that initiate these pathologies and the cellular responses involved, several commonalities are starting to emerge.



At least eight inherited human neurodegenerative diseases (including Huntington's disease and spinocerebellar ataxias) are caused by expansion of a CAG repeat, which results in an expanded tract of glutamines within the proteins. Polyglutamine expansion, beyond a critical threshold, leads to neuronal dysfunction and loss. Each disease is characterized by selective and distinct, yet overlapping, patterns of neurodegeneration, and a unifying pathological feature of these diseases is the formation of neuronal nuclear inclusions, possibly due to misfolding of the proteins. Protein aggregation has also been implicated in both Alzheimer's and Parkinson's disease. Mutations in α-synuclein have been linked to familial Parkinson's disease, a severe movement disorder, characterized by loss of dopaminergic neurons in the substantia nigra. Aggregates of α-synuclein forming structures known as Lewy bodies and Lewy neurites accumulate within specific dopaminergic neurons that progressively degenerate. In Alzheimer's disease patients, abnormally phosphorylated and aggregated forms of *tau*, a microtubule-binding protein, accumulate in degenerating neurons, forming intra-cytoplasmic neuronal inclusions known as neurofibrillary tangles.



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An additional important, common component of numerous nervous system disorders is neuron loss. For example, Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinocerebellar ataxias, and transmissible spongiform encephalopathies, to name a few, have been associated with pathological cell death, both apoptotic and necrotic. It is striking that despite the profound impact of necrotic cell death on human health, and contrary to apoptosis, the molecular events that transpire during cellular necrosis have long remained in obscurity. One major reason has been the lack of tractable genetic models of necrosis, similar to those that have greatly facilitated research on apoptosis. The dominant concept, permeating the field of necrosis research, prescribed that necrotic death is merely the chaotic breakdown of a cell under intolerable conditions and that the execution mechanisms involved are almost as diverse as the triggers initiating cell death. However, numerous studies utilizing an assortment of experimental systems converge to the conclusion that necrosis is not simply the decadent and inexorable fate of a cell otherwise not meant to die. The once thought chaotic biochemistry of necrotic cell death appears to obey certain orderly patterns. Understanding the ins and outs of necrosis inflicted by diverse initiators will shed light into the biochemical events that transpire during cell death. The molecules enacting these biochemical events are effectors of necrosis and should, in principle, constitute excellent targets for drug development and other methodologies designed to amelio-

rate or block pathological neuronal death.

Several experimental models of neurodegenerative disorders have been established in simple organisms that are amenable to genetic analysis, such as *Caenorhabditis elegans* and *Drosophila melanogaster*. The development of these nematode and fly models that faithfully reproduce features of brain pathologies in mammals has facilitated the infusion of both forward and reverse genetics approaches into our efforts to obtain a detailed description of the molecular events underlying neuronal dysfunction. The strong arsenal of molecular biology and biochemical tools available in *C. elegans* and *Drosophila*, coupled with their completely sequenced and highly annotated genomes, should greatly accelerate research on disease mechanisms. Many modern, high-throughput screening procedures such as whole-genome microarray analysis and systematic gene knockdown using RNAi allow comprehensive, genome-encompassing searches for genes involved in pathogenesis. Hence, these models should accelerate the dissection of the biochemical pathways mediating neuronal dysfunction, and provide knowledge that is essential for the development of effective protective measures against brain-specific diseases. These strategies have already started to pay off and promise even more discoveries in the near future.

"… the ultimate aim of facilitating innovative, educated approaches targeting brain disorders."

This issue of the Biotechnology Journal highlights diverse aspects of ongoing research efforts that impinge on neuronal function and dysfunction, with the ultimate aim of facilitating innovative, educated approaches targeting brain disorders. This is unquestionably a daunting endeavor, but mounting interdisciplinary ventures worldwide provide grounds for optimism and hold promise for eventual success.

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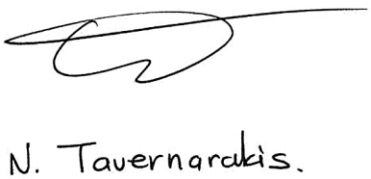

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