

## Editorial

Neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease and neurodegenerative conditions such as stroke and traumatic brain injury are leading causes of death in the Western world. Although displaying a diverse range of clinical symptoms, these neuropathologies have a commonality: the abnormal loss of neurons. While current treatments can reduce the symptoms associated with some of these pathologies, they do not stop the loss of neurons and hence do not slow down disease progression. Thus, there is an urgent need for the development of therapeutic drugs that will stop or reduce the loss of neurons in these diseases. Essential to this process of drug development is the identification of disease-related molecules that can be targeted by small molecule compounds and biomolecules. Compelling evidence gathered over the past decade has indicated that pathological neurodegeneration occurs as a result of an inappropriate activation of apoptosis, a cell suicide program. Intensive research has identified a large number of molecules and signal transduction pathways that promote or inhibit apoptosis. Inhibition of many of the molecules that promote apoptosis or stimulation of the activity of molecules that promote cell survival has been found to protect neurons in cell culture and in animal models of neurodegenerative disorders. Understanding the molecular mechanisms underlying apoptosis therefore offers promise of benefit to people suffering from neurodegenerative conditions.

The overall aim of the reviews in this issue is to describe the latest and most exciting information on the identification of intracellular molecular targets involved in neurodegenerative conditions, and the development of potential neuroprotective drugs that act on them. D'Mello and Chin provide a description of the molecular mechanisms underlying apoptosis in neurons. A section of the review covers neuroprotective compounds that modulate the activity of specific signaling molecules involved in the regulation of apoptosis. It is well established that caspases, a family of cysteine proteases, play a pivotal role in the apoptotic process in both neurons and non-neuronal cell types. Prunell *et al.* review the current information on caspases. Focus is placed on ischemic stroke and the role of caspases in this neurological condition. Another family of proteins consisting of both anti- and pro-apoptotic members are the Bcl-2 proteins. Shacka and Roth provide a description of the Bcl-2 proteins. Their involvement in the development of the nervous system and in various neurodegenerative diseases has been reviewed. A separate section covers neuroprotective strategies targeting Bcl-2 proteins. A number of small molecule activators and inhibitors of individual Bcl-2 proteins have recently been identified. The efficacy of some of these small molecule modulators in preventing death of cultured neurons and in animal models of neurodegenerative diseases is described in the review. Among the biological factors that stimulate the activity of anti-apoptotic proteins are estrogens. A separate review by Simpkins *et al.* describes the neuroprotective effects of estrogen. The protective effect of estrogens is likely to be mediated by supporting mitochondrial function. Compelling evidence for oxidative stress, bioenergetic impairment and mitochondrial failure in the etiology of neurodegenerative diseases has been presented in this review. Besides mitochondrial dysfunction, acetylation and deacetylation of histones within chromatin and of other nuclear and cytoplasmic signaling proteins has been found to regulate neuronal survival. Langley *et al.* review the evidence that misregulation of histone acetylase transferases and/or histone deacetylases are involved in certain neurological syndromes and in neurodegenerative diseases such as Huntington's disease, Alzheimer's disease and amyotrophic lateral sclerosis. The promise of histone deacetylase inhibition by small molecule compounds in the treatment of central nervous system disorders has also been discussed. Another target that is being explored for the treatment of neurodegenerative conditions is the c-Jun N-terminal kinase signaling pathway. CEP-1347, a compound that inhibits this pathway is already in a multi-center phase II/III clinical trial for the treatment of Parkinson's disease. Kuan and Burke review JNK signaling as a therapeutic target. Finally, Freeman and Barone describe the role of the hypoxia-inducible transcription factor (HIF) in neuroprotection. As described in the review, HIF is activated in response to stimuli such as hypoxia leading to the stimulation of cell survival genes. Several compounds which increase HIF activity have been developed and the utility of such compounds in the treatment of neurological disorders associated with hypoxia is being seriously considered.

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