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Aging
HEALTH

Drug treatment for neurodegenerative disorders among the elderly: re-engaging homeostatic programs

“Drugs that interrupt the apoptotic cascade may be intervening too late, keeping alive cells that have already sustained too much damage to function normally.”

With improvements in healthcare that have resulted in extended lifespan, the rate of diagnosis of neurodegenerative diseases among the elderly is increasing, creating a large, unmet medical need. Developing drug treatments for neurodegenerative disorders is challenging because these pathologies have diverse and poorly understood etiologies. Pathology results from the failure of cells and organisms to respond to challenges by engaging evolutionarily conserved adaptive programs that help to maintain homeostasis. A fundamental challenge of disease research is to discover what type of stress the body has failed to adapt to in each pathology, and to develop therapeutics that will re-engage endogenous adaptive programs, thus allowing cells to restore and maintain homeostasis [1].

Neurodegenerative disorders & aging: mechanisms of dysfunction

Neurodegenerative disorders result from deterioration of neurons in the brain or spinal cord and can cause deficits in motor and/or cognitive functions. The most common neurodegenerative diseases among the elderly are dementias, such as Alzheimer's disease, and movement disorders, such as Parkinson's disease. Many inherited neurodegenerative disorders appear and progress in an age-related manner, with more exaggerated genetic variants associated with earlier onset of symptoms, for example Huntington's disease, which is characterized by a combination of choreic movement disorders, emotional disturbances and cognitive deficits.

At present, drug treatments for neurodegenerative diseases are limited. Levodopa and deep brain stimulation have proven effective for many Parkinson's patients. Acetylcholinesterase inhibitors (e.g., donepezil, galantamine and rivastigmine) and NMDA-receptor antagonists (e.g., memantine) have proven moderately

effective in controlling symptoms of Alzheimer's disease, but have not demonstrated clinically relevant effects on delaying disease progression. The development of new drug treatments will require a better understanding of disease etiology and improved early diagnostic tools.

“Age-related changes in brain structure ... have been observed in elderly populations, hence, it is difficult but important to distinguish normal aging from pathology.”

The relationship between age and neurodegeneration is not entirely clear and probably varies between specific pathologies. Age-related changes in brain structure, particularly loss of white matter tissue volume and the appearance of white matter hyperintensities that indicate microcerebrovascular injury, have been observed in elderly populations, hence, it is difficult but important to distinguish normal aging from pathology [2]. With aging, mitochondrial DNA accumulates mutations at a much higher rate than nuclear DNA. These mutations can diminish the cell's ability to express genes that are constitutively required for normal function as well as genes that allow the cell to react to changes and defend itself against challenges. Since adult neurons do not divide and, thus, with few exceptions, are not replaced, these accumulated errors can cause dysfunction and lead to neuronal degeneration. Age-related changes in non-neuronal tissues also contribute to neurodegeneration. Blood vessels accumulate weak spots and thickened spots, which lead to microhemorrhagic and microischemic events. Glial cells that ensheath axons or monitor neuronal cells and circuits can fail to provide proper support and can produce aberrant inflammatory responses.

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Metabolic deficits have been observed in almost all neurodegenerative diseases and are associated with aging [3]. Mitochondrial dysfunction leads to reduced ATP production, which is required to fuel necessary cellular activities, as well as increased production of reactive oxygen and reactive nitrogen species. Without appropriate antioxidant defenses, these reactive species can wreak havoc in the cell by oxidizing and nitrosylating many cellular proteins, lipids and nucleic acids. This damage, compounded by genetic variants in coding or regulatory DNA, can also contribute to protein misfolding, induction of chaperone protein synthesis and sequestration of misfolded proteins into aggregates, such as the β -amyloid plaques and tau tangles observed in Alzheimer's disease and Lewy bodies observed in Parkinson's disease. Mitochondrial dysfunction can also initiate apoptotic cascades, which lead to the programmed death of that cell and to the release of proapoptotic factors that may influence neighboring cells. Apoptosis can be adaptive by limiting the harm caused by dysfunctional cells. Owing to the redundancy in the parallel-processing circuitry of the human brain, the loss of a few cells may have negligible effects on the function of neuron networks. Nonetheless, the accumulation of dysfunction and loss of nondividing neurons over a lifetime make the elderly more susceptible to experiencing cognitive, motor and other neurological impairments as a consequence of common cellular- and tissue-level injuries.

Harnessing cellular adaptive programs to promote homeostasis

Homeostasis is the ability of an organism, or of a single cell, to maintain a stable internal state. This requires sensing and responding to changes in environmental conditions. We enjoy good health when our adaptive programs respond appropriately to challenges; conversely, we suffer from disease when a stressor interrupts or overwhelms homeostatic mechanisms so that they cannot respond to challenges. Even in diseases for which the triggering event or pathogen is known, many of the symptoms result not from direct effects of the trigger, but from the body's inappropriate response to the trigger or to subsequent challenges.

Stroke is a prime example of dysfunction caused by failure of homeostasis after a known pathogenic event. Stroke is the most common neurological cause of disability in the USA and, similar to neurodegenerative diseases, the risk of stroke increases with age. A typical ischemic stroke, in which blood flow to a region of the

brain is substantially reduced, causes necrotic cell death in the core owing to energy failure in cells deprived of glucose and oxygen. The release of glutamate and signaling molecules from these cells will cause excitotoxicity and inflammation in neighboring cells, leading to delayed cell death via apoptosis in the penumbra over 48–72 h after onset of ischemia. Currently, the only US FDA-approved drug for stroke is tissue plasminogen activator, which can dissolve a clot to restore blood flow and provide benefit only if delivered within a few hours after stroke. Research is ongoing to identify novel molecular targets for pharmacological intervention in the hours to days following stroke that might protect cells on the cusp of life/death decisions and, thus, reduce penumbral infarct size, and that might promote plasticity for functional reprogramming to compensate for lost tissue.

“...the accumulation of dysfunction and loss of nondividing neurons over a lifetime make the elderly more susceptible to experiencing cognitive, motor and other neurological impairments as a consequence of common cellular- and tissue-level injuries.”

Drug-development strategies for neurodegenerative diseases may be informed by the successes of ischemic preconditioning in preventing neuronal loss after stroke [4]. A sublethal hypoxic challenge makes animals more resistant to tissue pathology and death following a later cerebral ischemic challenge that would typically be lethal. Similarly, a preconditioning peripheral nerve lesion can increase the regenerative capacity of spinal neurons [5]. These examples demonstrate the power of endogenous adaptive programs to detect injury and to respond by preparing the cell to better withstand future injuries and by promoting the capacity for repair. These adaptive programs require both an initial phase of post-translational modification of existing proteins, and a second phase of *de novo* protein synthesis. The latter effect is directed by changes in the expression levels of many genes, comprising large transcriptional programs that are coordinately regulated by a host of transcription factors, coactivators, corepressors and histone modifiers that recruit or exclude the transcription machinery from promoter regions.

Engaging broad programs of transcriptional regulation by which cells maintain homeostasis when challenged may prove more effective than targeting single genes or proteins, and may be particularly well suited to restoring order to chronically stressed neurons. Several master regulators of homeostatic responses have been identified. In response to low oxygen levels, hypoxia-inducible factor (HIF)-1 is stabilized and increases angiogenesis and anaerobic ATP production via glycolysis [6]. The peroxisome proliferator-activated receptor- γ coactivator (PGC-1 α) regulates mitochondrial respiration and antioxidant defenses, and is thought to mediate many of the beneficial effects of exercise in healthy bodies [7]. Since deficits in mitochondrial function and antioxidant defenses are observed in neurodegenerative diseases, PGC-1 α and other transcriptional regulators are promising therapeutic targets for neurodegenerative-disease drug treatments [8].

“...forcibly overactivating regulators of homeostatic processes may go beyond restoring balance to introduce new complications...”

Adaptive programs that produce homeostatic responses are very powerful and flexible, but not perfectly so. It is likely that the therapeutic benefits of using small molecules to activate mediators of adaptive programs will depend on the type and severity of the injury or disease. For example, promoting mitochondrial biogenesis may boost energetic support for cognitive functions in mildly impaired patients; however, in patients with advanced mitochondrial dysfunction, enlarging the mitochondrial pool may increase the release of proapoptotic factors, causing further damage and cell death. In addition, forcibly overactivating regulators of homeostatic processes may go beyond restoring balance to introduce new complications; for instance, ‘prosurvival’ signals, such as HIF-1 and protein kinase B (Akt), can suppress apoptosis but can also promote tumorigenesis.

Evolutionarily conserved adaptive programs may not always favor cell survival. For instance, HIF-1 induces proapoptotic genes as well as prosurvival genes [9]. In cases of severe injury, the decision of one cell to undergo apoptosis may be adaptive for the whole organism by preserving limited resources. Drugs that interrupt the

apoptotic cascade may be intervening too late, keeping alive cells that have already sustained too much damage to function normally. In evaluating the efficacy of neuroprotective agents in preclinical studies, care should be taken to measure not only the cellular hallmarks of pathology (e.g., size of infarct or lesion, extent of plaques, tangles and demyelination), but also the preservation of functional synaptic connectivity in protected neurons.

Future perspective

Earlier and finer sensors of changes in neuronal milieu, including pH, redox potential, acidosis and other disease-relevant cellular states, need to be discovered and harnessed to engage comprehensive endogenous adaptive programs. A better understanding of the mechanisms of action of these sensors and effectors of adaptive programs will help us evaluate the potential risks and benefits of targeting these molecules in patients. The development and validation of better animal and cell-culture models of neurodegenerative disease and normal human aging will be critical to the success of translational research.

“In evaluating the efficacy of neuroprotective agents in preclinical studies, care should be taken to measure not only the cellular hallmarks of pathology ... but also the preservation of functional synaptic connectivity in protected neurons.”

High-throughput screening and other unbiased approaches to identify small-molecule activators of endogenous homeostatic processes are providing promising candidates for novel drug treatments for neurodegenerative disorders.

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