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Commentary

Do Neurons Have a Choice in Death?

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In an article appearing in this issue of *The American Journal of Pathology*, Cribbs and colleagues[1] present compelling evidence for activation of caspase in vulnerable neurons in Alzheimer's disease (AD) based on specific caspase-mediated cleavage of a substrate protein. These findings add the cytoskeleton protein fodrin to actin and amyloid β protein precursor (AβPP) cleavage products demonstrating caspase activation in AD.[2,3] What is missing from this analysis, for these data to be consistent with an apoptotic cascade, is nuclear condensation/fragmentation and death at a rate predicted from the display of terminal events of cell death in most of the vulnerable neurons. In previous articles, we have argued that the dynamics of apoptotic death, which requires but hours, precludes the broad display of apoptosis for a chronic disease like AD.[4,5] Here we also argue that changes regarded as apoptotic in simple systems may not be *bona fide* apoptosis in complex living systems that use all available information to maintain homeostatic balance.

The complexity of biological systems so often presents such a formidable challenge that it is difficult to conceive that it is all based on interactions classified as covalent, ionic, van der Waals, and hydrogen bonds among a small number of atomic species. From such simple rules, the genetic code, subcellular and organismic morphogenesis, social structure, and the biosphere are defined, and have been so as long as there has been life on earth. With simple rules, reductionist approaches have served modern biology well to probe the basic pathways, but when so few features underlie a complexity that by its nature is self-regulating, by necessity the elements must have multiplicity of action among the determinants rather than the singularity necessitated by reductionist biology. This aspect has been no more clear than the results of reverse genetics. In most cases, the function of proteins linked to disease are undefined. This is due not to lack of identified function, but rather to the multiplicity of identified functions, suggesting that multiplicity, not singularity, is an intrinsic property of biological systems. Instead of occupying a single role, proteins, pathways, organ systems, and species occupy the available niche, which, like individuals, are determined by both intrinsic (composition) and extrinsic (environment) factors.

The enormous resources and intense efforts poured into AD research have made it possible for us to confront the distinctions between singularity and multiplicity. In this issue of the *Journal*, Cribbs and colleagues[1] examine the case for apoptosis as the mechanism for neuronal death in AD. As stated above, they find that caspase-mediated fodrin fragments can be added to actin and AβPP as evidence for activation of apoptosis as the mechanism of neuronal cell death in AD. Although they described caspase activation as neuritic, synaptic, somatic, or mitochondrial, activation does not mark *bona fide* neuronal death in AD. Instead, the investigators mix metaphors of singularity and multiplicity. *In vitro*, apoptotic changes always lead to death (singularity), while *in vivo*, they do not necessarily do so (multiplicity). In tissue culture, the death of each neuron is a singular event, little changing the chance for survival of its neighbor in the dish and certainly not those of other plates in the incubator. In contrast, loss of neurons in the human brain endangers the survival of the individual, his family, and, to some extent, society as a whole as it promotes disequilibrium and instability. While dynamism is critical to life, instability can quickly destroy the system, and destruction and removal are favored only if it promotes higher level organization.

Apoptosis is a program to remove cells detrimental to higher level organization in development, neoplasia, or after irreparable damage. That so many signs of apoptosis are activated in neurons in AD can be reconciled if we suspend reductionism and accept that one of the pathways by which cells deal with stress is activation of various proteolytic and structural changes, not as the proximal event to death but as a reconfiguration of cellular homeostasis. Unlike homogeneous organs, where death of damaged cells could be desirable, in the adult brain, conservation of brain cell topography is critical. Therefore, it is likely that evolution has promoted neuronal survival at all costs (see below) so that, in the context of a human brain, a multiplicity of responses will work to promote neuronal survival through factors not seen *in vitro* and maybe not even in *in vivo* models that have nonphysiological homeostatic balances. An instance of this is

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Aβ PP-overexpressing mice, which show amyloid-β (Aβ) deposits and other changes of AD.[6] In these mice, Aβ is being inappropriately recruited to a scene where it is neither called for nor wanted, and its presence may initiate changes coming from it, as well as the changes that normally precede it. Aβ and phosphorylated tau may instead be critical to homeostasis in AD. Classification as either the originator of the disease (singularity) or irrelevant to disease does a disservice to the multiplicity of roles that Aβ or phosphorylated tau may be playing. Increases in both during injury at any age, as well as the central tenet of biology of the preservation of higher order, argue for a homeostatic function of responses induced in disease rather than an etiological role. A protein's role may be absent or aberrant with genetic mutation, an argument certainly supported by the abnormalities in mice overexpressing normal Aβ PP or normal tau but promoted by mutations in either. With such strong pressure to live, as they do throughout normal aging, it is not unexpected that neurons, and possibly other postmitotic cells, have unusual redundancy in their ability to respond to insult by inducing anti-apoptotic signaling, and this balance is what defines neuronal homeostasis in AD. Instead of succumbing at death's door, neurons select other portals. It is these choices, we argue, that define neuronal longevity in normal aging as well as neuronal persistence in AD.

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