DEPRESSION GETS OLD FAST: DO STRESS AND DEPRESSION ACCELERATE CELL AGING?

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Depression has been likened to a state of "accelerated aging," and depressed individuals have a higher incidence of various diseases of aging, such as cardiovascular and cerebrovascular diseases, metabolic syndrome, and dementia. Chronic exposure to certain interlinked biochemical pathways that mediate stress-related depression may contribute to "accelerated aging," cell damage, and certain comorbid medical illnesses. Biochemical mediators explored in this theoretical review include the hypothalamic–pituitary–adrenal axis (e.g., hyper- or hypoactivation of glucocorticoid receptors), neurosteroids, such as dehydroepiandrosterone and allopregnanolone, brain-derived neurotrophic factor, excitotoxicity, oxidative and inflammatory stress, and disturbances of the telomere/telomerase maintenance system. A better appreciation of the role of these mediators in depressive illness could lead to refined models of depression, to a re-conceptualization of depression as a whole body disease rather than just a "mental illness," and to the rational development of new classes of medications to treat depression and its related medical comorbidities. Depression and Anxiety 27:327–338, 2010.

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CELL AGING: TELOMERES AND TELOMERASE

Telomeres are DNA-protein complexes that cap the ends of linear DNA strands, protecting DNA from damage.[146] When telomeres reach a critically short length, as happens when cells undergo repeated mitotic divisions without adequate telomerase activity (e.g., immune cells and stem cells, including neurogenic stem cells in the hippocampus), cells become susceptible to apoptosis and death. Even in nondividing cells, such as mature neurons, telomeres can become shortened by oxidative stress, which preferentially damages telomeres to a greater extent than nontelomeric DNA.[126,147] This non-mitotic type of telomere shortening also increases susceptibly to apoptosis and cell death. Telomere length is a indicator of "biological age" (as opposed to just chronological age) and represents a cumulative log of the number of cell divisions and a cumulative record of exposure to genotoxic and cytotoxic processes, such as oxidation.[20,22,23,126,146,148] Telomere length may also represent a biomarker for assessing an individual's cumulative exposure to, or ability to cope with, stressful conditions. For example, preliminary data point to accelerated leukocyte telomere shortening, a sign of cellular aging, in chronically stressed[22,23] and in depressed[149] individuals. The telomere shortening may, at least in part, be related to increases in stress-related cortisol and catecholamine output.[23,150] The estimated magnitude of the acceleration of biological aging is not trivial; it was estimated as approximately 9–17 additional years of chronological aging in the stressed caregivers and as much as 10 years in the depressed individuals. It should be noted that the subjects in the depression study had very chronic courses of depression (an average of nearly 26 years of lifetime depression).[149] Preliminary data suggest that telomere shortening is a function of the duration of the lifetime exposure to depression (Wolkowitz et al., unpublished) and may not be present in individuals with short lifetime exposures to depression. In non-depressed populations, shortening of leukocyte telomeres is associated with atherosclerosis and CV disease,[151–153] osteoporosis[154] and cognitive impairment,[155] and with increased medical morbidity and earlier mortality from a number of causes, including CV and infectious disease, and dementia.[156] For example, shortened telomeres are associated with a greater than three-fold increase in the risk of myocardial infarction and stroke, and with a greater than eight-fold increase in the risk of death from infectious disease.[157] In a more recent study, baseline telomere length (in women) and prospective rate of change in telomere length over a 2.5 year period (in men) predicted CV mortality over a 12-year period.[156] Thus, cell aging (manifest as shortened telomeres), associated with any of the mediators discussed above, provides a conceptual link between depression and its associated medical comorbidities and shortened life span.[20,102,148]

Telomerase is a reverse transcriptase enzyme that rebuilds telomere length, thereby delaying cell senescence, apoptosis, and cell death.[146] Telomerase also has antiaging or cell survival-promoting effects independent of its effects on telomere length by regulating transcription of growth factors, synergizing with the neurotrophic effects of BDNF, having antioxidant effects and intrinsic antiapoptotic effects, protecting cells from necrosis, and stimulating cell growth in adverse conditions.[145,158,159] Telomerase activity has not yet been characterized in individuals with major depression, but it has been reported to be diminished[22] or increased[160] in stressed caregivers compared to low stress controls. Several of the mediators discussed above can contribute to diminished telomere length and/or telomerase activity (e.g., cortisol,[150] oxidative stress,[147] and inflammatory cytokines[160,161]), highlighting the interlinked nature of cell-damaging and cell-protective mediators

in stress and depression. Important moderators of telomere length are rapidly being discovered (e.g., childhood maltreatment,[162] socioeconomic status,[163] race,[164,165] physical exercise,[166] and dispositional pessimism,[39] among others).