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Highlight

A Unified Model of Age-Related Disease

Michael Fossel *

Telocyte LLC, Grand Rapids, Michigan, USA; E-Mail: Michael.fossel@telocyte.com

* **Correspondence:** Michael Fossel; E-Mail: Michael.fossel@telocyte.com

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The empire, long divided, must unite; Long united, must divide.

- *The Three Kingdoms,* Luo Guanzhong

Geriatric medicine has been long divided as we try to understand the precise causes of age-related disease, such as atherosclerosis or dementia. On the other hand, geriatric medicine has been long united by unexamined assumptions about aging and how aging triggers disease. If we are to advance, we must examine our assumptions, dividing aging into the myriad complex genetic and cellular processes that are its basis. Only then can we unite in our understanding of how age-related diseases work and – more importantly – how to intervene safely and effectively.

The lack of an overarching systems model of age-related disease prompted a talk that I gave in Washington, by invitation of the Alzheimer's Association, in which I pointed out this lack. We have an in depth understanding of risk factors and a detailed knowledge of clinical presentations, but we have no unified model to explain precisely why those risk factors result in those presentations. For example, we know that exposure to certain toxins (such as paraquat) increases the risk of certain age-related diseases (such as Parkinson's disease), but we don't have a unified model to explain this relationship. Equally, we know that certain alleles (such as APOE4), some kinds of trauma (such as closed head injuries), and some infections can all increase the risk of beta amyloid plaques, tau tangles, and their clinical phenotype (Alzheimer's disease), but again we lack a unified model to precisely explain the assorted cascades of pathology that take us from risk factor to disease. The same problem occurs when we examine age-related vascular disease, osteoarthritis, osteoporosis, and other age-related clinical problems. Not only don't we have a clear model to

explain how known risk factors segue into known age-related disease, we don't even have a model to explain how aging itself results in age-related disease. As Leonard Hayflick, the father of cell senescence aptly observed in a private conversation: "The cause of aging is ignored by the same people who argue that aging is the greatest risk factor for their favorite disease."

In response to this problem, I wrote a recently published paper [1] to explain how such risk factors result in geriatric disease. The paper focuses upon age-related neurologic diseases (such as Alzheimer's), but the model pertains equally to all age-related disease, not only those of the central nervous system. Essentially, the model says that risk factors operate by affecting cell division and thereby affecting the rate of cell senescence in specific cells and cell types. As cells senesce (and long before replicative senescence occurs), gene expression changes subtly but pervasively. The cellular outcomes are a significantly slower molecular turnover (e.g., the production and recycling of mitochondrial enzymes, DNA repair enzymes, membrane lipids, scavenger molecules, etc.), thereby increasing the percentage of dysfunctional molecules, with a resulting cellular dysfunction that increases with both chronological age and the effects of the known risk factors. As cells become dysfunctional, so too do surrounding tissues. Glial cell dysfunction underlies most dementias, vascular endothelial cell dysfunction underlies most age-related cardiovascular disease, just as chondrocyte senescence results in osteoarthritis and osteocyte senescence results in osteoporosis. In every case, age-related disease can be traced downstream from the risk factors (including age itself), through cell senescence, and finally into the clinically evident diseases that are the domain of geriatric medicine.

The strength of the model is two-fold. Its first strength is that the model offers a single consistent "systems" approach to age-related disease. It not only explains exactly why and how age-related diseases occur and can account for all known risk factors, but it also explains why we see a variety of clinical diseases within a single organ system (such as Alzheimer's, Parkinson's, EOAD, FTD, vascular dementia, etc.). Moreover, it offers predictive validity, in that it predicts the way in which many clinical trials fail, predicting the shape of the outcomes of such trials before the data is available. For example, when Alzheimer's is treated with monoclonal antibodies to beta amyloid, the model predicts the initial and transient delay in disease course and the subsequent parallel vector of the disease course as the patients continue to decline.

The second (and far more important) strength of the model is that it predicts an entirely novel and potentially effective point of clinical intervention. Not only does it suggest that the most effective point of clinical intervention in age-related disease would be cell senescence itself, with the telomere as the best central target for reversing cell senescence, but such an approach is already within technical reach.

Geriatric medicine has long been a divided field, united only by our unexamined assumptions about the nature of aging. It is time that we divide aging into its component parts and unite in our understanding of how age-related disease can be cured. It is long past time that we improve the lives of our patients.

Author Contributions

Michael Fossel was the solo author.

Competing Interests

The author is the founder of Telocyte LLC, a biotechnology company working in this area.

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