Drugs that modulate aging: the promising yet difficult path ahead

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Once a backwater in medical sciences, aging research has emerged and now threatens to take the forefront. This dramatic change of stature is driven from 3 major events. First and foremost, the world is rapidly getting old. Never before have we lived in a demographic environment like today, and the trends will continue such that 20% percent of the global population of 9 billion will be over the age of 60 by 2050. Given current trends of sharply increasing chronic disease incidence, economic disaster from the impending silver tsunami may be ahead. A second major driver on the rise is the dramatic progress that aging research has made using invertebrate models such as worms, flies, and yeast. Genetic approaches using these organisms have led to hundreds of aging genes and, perhaps surprisingly, strong evidence of evolutionary conservation among longevity pathways between disparate species, including mammals. Current studies suggest that this conservation may extend to humans. Finally, small molecules such as rapamycin and resveratrol have been identified that slow aging in model organisms, although only rapamycin to date impacts longevity in mice. The potential now exists to delay human aging, whether it is through known classes of small molecules or a plethora of emerging ones. But how can a drug that slows aging become approved and make it to market when aging is not defined as a disease. Here, we discuss the strategies to translate discoveries from aging research into drugs. Will aging research lead to novel therapies toward chronic disease, prevention of disease or be targeted directly at extending lifespan? (Translational Research 2014;163:456–465)

Abbreviations: ADRB2 = β-adrenergic receptor; IGF = insulin-like growth factor; IIS = insulin/IGF signaling; LMNA = lamin A/C; NIA = National Institute on Aging; PKA = protein kinase A; TOR = target of rapamycin; TORC1 = target of rapamycin complex 1; TORC2 = target of rapamycin complex 2; SIR2 = silent information regulator 2; STACs = sirtuin activating compounds

While the quest for immortality goes back thousands of years, critical thinking about why we age begins, it can be argued, with Darwin and natural selection. If only the fittest survive, why would an organism age, lose functional capacity, and die. Yet aging occurs in almost every species.[1] Alfred Russel Wallace proposed an early version of group selection, where it would be beneficial for older individuals to be eliminated so that the reproducing younger individuals can have access to a larger allotment of available resources.

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The evidence for group selection with respect to aging is limited, but the question was right and the apparent answer at least in part comes from data on life expectancy. Essentially, average life expectancy among humans was under 25 and very few people died from age-related diseases.[2] More prevalent causes of mortality were infectious disease, childbirth, and malnutrition. There was no selective pressure to extend reproductive capacity or life expectancy since very few people lived long enough for it to matter. While beyond the scope of this review, evolutionary theories of aging have continued to evolve, with elegant hypotheses such as antagonistic pleiotropy and the disposable soma theory emerging.[3,4] Readers are encouraged to seek out the following reviews.[5-7]

What is worth considering here is whether the aging process is fixed or malleable? All data collected from the wild and from experimental organisms indicates the latter; life expectancy and the intrinsic aging process are relatively easily altered. For instance, similar species in the wild can have widely divergent life expectancies based on requirements imposed by evolutionary life history traits and other environmental factors.[8] Moreover, hundreds of genetic mutants have been identified with longer lifespan and often longer healthspan, the disease free and highly functional period of life.[9]

Against this backdrop, a dramatic change in demography has occurred within the last 2 centuries. Never before have humans been so old. Life expectancy has surpassed 80 in many countries and, coupled with a declining birthrate in many of those same countries, the percentage of seniors is skyrocketing. In the near future, up to 40% of the Japanese and Korean populations will be over 65 and the rest of the developed world will not be far behind (http://www.who.int/ageing/publications/global_health.pdf). Using current projections, 2 of the 9 billion people on the planet in 2050 will have lived at least 6 decades.

Older people offer experience and wisdom but are also increasingly beset with chronic disease. Aging itself is the biggest risk factor for most of the leading causes of disease burden and mortality, including cardiovascular and neurodegenerative disease, metabolic syndromes, and most forms of cancer. Add to that societal changes leading to over nutrition, lack of exercise and stress and the result is that most people over 65 in the US have 1–3 chronic diseases (http://www.who.int/ageing/publications/global_health.pdf). This reduces their productivity and dramatically escalates health care costs. In summary, the silver tsunami threatens to leave wrecked economies in its wake.

One partial solution is to keep people healthy longer and aging research may have much to offer. By delaying aging, it may be possible to prevent the onset of chronic diseases and increase healthspan. Healthy seniors could work longer at high rates of productivity and would certainly reduce the burden of healthcare. But aligning medical research on aging with prevention has its challenges. How do drugs that slow aging make it to market when aging is a slow process and not even recognized as a disease by the Food and Drug Administration. Prevention trials for chronic diseases are also slow and often expensive. Will drugs that slow aging be effective for treatment of chronic diseases? It is not obvious that a drug that slows aging will have any impact after an age-related disease is already creating havoc.

In this review, we cover briefly the progress in studies on the genetics of aging and then turn to small molecules that modulate aging. The 2 best studied, rapamycin and resveratrol will be discussed in some detail. Finally, we return to the question of the potential utility of aging drugs, making the argument that they will be effective therapeutic agents for disease states, but maybe not for the reasons that are most obvious.

THE GENETICS OF AGING

Before active pursuit of aging in invertebrates began in earnest, much of our understanding of the molecular and genetic events driving aging was based on correlative studies of young and old animals. However, starting in the 1960s, genetic studies of aging *Drosophila melanogaster* and *Caenorhabditis elegans*, simpler and cheaper model organisms, began to yield insights.[10-14] Studies in yeast replicative aging, the number of times 1 mother cell can divide and produce a daughter,[15,16] date back to 1959 and turned to genetics as well.[17,18] Yeast chronological aging, the survival of yeast cells in a postreplicative environment,[15,19] has also proven highly informative. It was clear from these studies that extending lifespan was possible through methods such as mutagenesis and screening,[10,12,20] or through selection, for instance, by isolating flies that maintain late reproductive capacity over many generations.[13,21]

The first longevity mutants began to be isolated in *C. elegans* and for yeast replicative aging in the 1990s and this field of research has gained steam in dramatic fashion ever since.[11,20] Worms and yeast have led the way in part because they are amenable to whole genome screening for longevity and hundreds of genes whose reduced expression lead to lifespan extension in both organisms have been identified.[22-30] Critically, in many cases, ortholog families have been identified that modulate aging across multiple species.[31,32] In addition, quantitative evidence has been generated that longevity pathways are conserved between *C. elegans* and yeast (replicative aging).[33] These results provide a demonstration that the aging process has significant