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INVITED REVIEW

THE IMMORTAL LIVES HYPOTHESES OF AGING

ABSTRACT

Some of the many hypotheses of aging advanced over the past 50 years are discussed and evaluated. Assessment of the experimental evidence suggests that , under particular environmental and genetic conditions any one of these may provide an accurate description of mechanisms by which aging occurs.

Key Words: Aging; Caloric Restriction; Cell Survival; Cytokines/metabolism; Immunity; Longevity; Models, Biological; Models, Chemical; Reactive Oxygen Species

DAVETLİ DERLEME

ÖLÜMSÜZ YAŞAMLAR-YAŞLANMA HİPOTEZLERİ

ÖZ

Yaşlanmanın mekanizmaları üzerine geliştirilen bazı hipotezler tartışılmış ve değerlendirilmiştir. Yapılan deneysel araştırmalar; çevresel faktörlerin ve bazı genetik özelliklerin yaşlanmanın mekanizması ile ilgili bu hipotezlerden bazılarının doğruluğunu açıklayabilmektedir.

Anahtar Sözcükler: Yaşlanma; Kalori Kısıtlaması; Hücre Yaşamı; Sitokinler/metabolizma; Bağışıklık; Uzun Yaşam; Biolojik Modeller; Kimyasal Modeller; Reaktif Oksijen Türleri

Introduction

The recent book by Rebecca Skloot ("The Immortal Life of Henrietta Lacks," Bantam Books, 2010) describes the important and continuing role of Ms. Lacks' cervical cancer cells (HeLa cells) in advancing understanding of aging and disease. A similar role is played by the many different hypotheses advanced to explain mechanisms of aging. Just why do we get old? Over the past 50 years a large number of hypotheses have been advanced suggesting that one particular mechanism or another is responsible for the progressive degeneration with time which characterizes the aging process. Usually these views are much-debated and then disappear, as different ideas emerge. However they are rarely disproved and many return as new evidence again suggests their validity.

Theories

A classic example of this scenario is the re-emergence of Roy Walford's "Immune Theory of Aging," formulated in 1964, and suggesting that decline of the immune system is responsible for aging (1). Largely forgotten since then, its importance was recently revived by experiments demonstrating that delay of involution of the thymus gland (a key component of immune function) was associated with extended longevity in laboratory mice (2). This was followed by recent data showing that elimination of "old" or senescent cells, including immune cells, in mice also extended longevity (3,4), suggesting a role for decline of the immune system in mechanisms of aging. Several reports of correlations between longevity and telomere length of peripheral lymphocytes in men and women also have strengthened the conviction that immune competence probably plays a role in

mechanisms of aging. Another example of a popular hypothesis of aging, is that functional decline is due to damage inflicted by oxidative free radicals generated in the course of usual metabolism (5). This view led to a highly profitable industry involved in the marketing of anti-oxidant compounds. However, the experiments of several groups using mice genetically engineered to either over- or under-express levels of endogenous anti-oxidant defenses have demonstrated no effects on longevity (6). These results suggest a minor role for oxidative damage in mechanisms of aging. In consequence, the "Oxidative Free Radical Theory of Aging" is no longer widely discussed, although these processes clearly play a role in several age-related diseases. The most recent example of the rise and fall of a postulated mechanism of aging relates to sirtuin genes. Transcription of these genes generates protein deacetylases which link gene expression to cellular redox status and energy metabolism. Much-publicized work in worms and flies suggested these genes may be responsible for the anti-aging effects of caloric restriction. However, later experiments were unable to confirm the results. Proponents on both sides of the "Sirtuin Theory of Aging" continue to disagree on the importance of this gene family for mechanisms of aging. However, it was recently suggested by a knowledgeable third party that perhaps "...all the results are likely to be correct.." (7). If so, this particular mechanism will no doubt continue to receive much future debate.

Calorie Restriction

My own research over the past 35 years has been directed at testing various hypotheses of aging, focusing on mechanisms by which calorie restricted diets slow aging processes. By far the most popular hypothesis during this time has been the "Rate of Living Theory of Aging"(8), based on the fact that small animals with high rates of metabolism for their size have much shorter lifespans than large animals, which have lower metabolic rates when referenced to their body weights. The fact that reduced feeding (as in calorie restriction, or CR) lowers metabolic rate (MR), suggests that the increased longevity of CR animals is a consequence of decreased MR(9). Since decreased MR would also be expected to generate lower levels of oxidative damage (as has been identified in CR animals), this view brought together both the "Rate of Living" and the "Oxidative Free Radical" hypotheses of aging. Our experiments in laboratory rats showed that the reduction in MR with CR was transient and that over the lifespan of these animals, mass-specific MR was the same for both fully-fed and restricted animals (10). Subsequent experiments in voluntarily-exercising rats confirmed this result, showing there was no decrease of longevity in exercising (high MR) versus sedentary (low MR) animals (11). Other researchers have found increased MR, no change in MR, or decreased MR with lifelong CR in different strains of rats, mice and non-human primates. It seems likely that all of these results, too, are correct. Thus the data suggest that intensity of metabolism is probably not a significant factor in mechanisms of aging. However, this has not deterred several investigators from continuing to suggest the singular importance of MR in aging processes. Another once-prominent view of aging we investigated was the "Glycation Hypothesis of Aging," suggested by Cerami in 1985 (12). This was based on the observation that diabetics frequently exhibit signs of accelerated aging and have chronically elevated levels of blood sugar. Since decreased levels of plasma glucose are characteristic of long-lived animals on CR, it seems possible that levels of blood sugar may be involved in age-related degeneration. We obtained mice genetically engineered to have the same levels of blood sugar as normal CR mice and we also measured engineered mice on the CR diet (whose plasma glucose levels were significantly lower than the other groups). Longevity and many functional properties of mice were measured and the results were clear: there was no effect of the level of plasma glucose on lifespan, function and tissue pathology (13). Obviously levels of blood sugar higher than normal may be harmful, but our data indicate that lower than normal glucose levels are probably not involved in the life-prolonging effects of CR. Reports do however continue to demonstrate effects of sugar-induced pathology in particular tissues . This suggests there will be continued interest in this hypothesis of aging and disease, particularly given the world-wide epidemic of diabetes and obesity.

Genetic Make-Up

The demonstration that the life-extending effects of a CR diet are heavily influenced by genetic make-up (14), indicates the importance of testing hypotheses of aging using animals of genetically heterogeneous background. Much of the world's literature in this area has involved the use of inbred laboratory animals. It is now clear that results obtained in these studies may not be relevant to our outbred human populations. With this in mind, our most recent studies have focused on testing hypotheses of aging using mice of heterogeneous genetic

background (HS mice), developed over many years by my colleague, Dr. Gerald McClearn. Using these mice, we have found no effect on longevity of restricting the intake of single amino acids such as methionine, in contrast to results of previous reports involving inbred mice. Similarly, we recently investigated the importance of plasma levels of the growth hormone IGF-1 (insulin-like growth factor 1) on the longevity and health of HS mice. Contrary to many previous findings in inbred animals, our experiments indicate only a small and conditional effect on longevity, of plasma levels of this hormone.

Conclusion

These and many other examples suggest an important point: It seems likely that, in general there is no single mechanism or genetic link which determines longevity and health. Rather, under particular environmental and genetic conditions relatively small contributions from many different genes and processes determine the health and longevity of complex organisms. As such, there may be many mechanisms of aging and all of the proposed hypotheses may indeed have "immortal" lives.

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