EDITORIAL

Genetics of Aging and Diseases

From Rare Mutations and Model Systems to Disease Prevention

RECENT STUDIES[1-4] indicate that the heritability of many adult-onset diseases, such as Alzheimer disease (AD), cardiovascular disease (CVD), and type 2 diabetes mellitus, is less than 40% and in the same range as the heritability of life span. These emerging findings suggest that noninherited environmental factors play a major causal role in age-related diseases and indicate limitations in applying information on common genetic polymorphisms to the diagnosis, treatment, and prevention of major diseases of aging. However, such limitations do not negate the importance of genetic research in understanding the molecular mechanisms of aging and its diseases. The identification of mutations in familial AD, Parkinson disease (PD), and other diseases has given important insights into the mechanisms in the more common sporadic forms of these diseases. Furthermore, comparative studies[5] of aging have identified signal transduction pathways that regulate resistance to cellular damage and longevity in organisms ranging from yeast to mammals. These recent findings set the stage for developing new drugs to prevent multiple age-related diseases.

The heritability of life span in humans and laboratory organisms ranging from worms to mice is consistently low and in the range of 10% to 35%.[1] For example, twin studies show that heritability of longevity nearly vanishes by the life expectancy.[1] Even simple animals in a homogeneous environment show low heritability of life span; eg, within a single culture dish of inbred nematodes, individual life spans range from 10 to 30 days.[6] These findings, however, do not exclude the possibility of longevity genes in rare families.[1]

An open question concerns how much of the nonheritable variance is due to environment as conventionally understood in terms of nutrition and lifestyle vs stochastic developmental variations in cell proliferation and migration that are evident in identical twins and inbred nematodes.[6] Menopause, for example, is determined by the ovarian pool of oocytes, which varies 3-fold between individuals, even in inbred mice. The developmental stochastics of egg cell numbers thus affect the age at menopause, which affects the risk of morbidity from bone fractures, heart attacks, and possibly cognitive impairments.

Consistent with the modest heritability of life spans, the major adult-onset diseases of aging also show heritabilities of less than 40%, which is evident for AD, cancer, CVD, and diabetes mellitus, as shown in perusals of these huge literatures. Nonetheless, sporadic forms of AD, CVD, cancer, and diabetes mellitus coexist with rarer familial forms, which are associated with rare but highly penetrant mutations.[2,3] Therefore, the working hypothesis that common polymorphisms would be highly penetrant in causing common age-related diseases does not appear to hold up generally. The *APOE*E4* allele is an instructive example because of the major attention it has drawn as a common disease risk factor for 2 major conditions of aging, AD and CVD. In most populations, the *APOE*E4* allele is present in 20% to 30% of the population. However, *APOE*E4* is now considered to be weakly associated with CVD.[7] As discussed herein, the association of *APOE*E4* with AD is stronger.[3] In neither disease is the *APOE*E4* genotype recommended for diagnosis or to guide treatment.

Such findings have generated concerns regarding the potential of genetic research to yield further advancements in disease prevention. Walter Willett recently commented in *Science*, "Overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health."[4(p69)] He proposed that improvements in diet and lifestyle could be more cost-effective than pharmacologic interventions to prevent multiple diseases. A tantalizing example is that modest caloric restriction (CR) slows many pathologic aging changes and increases life span of laboratory rodents.[8] Monkeys on CR also appear to have improved health and slower aging. The efficacy of CR may depend on broadly shared metabolic pathways found in nonmammalian models, as discussed herein. However, major diet and lifestyle changes are difficult to achieve for most mature adults. Despite its widely recognized adverse effects, obesity continues to increase in many aging populations.

Nonetheless, the identification of genetic variants, whether rare or common, remains a powerful strategy to finding preventions and treatments for diseases of aging. We extend the usual reach of this approach by examining pathways conserved in many organisms that protect against cellular damage and aging, which we believe offers a revolutionary strategy for the development of drugs for preventing multiple diseases of aging.

GENETICS OF AGE-RELATED NEURODEGENERATIVE DISEASES

Rare genetic mutations or common polymorphisms are risk factors for major neurodegenerative diseases, including AD, PD, amyotrophic lateral sclerosis, and Huntington disease. Alzheimer disease is classically associ-

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ated with neurofibrillary tangles and amyloid β (Aβ) peptides in senile plaques.[3] Recent investigations suggest that the soluble fibrillar form of Aβ may be more toxic than the aggregated form found in plaques.[9] This toxicity appears to be mediated by activated microglia, although Aβ can also kill neurons independent of microglia.[10] Several early-onset familial forms of AD are caused by rare mutations in the amyloid precursor protein (*APP*), *presenilin 1* (*PS1*), or *presenilin 2* (*PS2*) genes. Amyloid precursor protein is cleaved by γ-secretase to generate the neurotoxic Aβ. The *APP* mutations that cause early-onset AD are missense mutations in or near the domain encoding for Aβ that increase the secretion of Aβ.[3] In fact, *PS1* encodes for a membrane protein required for the γ-secretase activity. Mutations in *APP*, *PS1*, and *PS2* are rare but highly penetrant (>85%) autosomal dominant mutations.

By contrast to early-onset AD, no highly penetrant mutations or polymorphisms have been linked to late-onset AD. The *APOE*E4* allele is a risk factor for late-onset AD in sporadic and familial forms but is not sufficient to cause the disease, as shown in a few centenarians homozygous for *APOE*E4* who remain healthy. By some estimates, the contribution of this polymorphism to the total variation in onset of AD is less than 10%.[3] The low percent contribution of mutations and polymorphisms to sporadic AD indicates that environmental factors, mostly unknown, play a major role in the cause of AD, although a recent twin study suggests that genetic effects account for up to 78% of the variance in age of onset for AD.[11] Nonetheless, the AD-causing mutations in *APP*, *PS1*, and *PS2* have given valuable clues on the mechanisms of the disease and point to the importance of Aβ toxicity in sporadic AD. The highly penetrant mutations of early-onset AD implicate either Aβ or the intracellular enzymes responsible for its cleavage as a cause of the toxicity and neuronal loss associated with AD. The identification of *APOE*E4* as a risk factor for sporadic AD has contributed further to the understanding of AD by bringing cholesterol and lipid metabolisms into the model for Aβ toxicity. Therefore, genetic research has narrowed the search for AD culprits to a limited number of proteins and pathways associated with the processing, accumulation, and toxicity of Aβ.

Parkinson disease is a chronic disease that affects 1% to 2% of the population older than 65 years and is about 10-fold less common than AD.[12] Besides age as a risk factor, PD has rare familial forms. Mutations in *α-synuclein*, *parkin*, and *UCHL1* are associated with dopa-responsive PD.[12] Autosomal dominant mutations in *α-synuclein* cause PD at a mean age of 46. α-Synuclein is the major component of Lewy bodies, a hallmark of PD. Notably, the overexpression of the mutant form of *α-synuclein* that causes PD in mice or flies results in biochemical and pathologic abnormalities associated with PD.[12] A mutant *parkin* is implicated in juvenile parkinsonism in Japanese families.[12] Parkin is a ubiquitin ligase that binds to α-synuclein and 2 other identified substrates.

The identification of mutations and polymorphisms in AD and PD has played a major role in the understanding of the cause of these diseases. Similar strategies are used for other neurodegenerative diseases, including amyotrophic lateral sclerosis and Huntington disease. Therefore, the combination of genetic and molecular approaches remains a viable strategy for the development of drugs to treat neurodegenerative diseases.

CONSERVED REGULATION OF LONGEVITY AND CR: A STRATEGY FOR DISEASE PREVENTION?

We now describe a new strategy with great promise for revealing fundamental mechanisms in molecular aging that could underlie a large set of the diseases of aging. This strategy is based on the discovery of genes that regulate life spans in laboratory models for aging. The existence of conserved pathways that increase resistance to damage and postpone aging in organisms ranging from yeast to mammals indicates that it may be possible to prevent age-related diseases not by intervening on specific mediators but by a general delay of cellular damage and aging.

Aging is the major risk factor for sporadic forms of neurodegenerative diseases, including AD, CVD, PD, and amyotrophic lateral sclerosis. Because aging is traditionally viewed as an unavoidable process, there has been a limited research investment in the possibility of preventing multiple age-related diseases by postponing cellular damage and senescence. However, recent studies[5] in organisms, including yeast, worms, flies, and mice, suggest that longevity can be extended by down-regulating similar signal transduction pathways involved in glucose and insulin or insulin-like growth factor I (IGF-I) signaling. Therefore, it is possible that analogous pathways may be modulated to postpone major human age-related diseases.

There are remarkable similarities between the genes and pathways that regulate longevity in yeast and worms.[5] In yeast, the inactivation of the *ras* and Sch9 pathways, which are activated by glucose and other nutrients, extends longevity. In worms, the inactivation of the daf2 pathway, which normally occurs during periods of famine, also extends survival.[13] *daf2* is the worm homolog of the mammalian IGF-I receptor gene and of the fly *Inr* gene. The yeast *ras*-Sch9 and worm daf2 pathways share several homologous genes that encode for serine threonine kinases, antioxidant enzymes, and heat shock proteins.[5] In fact, long-lived yeast and worms are resistant to oxidative damage and heat shock, suggesting that longevity is extended in part by increasing protection against multiple insults and preventing macromolecular damage.

Recent work implicates an IGF-I–like signaling pathway in fly longevity. Mutations in the IGF-I pathway, which shares similar genes with the yeast *ras*-Sch9 and worm daf2 pathways, extend the life span of fruit flies by up to 85%.[13] Analogous to their role in yeast and worms, mutations in the fly IGF-I pathway increase the storage of nutrients and superoxide dismutase expression.[13] The IGF-I pathway may also be involved in regulating longevity and stress resistance in mammals. Mice homozygous for mutations in the *Prop1* gene show developmental growth defects but live more than 50% longer

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than wild-type mice.[13] *Prop1*-deficient mice lack the cells that produce growth hormone (GH) and consequently also lack plasma IGF-I, which is secreted by liver cells on stimulation with GH. The plasma GH deficiency appears to be responsible for the effects of *Prop1* mutations on longevity; mice that cannot release GH in response to GH-releasing hormone also live longer.[14] Although the role of IGF-I in longevity regulation has not been tested in mammals, treatment of mice hepatocytes with GH or IGF-I decreases the activities of superoxide dismutases and catalase. Antioxidant enzymes are decreased in transgenic mice overexpressing GH, and IGF-I attenuates cellular stress response and the expression of a heat shock protein in rats.[5] The effect of IGF-I on stress resistance in mammalian cells is consistent with the hypothesis that partially conserved glucose or IGF-I signaling pathways regulate stress resistance and longevity in many eukaryotes.[5,13] Notably, the yeast glucose and mammalian IGF-I signaling pathways share the *Ras* protein, which has not been implicated in IGF-I life span–regulating pathways in worms and flies.

As already noted, the only other intervention consistently shown to extend longevity and stress resistance in organisms ranging from yeast to mammals is CR.[8] In mice and rats, CR also decreases inflammation and delays the onset and course of immunosenescence, several types of tumors, kidney disease, and other age-related diseases.[8] Like the long-lived dwarf mice, mice on CR have reduced body weight and decreased IGF-I, insulin, and glucose levels. Therefore, longevity extension in CR may be mediated in part by decreasing IGF-I signaling. As the molecular mechanisms of CR are revealed, it may be possible to develop drugs that simulate effects of CR in postponing cellular and molecular changes that are already implicated in many diseases of aging.

It is fair to say that research on basic mechanisms of aging has followed a different path from that of research focused on specific diseases of aging. However, these recent discoveries indicate the importance of understanding basic molecular mechanisms of aging, such as those associated with oxidative stress or inflammation, that are implicated in each of the major age-related diseases. Understanding of these basic mechanisms may plausibly be applied to the prevention of age-related diseases. Moreover, many species have evolved strategies to postpone aging during periods of nutrient deficiency by shifting energy investment from reproduction to somatic maintenance until food becomes available. As we learn more details about the molecular pathways that regulate this shift, we may be able to simulate CR to postpone age-related diseases without causing collateral damage.

In summary, the identification of highly penetrant rare mutations and of common polymorphisms associated with diseases will continue to be a valuable approach to understand the mechanisms of specific diseases and to develop treatments. By contrast, the application of the genetics, molecular, and evolutionary biology of aging to the development of drugs that postpone cellular aging may be the best approach to prevent multiple age-related diseases.

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