Essay

Gene: The Pace Control of Aging

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SUMMARY

Gene plays a significant role in aging. all aging process can depend on just the mutation of a single gene. Longevity of life is heritable and shows at old age, at some points in time the rate at which human and other animals' age increase rapidly as a result of certain mutation. It has been observed that some living organisms show sign of aging at a very tender age due to some set of syndromes that are known as progeroid syndromes. Aging is not really characterised by brain aging but by old skin, early cataract and some other signs. It was discovered by some scientist that aging can be delayed in living organisms using Calorie Restriction, hundreds of genes identified to regulate aging provide strong evidence that aging has a strong genetic basis and that indeed a basic aging process exists. Although daf-2 can limit expansion of life when not mutated, Daf-2 and daf-16 are two types of gene that plays the major role of life expansion and aging. The gene helps to interfere with life span by controlling other gene that coordiate the survival system.■

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There are many factors responsible for aging but gene is one of the most important factors that aging depends on, although it is difficult to believe because of the other factors that are used in the determination of aging. Aging can solely depends on just a single gene.

HOW GENES CAN REGULATE THE AGING PROCESS?

The way single gene can modulate the aging process is a great evidence of seeing aging as having a unified basis. According to the GenAge database, there are more than 1,500 genes that individually manipulated can alter aging and/or lifespan have been identified in model organisms. The plasticity of lifespans in invertebrates shows how one or a few genes can regulate the entire aging process (1). For example, in worms, single gene mutations can extend lifespan by almost ten folds. In mice, there are several examples of single genes that can extend longevity, in some cases by around 50%, increase the MRDT,and delay the onset of multiple age-related changes and diseases (2). These results clearly argue that genetic mechanisms can, up to a certain degree, regulate aging in mammals. (These genes and their mechanisms are further detailed elsewhere (3)). Human studies have shown a significant degree of heritability of longevity, in particular, at later ages. Studies in centenarians, in fact, have shown that the offspring of long-lived parents are protected against age-related diseases. Genetic variants (alleles) in human homologs of genes shown to regulate aging in model organisms have also been associated with human longevity. Albeit effects as marked as those observed in model organisms have not been observed in humans. In fact, in spite of individually having a small effect, dozens of genetic variants have been associated with human longevity, as compiled in the longevityMap database (4). Lastly, it has been argued that the rapid evolution of longevity in the human lineage indicates that maybe a small number of genes are able to regulate the pace of aging.

One of the most intriguing phenotypes in the biology of aging is the accelerated aging witnessed in humans and animals as a result of certain mutations. Progeroid syndromes, as they are called, are rare genetic diseases that originate a phenotype that resembles accelerated aging. The three most studied such syndromes are Werner's (WS), Cockayne, and Hutchinson-Gilford's syndrome (5). Though patients with Down syndrome or trisomy 21 often also exhibit progeroid features, this disease has not gathered as much attention from the perspective of aging research as the other three syndromes named above. In particular, patients with WS exhibit striking features resembling accelerated aging and show an early onset – compared to normal aging – of multiple age-related diseases like diabetes, cataracts, osteoporosis,baldness, and atherosclerosis. Though differences exist in terms ofpathology, what most markedly distinguishes these syndromes is age of onset with Hutchinson-Gilford's and Cockayne syndrome almost exclusively affecting children while WS patients normally reach adulthood.

There are also five reported cases of a neonatal form of progeria called Wiedemann-Rautenstrauch syndrome, in which babies appear to be born old, but further research is needed to confirm or dismiss such cases as accelerated aging (6). George Martin suggested that WS mimics about 50% of aging characteristics: early cataracts, old skin, gray hair, etc., but not brain aging (7). This is a high proportion since it is not clear that these diseases are indeed accelerated aging. Moreover, the WS phenotype tends to affect tissues where WRN, the gene in which mutations result in WS, is expressed, so it makes sense that not all organs display signs of accelerated aging in WS. Such diseases demonstrate the hierarchical essence of aging in which a single gene can regulate a vast array of complex age-related changes (8).

One key discovery in the biology of aging was made in 1935, following earlier findings by veterinary nutritionist Clive McCay and colleagues. As Previously mentioned, they discovered they could slow aging in laboratory rats just by making them eat less calories while maintaining normal levels of proteins, vitamins, and minerals. This process became known as caloric restriction (CR) and appears to work in many animals; it has been particularly well-studied in mice. From mice, we know that CR not only increases longevity by up to 50% but it also postpones or diminishes the incidence of most age-related diseases, decreases the rate of aging and delays development (9). Doubts have for long existed on whether CR results from some technical artifact. Even so, CR remains the most impressive way to delay aging in mammals,particularly since it derives from a quite simple intervention. Like WS, CR demonstrates how it is possible to delay the aging process as a whole, suggesting that aging has a unifying clock, but the mechanisms of CR are still under debate.

Recent large-scale gene expression studies have revealed a degree of coordination in age-related changes in gene expression; in mice different issues age in a coordinated fashion so that a given mouse may exhibit rapid aging while another age slowly across multiple tissues. This suggests the existence of common or synchronizing mechanisms, or at least systemic factors, in the aging phenotype. On the other hand, individual organs have some unique gene expression changes with age. Besides, only a small percentage of genes (less than 5%) are expressed in all tissues which suggests that aging may have multiple modulators in individual tissues. For example, even if one particular type of damage (e.g., DNA damage) is the underlying cause of aging different tissues will respond differently and be affected in different ways (10). Like

many others, there is a uniform, unifying genetic-based core that synchronizes most facets of aging. Nonetheless, it is plausible – even likely – that some age-related changes and diseases are independent of this core process; causes of disease and causes of aging can be different. For example, Machado-Joseph is a neurodegenerative genetic disease with a typical adult onset that results from a single gene defect that appears to result in a toxic form of the protein. Similarly, many genes can influence individual age-related changes. Furthermore, there is a great variability in age-related changes among individuals, suggesting that lifestyle can influence aging to some degree (11). Nonetheless, it is interesting to note that, in worms, retarding aging also reduces aberrant protein aggregation as observed in neurodegenerative diseases like Alzheimer's disease. Even for diseases that involve a toxic gain of function, the length of time until the disease develops often correlates with the organism's lifespan, possibly because such diseases are rarely the result of a single defect and thus can be influenced by a number of processes and additional insults. In conclusion, all the hundreds of genes identified to regulate aging provide strong evidence that aging has a strong genetic basis and that indeed a basic aging process exists. It is clear now that aging is not just a passive, random process. There may even be a single mechanistic clock, though this is not yet proven and considered by many to be unlikely. Nonetheless, age-related changes in individual organs may be subject to unique constraints, both environmental and genetic.

Although the broad aim of this work is to unravel the aging process.It is believed that focusing on this fundamental causes of aging, the genetic basis for differences in rate of aging between similar species and between individuals, is the most appropriate strategy, an idea long defended by many others. The proportion of diseases that are independent of – or largely unaffected by – the fundamental cause(s) of aging seem low, but cannot exclude that the impact of such fundamental mechanism(s) is overestimated. Besides,no doubt independent causes and risk factors (including environmental factors) contribute to the development of age-related diseases, even if influenced by unifying aging mechanisms. Of course, humans do not appear to have death genes like the salmon, so no doubt many genes interacting with each other are involved in aging; yet elucidating the genes and mechanisms controlling aging is paramount to develop interventions that delay aging and ultimately to cure aging . Candidate mechanisms of aging are discussed elsewhere.

As mentioned before, more resources are aimed at trying to cure age-related diseases than aging, or senescence, itself. This is partly due to the belief that aging is a complex, difficult to understand process that has eluded generations of gerontologists. Such way of thinking may lead to complacency and unambitious objectives. On the other hand, if one sees aging as caused by unifying mechanism objectives become more ambitious; CR and recent findings in the genetics of aging prove that aging can be manipulated in model organisms, and the prospects of developing drugs that delay aging is excellent. That said, just because aging has a genetic core does not mean that curing it will be easy. Naturally occurring genetic variants in mice (and possibly inhumans too) can delay aging, but only to a certain point. Therefore, even when we identify the genetic mechanisms behind human aging, curing aging will be an Herculean task.

One particular gene affected by daf-2 is daf-16; this gene encodes atranscription factor, or a protein that determines when and where hundreds of other genes are turned on. Normally, the DAF-2 protein (which is an insulin receptor) exerts a dampening effect on the DAF-16 protein through phosphorylation, or the addition of a phosphate group. In the mutant worms, however, DAF-16 is not phosphorylated, and it is thus active and present in cell nuclei. Experiments have determined that this activation of DAF-16 (caused by the absence of a phosphate group) is a necessary step toward life span extension.

WHY LIMIT LIFE SPAN?

Why, then, do animals have a gene such as daf-2, whose apparent purpose (when not mutated) is to limit life span? Try considering that question from a different point of view. The daf-2 gene seems to be just one cog in an extended genetic system that allows worms to regulate their development according to their circumstance. Thanks to this system, those aspects of growth and development that are necessary for reproduction can be put on hold if environmental conditions are poor.

Indeed, growing worms are actually able to suspend their own development in a phase known as dauer. This allows them to wait—for months, if need be—for better times. Long before Kenyon's work, other researchers, linked daf-2 and daf-16 to this arrested form of development.

In fact, the genes' names derive from the phrase "dauer formation." Moreover, experimentally "knocking out" the activity of daf-2 sends a developing worm right into the dauer state, whether or not nutrients are scarce. But is this sort of insulin signaling critically involved in longevity in humans as well? Scientists take that question seriously for a number of reasons. One clue to the hormone pathway's importance is that it has been conserved through evolution , a fact that always interests scientists because it is akin to a vote of confidence from Mother Nature. Another clue is the role that the insulin pathway plays in diseases like diabetes and cancer (12). For example, insulin resistance at the cellular level is a key feature of type II diabetes.

Similarly, mutations along the pathway that insulin/IGF-1 receptors put into motion have been associated with the dysregulation of growth that characterizes cancer. The disease idea is especially tantalizing, as the risk of both diabetes and cancer increases with age. So, how does one gene control life span? Quite simply, it acts by controlling a lot of other genes that just happen to coordinate the survival system within worms (13). ■

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