Role of the IGF/insulin system in longevity.

Ruolo del sistema IGF/insulina nella longevità.

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Abstract

Human life expectancy is influenced by multiple determinants, including various environmental and genetic factors. Though the non-genetic factors are important, it is estimated that approximately 25–32% of the overall difference in human lifespan for survival after the age of 60 years depends on for by genetic polymorphisms among individuals. In addition, there are human homologues to many genes that affect lifespan in model organisms. In people, longevity genes might slow the rate of age-related changes in cells, increase resistance to environmental stresses like infection and injury, and reduce the risk of many age-related conditions. The best studied longevity pathway is probably the one involving insulin/IGF-1 signaling. The important role of IGF and insulin-related signaling pathways in the control of longevity of worms and insects is very well documented. In the mouse,

several spontaneous or experimentally induced mutations that interfere with GH/IGF axis modulation lead to extended longevity. Increases in the average life span in these mutants range from approximately 20–70% depending on the nature of the endocrine defect, gender, diet, and/or genetic background. All the data in animals models and in the population studies support the evidence that this pathway drives an evolutionarily conserved network that regulates lifespan and affects longevity across species. Results obtained in humans are still controversial and further extensive studies are required to firmly establish a role of the IGF1 axis in modulation of human longevity. A better knowledge of the role of this pathway in humans may assist in the design of improved treatment methods for age-related diseases, delay the aging process and prolong the human lifespan.

Key words: longevity, insulin/IGF-1, genetic.

Introduction

Longevity is determined by a mix of genetic, environmental, and chance elements. Several studies are currently being made to identify the genetically determined pathways and mechanisms of healthy longevity in humans, because these might provide targets for specific interventions aimed at preservation of disease-free longevity. Of the genetically determined pathways that have been implicated in longevity in model organisms, in current literature the best studied pathway is the insulin and insulin-like growth factor-1 (IGF-1) signaling (IIS) pathway. This pathway was originally identified in C. elegans[1, 2], where it has been studied to the greatest extent. Several work, points to evolutionary conservation of this pathway in fruit flies [3] and mice [4,5] making this an important therapeutic target for longevity modulation in humans[6,7].

The IGF/insulin system in lower species

Recent studies on model organisms have shown that the insulin/insulin-like growth factor-1 (IGF-1) signaling pathway (IIS) plays a significant role in the regulation of longevity and extension of life span [3, 5, 8-10]. The important role of IGF and insulin-related signaling pathways in the control of longevity of worms and insects is very well documented. Many insulin/IGF-1-pathway mutations have been shown to influence lifespan in flies. In the mouse, genetic alterations that interfere with the GH/IGF axis or sensitivity to IGF-I lead to extended longevity. IIS is an important nutrient-sensing pathway that coordinates processes such as development, fat metabolism, growth and reproductive maturation. As such, this pathway is a good candidate for regulating longevity in response to energy availability. In C. elegans, environmental unfavorable growth conditions (such as food deprivation and over-crowding) triggers an increase secretion of pheromones and the warm enters an alternative larval stage, known as the dauer, that can withstand adverse conditions for prolonged periods [11]. This is consistent with the function of IIS pathway in worms, where it regulates a hibernation-like state, that can occur during development if resources are scarce [12]. Animals in this dauer stage are very resistant to thermal [13] and oxidative stresses[14] and are considerably long-lived. It is possible that the long lived C. elegans IIS mutants are activating and benefiting from the same protective mechanisms that allow dauers to live long, but without the hibernation phenotypes.

Genetic regulation of IGF/insulin-like signaling pathways

The pathway involving insulin/IGF-1 signaling is evolutionarily conserved: mutations in many insulin and IGF-1-pathway genes extend the lifespan of lower species and in mammals. Reduced function of this pathway is associated with prolonged lifespan in several species [15]. Mutations in many other signaling elements in this pathway, for example age-1 and daf-16, also affect longevity. These same genes are involved in the response to oxidative stress [15] up regulating the heat shock proteins, as well as tumor suppression [16, 17]. In the Drosophila, mutations of the daf-2 homologue

insulin receptor, or a loss-of-function mutation in a homologue of the insulin receptor substrate, increase lifespan [3, 18]. Mice with a fat-specific insulin receptor knockout (FIRKO) live about 20% longer than controls [4]. Heterozygous knockout mice with deletion of the IGF-1 receptor appear to have longer lifespan, although the effect may be specific to females [5]. Thus, decreased insulin signaling in certain tissues may extend life. In growth hormone receptor knockout mice, the decreased growth hormone and IGF-1 are responsible for increased life span [19]. The function of the insulin/IGF-1 signaling pathway in these mice is also decreased [20]. Thus, the signaling system may act in a similar way in these mice as in C. elegans: mutation may result in physiological homeostasis that favors longevity, and the Snell dwarf mutant conforms to the nematode longevity paradigm. Several rare mutations in the growth hormone receptor in humans are associated to short stature [21] but their effects on lifespan are uncertain. Bonafè [22] et al first demonstrated that free

IGF-1 plasma levels and human longevity are coregulated by an overlapping set of genes, describing an association between a SNP in the IGF-1 receptor gene (a G to A substitution at codon 1013) and human longevity. This SNP was also associated with lower circulating levels of IGF-1.

There is considerable evidence to suggest that the genetic and endocrine mechanisms that influence aging and longevity in mice may play a similar role in other mammalian species, including the human.

The influence of IGF/insulin system on human longevity.

IGF-1 plays a number of important roles in the human body. It is involved in physiological processes such as growth, development, and metabolism[23] and has been implicated as a factor in the development of common diseases [24]. Serum IGF1 levels seems to influence susceptibility to disease, and therefore longevity. It is well known that people with a high level of circulating IGF1 are more susceptible to cancers, while a low level of circulating IGF1 is a risk factor for cardiovascular diseases, premature atherogenesis, and diabetes [25]. Pathological increased IGF1

levels as seen in uncontrolled acromegaly are associated with a substantially reduced lifespan, diabetes and cardiac disease [26, 27]. In contrast, the study from the Framingham cohort has demonstrated the protective role of IGF1 on the risk of developing heart failure [28]. The results on top levels athletes have suggested a positive association between IGF1 levels and cardiac contractility assessed by echocardiography [29]. Suh et al.[7] recently studied IGF system in a cohort of Ashkenazi Jewish centenarians, their offspring, and offspring-matched controls. Female centenarians' offspring showed higher serum IGF-I levels and shorter stature than controls. In this study genetic alterations in the human IGF1R that result in altered IGF signaling pathway confer an increase in susceptibility to human longevity. Data used from the Longitudinal Aging Study Amsterdam (LASA), an ongoing multidisciplinary cohort study in the general Dutch population of older persons (65 yrs. old) demonstrated an increased risk of all causes of mortality for older persons with IGF-I values in the lowest quintile as compared to the middle quintile [hazard ratio (HR), 1.28; 95% confidence interval (CI), 1.01–1.63]. A more than 2-fold increased risk of CVD mortality was revealed for both low-normal (HR, 2.39; 95% CI, 1.22–4.66) and high-normal (HR, 2.03; 95% CI, 1.02–4.06) IGF-I values [30]. Significant associations of serum IGF-I with nonfatal CVD and fatal and nonfatal cancer were not observed. In the Leiden population study intron 4 A/T SNP of GH1 was significantly associated with female longevity (relative mortality risk = 0.8) [31]. Bonafè et al[22] carried out a cohort study that enrolled a total of 496 healthy Italian subjects, including 278 young people (76 males and 202 females; mean age 54.8 years) and 218 long-lived people (56 males and 162 females; mean age 98.0 years). The results demonstrated that lower free IGF1 plasma levels were more frequently found in individuals carrying at least an A allele at insulin-like growth factor 1 receptor, IGF1R (AG and AA genotypes) than in GG genotype subjects. The study of insulin/IGF-1 signaling and FOXO (DAF-16) proteins in ageing has been recently explored and new link to human longevity was suggested. Impaired IGF-1 receptor activity has been associated to exceptional longevity in Ashkenazi Jews, and FOXO DNA variants have been

correlated in Hawaiians centenarians of Japanese descent, Germans, Italians Californians, New Englanders, Ashkenazi Jews and the Chinese. Recently Pawlikowska et al. [32], genotyped 291 common variants in 30 genes encoding proteins in the IIS signaling pathway in the 293 long-lived cases (age older than 92 years, mean age 95.3 years), and 603 younger controls (age less than 79 years, mean age 75.7 years) selected from the SOF cohort. They demonstrated a modest excess of variants associated with human lifespan. Then, the genotyping was replicated in the two additional cohorts and a meta-analysis was performed across the three cohorts. They showed that an intronic SNP (rs3803304) in AKT1 was significantly associated with lifespan (OR = 0.78, adjusted p = 0.043).

In elderly population insulin sensitivity declines with age, consequently to a reduction in lean tissue, despite a decrease in BMI. Paolisso[33] et al. previously reported that healthy centenarians have glucose tolerance and insulin action better than individuals aged >75 years and not different from those aged about 50 years. Centenarians had preserved insulin sensitivity, comparable with that of healthy young subjects. In fact, there is increasing evidence that IGF-I plays an important contributory role in the modulation of glucose metabolism. Higher bioactive IGF-I levels are reported in the less insulin sensitive subjects [34].

Conclusions

Despite the well-established role of the GH/IGF axis in modulation of lifespan in laboratory animals, its role in human longevity has been controversial. Moreover, human aging is associated with a decline in the levels of GH and IGFI, and it has been proposed that GH therapy may reverse some of the physiological features of aging [35]. Therefore, at the current time, the role of IGF signaling in human longevity is far from clear. Previous reports have shown that the offspring of centenarians have a moderately lower prevalence of metabolic syndrome than their partners [36]. Moreover, it has been reported that centenarians had preserved insulin sensitivity, comparable with that of healthy young subjects [33]. Additional comprehensive studies in the centenarians and their

offspring may reveal other molecules within the GH/IGF pathway that are operative in human longevity. Comprehensive analysis of all genes within this axis will be required to firmly establish a role of the IGFI axis in modulation of human longevity. So far, the best studied longevity patwhway involves insulin/IGF-1 signaling and supports the notion that the insulin/IGF-1 pathway drives an evolutionarily conserved network that regulates lifespan and affects longevity across species.

Riassunto

L'aspettativa di vita è influenzata da molteplici fattori, genetici e ambientali. Benché i fattori ambientali siano importanti, si ritiene che circa il 25-32% della sopravvivenza nell'uomo sopra i 60 anni dipenda dalla differente presenza di polimorfismi genetici tra i singoli individui.

Nei modelli animali vi sono omologhi umani che condizionano la durata della vita. Nell'uomo i geni che influenzano la longevità rallentano i cambiamenti cellulari età-correlati, aumentano la resistenza allo stress e alle infezioni e riducono il rischio di contrarre patologie età-correlate. Il sistema meglio studiato che influenza la longevità è forse quello dell'insulina/IGF-1. Nei vermi e negli insetti il ruolo di questo sistema correlato alla longevità è stato ben documentato. Nel topo molte varianti genetiche spontanee o sperimentali che interferiscono con la modulazione dell'asse GH/IGF causano un prolungamento della vite. In questi mutanti la vita media aumenta del 20-70%, secondo la natura del deficit endocrino, della dieta e/o dal background genetico. Tutti i dati nei modelli animali e negli studi di popolazione supportano l'evidenza che questo sistema fa parte di una reta conservata nell'evoluzione che regola la durata della vita e condiziona la longevità delle specie.

I risultati ottenuti nell'uomo sono controversi e sono necessari studi più ampi e completi per stabilire definitivamente il ruolo dell'asse IGF1 nella modulazione della longevità. Una più approfondita conoscenza del ruolo di questo sistema nell'uomo potrà condurre a migliori possibilità

terapeutiche per le malattie età-correlate allo scopo di ritardare il processo di invecchiamento e prolungare l'aspettativa di vita nell'uomo.

Parole chiave: longevità, insulina/IGF-1, genetica.

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