A grand challenge for genetics of aging: adding healthy years to our lives

Health & Medicine

We all age. The questions that surround this one of life's certainties are: why are we aging?" " What are the mechanisms of aging?" " Can we delay aging?" " Can we continue to be productive even late in life?" The search for the fountain of youth started thousands of years ago. However, only recently have advances in the genetics of aging started to reveal some answers to these questions. Aging is a complex process associated with the accumulation of age-related changes, and it is characterized by a progressive decline of physiological functions, increased frailty, and increased incidence of diseases. For years this was thought to be result of a passive decline due to wear and tear and accumulation of damage, a process that was not genetically regulated. Only in the last several decades have many groundbreaking discoveries clearly shown that aging is regulated. A genetic component of aging was first discovered in 1983 when Klass (1983) reported a longevity extension of *C. elegans* associated with gene mutations. Friedman and Johnson, (1988) mapped this longevity extension to the *age-1* gene mutation and Kenyon's et al. (1993) group identified the *daf-2* longevity gene mutation. The identifications of *age-1* and *daf-2* mutations were truly groundbreaking discoveries. First, they showed that single gene mutations could affect aging. Second, they encouraged the search for and identification of other single gene mutations that affect longevity. Lastly, since AGE-1 (phosphatidylinositol-3-OH kinase catalytic subunit) and DAF-2 (insulin receptor-like protein) are members of the insulin/IGF-1/FOXO signaling pathway, they revealed major role of the insulin signaling in aging (Morris et al., 1996 ; Kimura et al., 1997). Although it was known that genes are highly conserved across the species, it was extremely exciting to see

that mutations in insulin/IgF-1/FOXO signaling affect longevity in other species such as yeast, flies, and mice (Fabrizio et al., 2001 ; Clancy et al., 2001 ; Tatar et al., 2001 ; Taguchi et al., 2007 ; Kenyon, 2010). Remarkably, FOXO DNA variants have been associated with exceptional longevity in several populations (Kuningas et al., 2007 ; Willcox et al., 2008 ; Flachsbart et al., 2009). These discoveries also showed the advantage of using genetic model organisms such as yeast, worms, flies, and mice in longevity studies and the likelihood of translating our findings from invertebrate model organisms to mammals. Since the role of the insulin/IgF-1 signaling was discovered, a number of pathways involved in determination of longevity have been identified such as the Sirtuin family (Sir2), the Target of rapamycin (Tor) signaling pathway, AMP kinase, JNK signaling. Since many of these pathways alter metabolism and catabolism, respiration, and protein synthesis have also been implicated in longevity extension (Kaeberlein et al., 1999 ; Kapahi et al., 2004 ; reviewed in Kenyon, 2010). One potential application of this knowledge is to develop drugs that affect some of these pathways. Rapamycin is one of the examples of such a drug, as it extends longevity in mice, and flies by affecting the Tor signaling pathway (Harrison et al., 2009 ; Bjedov et al., 2010). Recently studies in model organisms have been complimented by longitudinal studies in humans, which provide an unbiased approach to identify genetic variants that contribute to longevity. Particularly, studies in centenarians have already contributed to our knowledge of the aging process by revealing the association of specific genotypes with longer life span (Barzilai and Gabriely, 2010).

Remarkably, longevity extensions associated with single gene mutations are often associated with a variety of beneficial effects on physiology and functions of long lived animals and could be seen as delayed accumulation of age-related changes and preservation of functions late in life. This again, illustrates that a single gene mutation initiates cascade of changes in gene expression and function, which all contribute to the well being of the whole organism. One of the grand challenges in genetics of aging is to determine how changes in single genes affect other genes and pathways. How do these networks interact and how does this interaction influence the aging process?

Another remarkable finding that changed our knowledge about aging is the discovery that aging can be affected by the environment, mainly by exposure to different nutrients and stress. Calorie restriction (CR) is an environmental manipulation that delays age-related changes and extends longevity in a wide variety of species first described in McCay et al. (1935) . Although several genetic components of the CR longevity pathway have been identified, such as the Sirtuin family of genes, the Tor and the insulin-signaling pathway, the grand challenge is to determine the exact mechanism of the CR effect. Sir2 is thought to mediate some aspects of the CR response and has already been used as a target for drug screens to identify CR mimetic. These searches resulted in identification of several compounds such as resveratrol, which extends longevity in yeast, worms, flies, and fish, but not in mice on regular diet and some studies (Howitz et al., 2003 ; Wood et al., 2004 ; reviewed in Agarwal and Baur, 2011).

A major grand challenge in the genetics of aging is to harness the knowledge that could be gained by new genetics, molecular, and proteomics techniques. Genome-wide association (GWA) studies allow identification of associations between single nucleotide polymorphisms (SNPs) and longevity and may also reveal novel pathways that contribute to slowing aging (Barzilai and Gabriely, 2010). Advanced genetics techniques, such as RNASeq, allow easy generation of large amounts of data, however, they also require sophisticated data analysis in order to allow identification of additional layers of regulation such as alternative splicing, RNA-editing, miRNA, and other non-coding RNA, which could all affect aging process. For instance, several findings illustrate the role of miRNA in aging and DR (De Lancastre et al., 2010 ; Khanna et al., 2011). Protein synthesis regulation and post-translational modifications may have significant roles in aging, and will be revealed by new proteomic techniques.

Lastly, the grand challenge in the genetics of aging is to improve lives by using the knowledge of the role of specific genes and signaling pathways to find drugs that can slow aging and improve physiological function later in life. This would allow us to reach our ultimate goal – to find interventions that extend healthy life span. The goal of *Frontiers in Genetics of Aging* is to be a forum for publication of findings that will extend our understanding of the genetic and molecular basis of the aging process, and of the interaction between genes and the environment. Identification of new genes and new pathways involved in aging will open new possibilities for identification of the pharmacological treatments that promote health span, homeostasis, and longer life span.

Acknowledgments

This work was supported by grant from the NIH (AG023088).

References

Agarwal, B., and Baur, J. A. (2011). Resveratrol and life extension. *Ann. N. Y. Acad. Sci.* 1215, 138–143.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Barzilai, N., and Gabriely, I. (2010). Genetic studies reveal the role of the endocrine and metabolic systems in aging. *J. Clin. Endocrinol. Metab.* 95, 4493–4500.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Bjedov, I., Toivonen, J. M., Kerr, F., Slack, C., Jacobson, J., Foley, A., and Partridge, L. (2010). Mechanisms of life span extension by rapamycin in the fruit fly *Drosophila melanogaster* . *Cell Metab.* 11, 35–46.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Clancy, D. J., Gems, D., Harshman, L. G., Oldham, S., Stocker, H., Hafen, E., Leevers, S. J., and Partridge, L. (2001). Extension of life-span by loss of CHICO, Aa Drosophila insulin receptor substrate protein. *Science* 292, 1040106.

CrossRef Full Text

De Lancastre, A., Pincus, Z., Zhou, K., Kato, M., Lee, S. S., and Slack, F. J. (2010). MicroRNA both promote and antagonize longevity in *C. elegans* . *Curr. Biol.* 20, 2159–2168.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Fabrizio, P., Pozza, F., Pletcher, S. D., Gendron, C. M., and Longo, V. D. (2001). Regulation of longevity and stress resistance by Sch9 in yeast. *Science* 292, 288–290.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Flachsbart, F., Caliebe, A., Kleindorp, R., Blanche, H., von Eller-Eberstein, H., Nikolaus, S., Schreiber, S., and Nebel, A. (2009). Association of FOXO3A variation with human longevity confirmed in German centenarians. *Proc. Natl. Acad. Sci. U. S. A.* 106, 2700–2705.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Friedman, D. B., and Johnson, T. (1988). A mutation in the age-1 gene in *Caenorhabditis elegans* lengthens life and reduces hermaphrodite fertility. *Genetics* 118, 75–86.

Pubmed Abstract | Pubmed Full Text

Harrison, D. E., Strong, R., Sharp, Z. D., Nelson, J. F., Astle, C. M., Flurkey, K., Nadon, N. L., Wilkinson, J. E., Frenkel, K., Carter, C. S., Pahor, M., Fernandez, E., and Miller, R. A. (2009). Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 460, 392–395.

Pubmed Abstract | Pubmed Full Text

Howitz, K. T., Bitterman, K. J., Cohen, H. Y., Lamming, D. W., Lavu, S., Wood, J. G., Zipkin, R. E., Chung, P., Kisielewski, A., Zhang, L. L., Scherer, B., and Sinclair, D. A. (2003). Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* 425, 191–196.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Kaeberlein, M., McVey, M., and Guarente, L. (1999). The SIR2/3/4 complex and SIR2 alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms. *Genes Dev.* 13, 2570–2580.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Kapahi, P., Zid, B. M., Harper, T., Koslover, D., Sapin, V., and Benzer, S. (2004). Regulation of lifespan in *Drosophila* by modulation of genes in the Tor signaling pathway. *Curr. Biol.* 14, 885–890.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Kenyon, C., Chang, J., Gensch, E., Rudner, A., and Tabtiang, R. (1993). A *C. elegans* mutant that lives twice as long as wild type. *Nature* 366, 461–464.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Kenyon, C. J. (2010). The genetics of ageing. *Nature* 464, 504–512.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Khanna, A., Muthusamy, S., Liang, R., Sarojini, H., and Wang, E. (2011). Gain of survival signaling by down-regulating of three key miRNA in brain of calorie-restricted mice. *Aging* 3, 223–236.

Pubmed Abstract | Pubmed Full Text

Kimura, K. D., Tissenbaum, H. A., Liu, Y., and Ruvkun, G. (1997). daf-2, an insulin receptor-like gene that regulates longevity and diapause in *Caenorhabditis elegans* . *Science* 277, 942–946.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Klass, M. R. (1983). A method for the isolation of longevity mutants in the nematode *Caenorhabditis elegans* and initial results. *Mech. Ageing Dev.* 22, 279–286.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Kuningas, M., Magi, R., Westendorp, R. G., Slagboom, P. E., Remm, M., and van Heemst, D. (2007). Haplotypes in the human Foxo1a and Foxo3a genes; impact on disease and mortality at old age. *Eur. J. Hum. Genet.* 15, 294–301.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

McCay, C. M., Crowell, M. F., and Maynard, L. A. (1935). The effect of retarded growth upon the length of life span and upon the ultimate body size. *J. Nutr.* 10, 63–79.

Morris, J. Z., Tissenbaum, H. A., and Ruvkun, G. (1996). A phosphatidylinositol-3-OH kinase family member regulating longevity and diapause in *Caenorhabditis elegans* . *Nature* 384, 536–539.

CrossRef Full Text

Taguchi, A., Wartschow, L., and White, M. F. (2007). Brain IRS2 signaling coordinates life span and nutrient homeostasis. *Science* 317, 469–372.

CrossRef Full Text

Tatar, M., Kopelman, A., Epstein, D., Tu, M. P., Yin, C. M., and Garofalo, R. S. (2001). A mutant *Drosophila* insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science* 292, 107–110.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Willcox, B. J., Donlon, T. A., He, Q., Chen, R., Grove, J. S., Yano, K., Masaki, K. H., Willcox, D. C., Rodriquez, B., and Curb, J. D. (2008). FOXO3A genotype is strongly associated with human longevity. *Proc. Natl. Acad. Sci. U. S. A.* 105, 13987–13992.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text

Wood, J. G., Rogina, B., Lavu, S., Howitz, K., Helfand, S. L., Tatar, M., and Sinclair, D. A. (2004). Sirtuin activators mimic caloric restriction and delay ageing in metazoans. *Nature* 430, 686–689.

Pubmed Abstract | Pubmed Full Text | CrossRef Full Text