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- Review -

Animal Models for the IGF-1 Signal System in Longevity

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Longevity is an exciting but difficult subject to study because it is determined by complex processes that require the coordinated action of several genetic factors as well as physiological and environmental influences. Genetic approaches have been applied to animal models to identify the molecular mechanism responsible for longevity. Several experimental model organisms obtained over the last decades suggest that the complete deletion of a single gene by gene targeting has proven to be an invaluable tool for the discovery of the mechanisms underlying longevity. The first discovery of long-lived mutants came from *Caenorhabditis elegans* research, which identified the insulin/IGF-1 pathway as responsible for longevity in this worm. IGF-1 is a multifunctional polypeptide that has sequence similarity to insulin and is involved in normal growth and development of cells. Several factors in the IGF-1 system have since been studied by gene targeting in the control of longevity in lower species, including nematode and fruit fly. In addition, significant progress has been made using mice models to extend the lifespan by targeted mutations that interfere with growth hormone/IGF-1 and IGF-1 signaling cascades. A recent finding that IGF-1 is involved in aging in mice was achieved by using liver-specific knockout mutant mice, and this clearly demonstrated that the IGF-1 signal pathway can extend the lifespan in both invertebrates and vertebrate models. Although the underlying molecular mechanisms for the control of longevity are not fully understood, it is widely accepted that reduced IGF-1 signaling plays an important role in the control of aging and longevity. Several genes involved in the IGF-1 signaling system are reviewed in relation to longevity in genetically modified mice models.

Key words : Longevity, IGF-1, growth hormone, mouse, gene targeting

Introduction

The understanding of the biology that modulates lifespan was not an easy subject until the last few decades. Significant advances have been made for the genetics of ageing by using experimental model organisms including nematode, fruit fly and mouse over the last decades. Gene targeting technique that removes a specific single gene in animals provides valuable tool for the study of ageing or longevity. Many factors such as genetic background and nutritional and environmental conditions for animal researches could be tightly controlled and managed in these models. Recent discoveries in long-lived mutants model have been shown that many genes are involved in the process of ageing and they are involved in the regulation of metabolism, growth and differentiation of cells. Among several genes and biochemical pathways, the insulin/insulin-like growth factor-1 (IGF-1) system is widely studied for ageing and lifespan in nematode and fruit fly and mouse [1,2,4,14]. Insulin/IGF-1 signaling pathway is evolutionarily conserved among species including *Caenorhabditis elegans*, *Drosophila melanogaster*, mouse and human [1,14,20]. The important roles of Insulin/IGF-1 signaling pathway for the control of longevity in experimentally induced mutant animals are very well documented.

The insulin-like growth factor-1 is a multi-functional polypeptide which consists of 70 amino acids and plays an critical role in normal growth and development [12,16,32]. The IGF-1 is closely related to the insulin that controls metabolism. The IGF family includes IGF-1, its receptor and six binding proteins (IGFBP1-6) that modulate the actions of IGF-1 in the bloodstream [13]. IGF-1 binds to cell surface receptor, IGF-1 receptor, which is a transmembrane receptor containing tyrosine kinase [9]. Binding of IGF-1 promotes tyrosine phosphorylation of the IGF-1R and induces the cytoplasmic binding of Insulin receptor substrate-1 (IRS-1) to IGF-1R [26]. IRS-1 then activates MAP kinase (MAPK) and phosphoinositide 3-kinase (PI3K) and PI3K activates Akt (serine/threonine protein kinase B) (Fig. 1) [26,31]. The activated signal cascades by IGF-1 system play critical roles in

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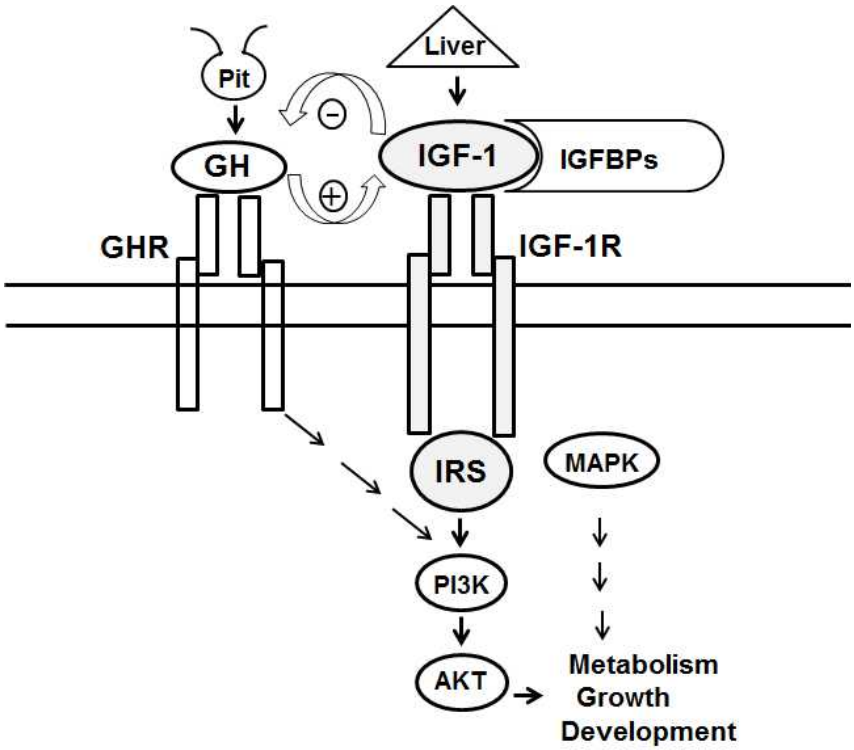

Fig. 1. The components of the GH/IGF-1 system. The IGF-1 binds its receptors (IGF-1R) and six binding proteins (IGFBPs). Binding of IGF-1 activates IGF-1R and induces binding of Insulin receptor substrate-1 (IRS-1). IRS-1 then activates MAP kinase (MAPK) and phosphoinositide 3-kinase (PI3K) and PI3K activates Akt (serine/threonine protein kinase B).Growth hormone (GH) is secreted by pituitary (Pit) and bind its receptor (GHR) and stimulates the liver to produce IGF-1 and then elevated IGF-1 suppresses secretion of GH from pituitary.

regulating cell proliferation/differentiation and resistance to cell death (apoptosis) [17,23].

Main source of the production of IGF-1 in animal is the liver as an endocrine hormone (Fig. 1) and its production is stimulated by growth hormone (GH) [7,16,17]. Growth hormone releasing hormone from hypothalamus stimulates somatotrophs in anterior pituitary to secrete GH. GH is released into the blood and then stimulates the liver to produce IGF-1 (Fig. 1, 2) [16,17]. In addition to liver-originated endocrine IGF-1, extra-hepatic IGF-1 is also produced by many peripheral tissues/cells. This local IGF-1 is released by tissues/cells into the own/adjacent tissues/cells rather than into the bloodstream (autocrine/paracrine) (Fig. 2) [10,21].

Animal model for longevity in relation with insulin/IGF-1 signal system

Recent scientific discoveries in model animals for the extension of lifespan have been shown that several genes and pathways are involved in the process of ageing. The signal pathway of the insulin/IGF-1 is an important factor for the longevity in many organisms and Insulin/IGF-1 signal system is conserved in many organisms from worms to human [1,14]. The first result showing that the insulin/IGF-1 signaling pathway could control lifespan was obtained in worms. The mutation in the *daf*-2 gene, which is *C. elegans* the only insulin/IGF-1 receptor (IR), could extend the lifespan of the worms up to twice than their controls by inducing developmental and metabolic changes [14,15]. In addition to worms, mutants flies of insulin/IGF-1 receptor also exhibited extended lifespan (up to 85% increase in female mutants than their controls)and both males and female $IR^{(-/-)}$ flies exhibited dwarf phenotype [29]. Also mutant flies of chico, which is homologous to vertebrate insulin receptor substrates (IRS), have been shown to double the lifespan of the flies than their controls [6], and these $IRS^{(-/-)}$ flies have only half the size of normal flies by the mutation of insulin/IGF-1 signaling. These results clearly demonstrate that the insulin/IGF-1 pathway is a critical determinant of the extension of lifespan in both worm and fly.

In addition to invertebrate, transgenic or knockout mice models for the IGF-1 signaling research are well documented

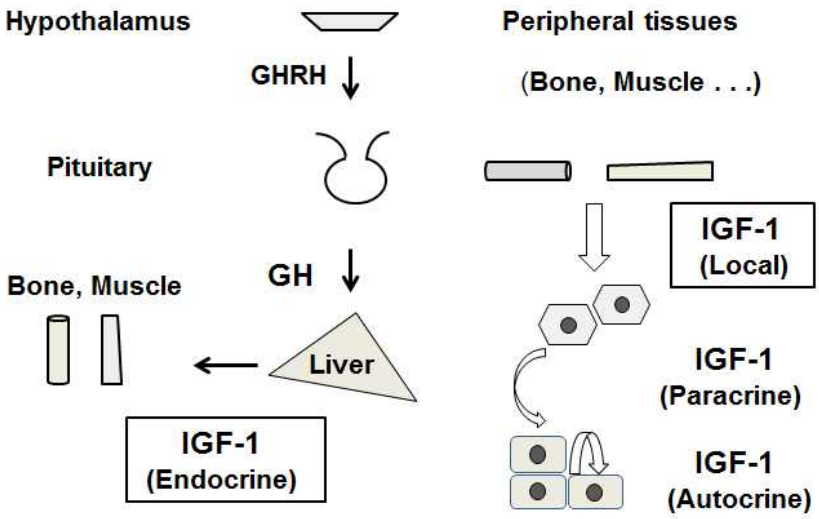

Fig. 2. Growth-hormone-releasing hormone (GHRH) from hypothalamus stimulates pituitary to produce GH and then GH stimulates hepatic IGF-1 secretion to peripheral tissues such as bone and muscle through blood (liver-originated endocrine IGF-1). In addition, extra-hepatic IGF-1 (local IGF-1) is also produced by many other cells/tissues by autocrine/paracrine fashion, secretion released by cells into the own/adjacent cells or tissues rather than into the bloodstream.

and several experimentally induced mutations which interfere with IGF-1 signaling could extend lifespan of mice. Mice carrying null mutation in the IGF-1 receptor (IGF-1R) were small in size and died at birth [19]. It demonstrates that IGF-1 is a very important factor for the growth and development. However, the early death of these mutant mice make impossible for the further research of the involvement of IGF-1R in the longevity. In order to avoid this problem, Holzenberger *et al.* [11] developed heterozygous knockout mice of IGF-1 receptor, that is homologue of the *C. elegans daf*-2 [15]. These IGF-1R$^{(+/-)}$ mutant mice exhibited normal size and any significant phenotype differences were not observed. Interestingly, these mutant mice live 26% longer than their controls. Female IGF-1R$^{(+/-)}$ mice live 33% longer than control females and IGF-1R$^{(+/-)}$ male mice live 16% longer than control males. These IGF-1R$^{(+/-)}$ mice also exhibited resistance to oxidative stress and a reduced glucose tolerance than their control mice [11]. These results from mutants of worms, flies and mice clearly demonstrate that IR/IGF-1R is an crucial factor for the control of longevity in animal and also suggest that the decreased signaling of insulin/IGF-1 by the mutation of the IGF-1R might play an important role in mammalian longevity. The downstream effector of the IGF-1/IGF-1R is the insulin receptor substrate (IRS)-1, which bind to IGF-1R. Mutants mice of IRS-1$^{(-/-)}$ also exhibited extended lifespan up to 18% (mainly due to 32% in female mice than wild type controls) in initial study [24] and extended lifespan by 16% in male IRS-1$^{(-/-)}$ mice than control mice in further study by the same group [25]. In addition, increased resistances to several ageing related symptoms such as skin, bone and motor dysfunction were observed in aged IRS-1$^{(-/-)}$ mice [24,25]. Deletion of chico, homologue of IRS of *D. melanogaster*, also exhibited extend life span by up to 50% [6]. These suggest that evolutionally conserved IRS-1 could be an important regulator of lifespan in many animals and also could serve as a good model system for the study of the age related symptoms.

Animal model for the longevity in relation with GH

The secretion of GH from pituitary declines with ageing and the serum levels of the IGF-1 decline consequently in human [20,30]. Although, the reason for age related decrease in GH secretion is not well understood, several evidences from mice models related GH axis strongly support that GH axis is an important factor for the regulation of mammalian longevity. Over-expression of GH by transgenic mice resulted in early onset of ageing related symptoms including shortened reproductive span [3]. Importantly, these GH transgenic mice resulted in shortened lifespan than their normal controls. In contrast, Ames/Snell dwarf mice, which are well known for the deficiency of GH, exhibited extended lifespan than their normal controls and these dwarf mice also exhibited reduced levels of serum insulin and IGF-1 [4].

In addition to mutants mice of GH, knockout mice of GH receptor (GHR) had been developed for the study of ageing. Targeted disruption of GHR in mice also resulted in increased lifespan up to 65% than normal controls [5]. As expected, these mice also exhibited decreased body weights, insulin and IGF-1 level. These results clearly demonstrate that high levels of GH could accelerate aging and low levels of GH could delay aging in mice. Reduced serum levels of the IGF-1 were observed in both GH-deficient and GH-resistant GHR$^{(-/-)}$ mice [3-5]. It strongly suggests that GH is actively involved in the control of the lifespan in mice by regulating the production of the IGF-1 and GH/IGF-1 axis is a key regulator of longevity in mice.

Animal model for IGF-1 in the longevity

Although, many studies in various model organisms indicate that IGF-1 system is important factor in the determination of lifespan, there is limited information available for the mutant animal for IGF-1 itself for the involvement of ageing. Growth retardation and postnatal lethality of traditional knockout mice of the IGF-1 suggests that IGF-1 is an essential growth factor for growth and development [19]. However, early lethality of these mice make impossible for further study of the involvement of IGF-1 in longevity. In order to avoid this critical problem, liver specific- (Li-) IGF-1 knockout mice had developed by utilizing Cre/loxP system [18,27]. As expected, these mutant mice exhibited 75% reduction in total serum IGF-1 levels (liver-originated endocrine IGF-1). However, Li-IGF-1$^{(-/-)}$ mice resulted in normal growth and development unexpectedly, and they exhibited average body weight [18,27]. These results of Li-IGF-1$^{(-/-)}$ mice suggest that endocrine IGF-1 is not a critical factor for the postnatal growth. It suggests that increased serum levels of GH by decreased levels of IGF-1 might be involved in normal growth of these up to 12 months of age of Li-IGF-1$^{(-/-)}$ mice [27,28]. It is known that the highest expression is found in the liver but also local expression of IGF-1 in most cells of peripheral tissues of the animal is well documented [10,21]. It suggests that local production of the IGF-1 from several tissues which were not affected by liver specific mutation might responsible for the postnatal growth of Li-IGF-1$^{(-/-)}$ mice [27,28]. Then, the role of liver derived IGF-1 *in vivo* still remain unanswered. The role of liver derived endocrine IGF-1 might be involved in the regulation of ageing is supported by the recent finding of a significant extension of lifespan in mice with Li-IGF-1$^{(-/-)}$. Svensson *et al* [28] observed the mean life span of these mutant mice increased 10%, mainly due to 16% increased lifespan of female Li-IGF-1$^{(-/-)}$mice, than their control mice. In addition, these mutant mice exhibited decreased body weight and body fat and increased GH secretion was observed in aged Li-IGF-1$^{(-/-)}$ mice [28]. Although, these mutant mice exhibited a moderately increased mean lifespan, this finding is the first evidence showing that the knockout of IGF-1 gene itself is directly involved in the determination of longevity by genetically manipulated mice.

Conclusion

The observation can be summarized that the downstream signals of insulin/IGF-1 system (IR and IRS) are important factors in the control of longevity in both invertebrates and vertebrates. In addition, the upstream signals of insulin/IGF-1 signal (GH and GHR) in mice are also involved

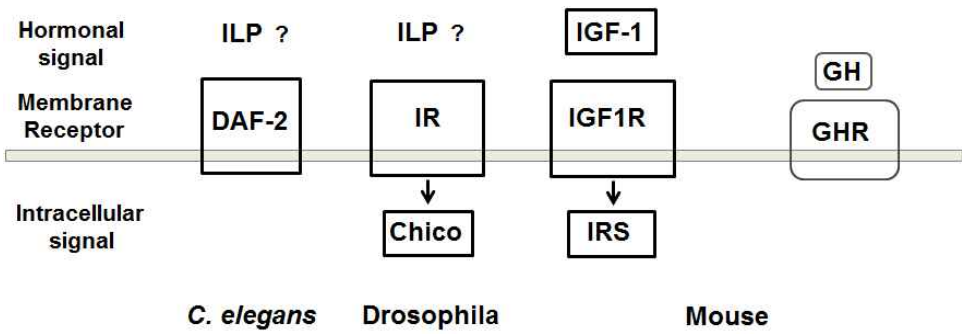

Fig. 3. Longevity animal models in evolutionarily conserved Insulin/IGF-1 signaling pathway in *C. elegans*, *D. melanogaster* and mouse. DAF-2 is a Insulin/IGF-1 receptor (IR) of *C. elegans*, dIR as *Drosophila* IR and IGF-1R as mouse IR, respectively. C. *elegans* and *D. melanogaster* have insulin-like peptide (ILP) and their function are unknown (?). IRS is insulin receptor substrate of mouse and chico is IRS of *D. melanogaster*. All of mutant animal models in box exhibited longevity phenotype including mutant mice of GH and GHR.

in the determination of the lifespan. IGF-1 connects upstream and downstream of this signal pathway and this GH/IGF axis is the most important signal system in the determination of longevity in animals. It might suggest that IGF-1 is a key hormone for the longevity of the animal. Reduced insulin/IGF-1 signaling and reduced IGF-1 levels were commonly observed in long-lived most oh mutants above mentioned. All the animals models above mentioned strongly support that an evolutionarily conserved insulin/IGF-1 signaling regulates lifespan across species (Fig. 3). Now we know that the rate of ageing could be controled by genetic regulation of the insulin/IGF-1 signaling. However, the molecular mechanism for the roles of reduced insulin/IGF-1 signaling in the biology of aging largely remains unknown. It is well known that calorie restriction (CR) play important roles in the biology of aging. CR reduces plasma concentration of GH and insulin/IGF-1 and CR can improve insulin sensitivity and increase lifespan in normal control mice [8,22]. However, insulin/IGF-1 signaling was not changed by CR in $GHR^{(-/-)}$ mice and CR failed to further increase lifespan in $GHR^{(-/-)}$ mice [8,22]. This is a good example of difficulty of studying complicated metabolic pathways in mammalians for the study of longevity. The subjects of human longevity in relation with insulin/IGF-1 signal system are more complicated and it is still inconclusive for the involvement of the GH/IGF axis in longevity. Although, we start to understand the insulin/IGF-1 signal system in the regulation of longevity, further investigations for the downstream pathways of this signal system are needed, so we will get more clear understanding of biology of ageing by insulin/IGF-1 signal system in higher animal including human.

References

1. Barbieri, M., Bonafè, M., Franceschi, C. and Paolisso, G. 2003. Insulin/IGF-I-signaling pathway: an evolutionarily conserved mechanism of longevity from yeast to humans. *Am. J. Physiol. Endocrinol. Metab.* **285,** E1064-1071.
2. Bartke, A. 2001. Mutations prolong life in flies; implications for aging in mammals. *Trends Endocrinol. Metab.* **12,** 233-234.
3. Bartke, A. 2003. Can growth hormone (GH) accelerate aging? Evidence from GH-transgenic mice. *Neuroendocrinology* **78**, 210-216.
4 Bartke, A. and Brown-Borg, H. 2004. Life extension in the dwarf mouse. *Curr. Top. Dev. Biol.* **63,** 189-225.
5. Bonkowski, M. S., Pamenter, R. W., Rocha, J. S., Masternak, M. M., Panici, J. A. and Bartke, A. 2006. Long-lived growth hormone receptor knockout mice show a delay in age-related changes of body composition and bone characteristics. *J. Gerontol. A Biol. Sci. Med. Sci.* **61**, 562-567.
6. 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, a Drosophila insulin receptor substrate protein. *Science* **292**, 104-106.
7. Clemmons, D. R. and Underwood, L. E. 1992. Role of insulin-like growth factors and growth hormone in reversing catabolic states. *Horm. Res.* **38,** 37-40.
8. Giani, J. F., Bonkowski, M. S., Muñoz, M. C., Masternak, M. M., Turyn, D., Bartke, A. and Dominici, F. P. 2008. Insulin signaling cascade in the hearts of long-lived growth hormone receptor knockout mice: effects of calorie restriction. *J. Gerontol. A Biol. Sci. Med. Sci.* **63,** 788-797.
9. Grønborg, M., Wulff, B. S., Rasmussen, J. S., Kjeldsen, T. and Gammeltoft, S. 1993. Structure-function relationship of the insulin-like growth factor-I receptor tyrosine kinase. *J. Biol. Chem.* **268,** 23435-23440.
10. Hammond, J. M., Mondschein, J. S., Samaras, S. E. and Canning, S. F. 1991. The ovarian insulin-like growth factors, a local amplification mechanism for steroidogenesis and hormone action. *J. Steroid Biochem. Mol. Biol.* **40,** 411-416.
11. Holzenberger, M., Dupont, J., Ducos, B., Leneuve, P., Géloën, A., Even, P. C., Cervera, P. and Le Bouc, Y. 2003. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature* **421**, 82-87.
12. Jansen, M., van Schaik, F. M., Ricker, A. T., Bullock, B., Woods, D. E., Gabbay, K. H., Nussbaum, A. L., Sussenbach, J. S. and Van den Brande, J. L. 1983. Sequence of cDNA encoding human insulin-like growth factor I precursor. *Nature* **306**, 609-611.
13. Jones, J. I. and Clemmons, D. R. 1995. Insulin-like growth factors and their binding proteins: biological actions. *Endocr. Rev.* **16**, 3-34.
14. 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.
15. 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.
16. LeRoith, D. and Roberts, C. T. Jr. 1993. Insulin-like growth factors. *Ann. N. Y. Acad. Sci.* **27,** 1-9.
17. LeRoith, D. 2000. Regulation of proliferation and apoptosis by the insulin-like growth factor I receptor. *Growth Horm. IGF Res.* **10,** S12-13.
18. Liu, J. L., Yakar, S. and LeRoith, D. 2000. Conditional knockout of mouse insulin-like growth factor-1 gene using the Cre/loxP system. *Proc. Soc. Exp. Biol. Med.* **223,** 344-351.
19. Liu, J. P., Baker, J., Perkins, A. S., Robertson, E. J. and Efstratiadis, A. 1993. Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type 1 IGF receptor (Igf1r). *Cell* **75,** 59-72.
20. Lombardi, G., Di Somma, C., Rota, F. and Colao, A. 2005. Associated hormonal decline in aging: is there a role for

GH therapy in aging men? *J. Endocrinol. Invest.* **28,** 99-108.
21. Lund, P. K., Moats-Staats, B. M., Hynes, M. A., Simmons, J. G., Jansen, M., D'Ercole, A. J. and Van Wyk, J. J. 1986. Somatomedin-C/insulin-like growth factor-I and insulin-like growth factor-II mRNAs in rat fetal and adult tissues. *J. Biol. Chem.* **261**, 14539-15444.
22. Masoro, E. J. 2005. Overview of caloric restriction and ageing. *Mech. Ageing Dev.* **126**, 913-922.
23. Salminen, A. and Kaarniranta, K. 2010. Insulin/IGF-1 paradox of aging: regulation via AKT/IKK/NF-kappaB signaling. *Cell Signal* **22**, 573-577.
24. Selman, C., Lingard, S., Choudhury, A. I., Batterham, R. L., Claret, M., Clements, M., Ramadani, F., Okkenhaug, K., Schuster, E., Blanc, E., Piper, M. D., Al-Qassab, H., Speakman, J. R., Carmignac, D., Robinson, I. C., Thornton, J. M., Gems, D., Partridge, L. and Withers, D. J. 2008. Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice. *FASEB J.* **22**, 807-818.
25. Selman, C., Partridge, L. and Withers, D. J. 2011. Replication of extended lifespan phenotype in mice with deletion of insulin receptor substrate 1. *PLoS One* **6,** e16144.
26. Sun, X. J., Crimmins, D. L., Myers, M. G. Jr., Miralpeix, M. and White, M. F. 1993. Pleiotropic insulin signals are engaged by multisite phosphorylation of IRS-1. *Mol. Cell. Biol.* **13**, 7418-7428.
27. Svensson, J., Söderpalm, B., Sjögren, K., Engel, J. and Ohlsson, C. 2005. Liver-derived IGF-I regulates exploratory activity in old mice. *Am. J. Physiol. Endocrinol. Metab.* **289**, E466-473.
28. Svensson, J., Sjögren, K., Fäldt, J., Andersson, N., Isaksson, O., Jansson, J. O. and Ohlsson, C. 2011. Liver-derived IGF-I regulates mean life span in mice. *PLoS One* **6,** e22640.
29. 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.
30. Toogood, A. A., O'Neill, P. A. and Shalet, S. M. 1996. Beyond the somatopause: growth hormone deficiency in adults over the age of 60 years. *J. Clin. Endocrinol. Metab.* **81,** 460-465.
31. Valentinis, B. and Baserga, R. 2001 IGF-I receptor signalling in transformation and differentiation. *Mol. Pathol.* **54,** 133-137.
32. Yakar, S. and Adamo, M. L. 2012. Insulin-like growth factor 1 physiology: lessons from mouse models. *Endocrinol. Metab. Clin. North Am.* **41**, 231-247.

초록 : 장수와 관련된 IGF-1 신호 시스템을 연구하기 위한 동물 모델

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장수 또는 노화에 관한 연구는 여러 가지 유전적 요인과 생리학적 및 환경 요인들의 복잡한 조합에 의해 결정되므로, 이와 관련된 연구는 매우 흥미로운 분야이나 또한 어려운 주제이다. 지난 수십 년 동안 장수 또는 노화에 관여하는 분자 메커니즘을 찾기 위하여 동물 모델을 사용한 유전학적 접근법으로, 특이적 유전자를 결손 시키는 연구는 귀중한 도구임이 입증되었다. 장수에 관한 첫 번째 연구는 꼬마선충의 돌연변이체에서 발견되었으며, 이 선충의 인슐린/인슐린유사 성장인자-1 회로가 장수에 관여함이 밝혀졌다. 인슐린유사 성장인자-1은 인슐린과 유사한 아미노산 서열을 가진 폴리펩타이드로, 세포의 정상적인 성장과 발달에 관여한다. 이 발견 이후 인슐린/인슐린유사 성장인자-1 회로에 관여하는 많은 인자들이 선충과 초파리 연구에서 장수에 관여함이 밝혀졌다. 또한 특이적 유전자를 결손 시킨 생쥐 모델을 이용한 연구에서도 인슐린/인슐린유사 성장인자-1 회로뿐 아니라 성장호르몬/인슐린유사 성장인자 회로도 장수에 관여함이 지난 수십 년 동안의 연구결과로 밝혀졌다. 간 조직 특이적으로 인슐린유사 성장인자-1 유전자를 결손 시킨 생쥐모델을 이용한 최근의 연구 결과에 의하면 인슐린유사 성장인자-1 자체도 장수에 관여함이 최초로 밝혀졌으며, 이는 인슐린유사 성장인자-1 회로가 무척추동물뿐 아니라 척추동물에서도 장수에 관여함을 명백하게 보여주는 결과이다. 장수를 조절하는 분자 메커니즘은 아직 완전하게 설명되지 않지만, 감소되어진 인슐린유사 성장인자-1의 신호가 장수와 노화의 조절에 중요한 역할을 하며, 인슐린유사 성장인자-1 회로에 관여하는 여러 가지 유전자들의 장수에서의 역할을 유전자 조작된 생쥐모델을 이용하여 집중적으로 검토하려 한다.