*Roles of insulin signaling pathways in Age-Related Locomotor Impairment*

1. Introduction

Aging affects all organisms. During aging, Age-Related Locomotor Impairment (ARLI) is one of serious arising concerns. What is ARLI? Age-related locomotor impairment is a decrease in muscle mass and body movement due to aging. Patients with ARLI are at greater risk for falling, skeletal fractures, and possibly cause complications with obesity, diabetes, hypertension, and more [reference]. How can we contribute to the society and rescue patients from ARLI? Unfortunately, genes and genetic pathways that influence ARLI are not commonly known.

In one of the ARLI studies, Jones et al (2009) implicates insulin signaling as a key regulator of ARLI. What is insulin signaling? Insulin is a hormone produced by pancreatic cells to regulate amount of glucose in the blood. Also insulin triggers the uptake of glucose, fatty acids, and amino acids into liver and stores them in forms of glycogen, lipids, and proteins respectively. Insulin signaling is very complex network that controls multiple processes in the body. Studying insulin signaling from humans is very complex and challenging, in many studies they use fruit flies called Drosophila instead. Drosophila is a commonly used model organism in biological and genetic studies due to their short lifespan.

How do Jones et al (2009) determine whether insulin signaling is a key regulator? They conducted an experiment using fruit fly Drosophila. They preselected 729 EP and 364 pGawB transposon insertion sites and tested by observing behaviors of Drosophila over a specified period of time. [Why EP and pGawB?] The best 24 transposon sites were chosen depending on strong negative geotaxis. Negative Geotaxis is a walking behavior that becomes impaired during aging. They measured negative geotaxis of control group Drosophila and genetically modified Drosophila. In result, they found that EP837 insertion in PDK1 causes delay in ARLI. In addition, they reason that since PDK1 functions immediately downstream of phosphatidylinositol 3-kinase (P13K) and immediately upstream of AKT in the insulin signaling pathway, they decided to repeat previous steps for genes Dp110 and Akt.[Why Dp110 and Akt?]. Conceivably, the insertion of certain transposon in Dp110 and Akt caused delay in ARLI.

Is there any other insulin signaling genes? According to Taniguchi et al, the insulin receptors are connected to two insulin signaling pathways: the phosphatidylinositol 3-kinase (PI3K)-AKT/protein kinase B (PKB) pathway and Ras-mitogen-activated protein kinase (MAPK) pathway. In Jones et al, they focused on PDK1 which is essentially similar to PKB pathway. How about the other pathway? The new experiment will be based on MAPK pathway to see if insulin genes of MAPK pathway also influence ARLI. If the experiment based on MAPK pathway becomes successful, treatments using insulin signaling must be developed in order to lessen pains for ARLI patients and their caregivers.

1. Experiment

IIA. Identify insulin signaling genes

The first step to the experiment is identifying any insulin genes that are associated with MAPK pathway. The upstream genes of MAPK are RAS, RAF, MEK and the downstream gene of MAPK is ERK1. [How did we know that?]

IIB. P-element insertion

In order to identify any MAPK genes that influence ARLI, the method of P-element insertion is needed. P-element is a DNA sequence that could copy its own sequence and insert into a different position of same genome. P-element insertion is a method used to insert P-element into an insertion site in order to create genetically modified flies. In this case, P-elements will be inserted into MAPK genes. How do they know where to insert transposons? The same insertion sites from Jones et al (2009) will be used to identify genes that influence ARLI. Jones et al (2009) chose following as best insertion sites: EP937, Ep3553, BG02759, EP1150, DJ708, c00368, e03435, and c02098.

IIC. Negative geotaxis

The last step to the experiment will be measuring negative geotaxis for each gene with different P-element insertions. There are a total of 32 combinations and 1 control group since there are 4 genes and 8 different insertion sites. Any of the results that are higher than control group will be consider as delaying ARLI, and any of the results that are lower than control group will be consider as delaying ARLI, or not affective at all.

1. Discussion

Nonetheless, we hope to see that any of the MAPK insulin genes influence ARLI. If the experiment becomes successful, insulin signaling can be used as a key regulator of ARLI. Not so more in Drosophila, tracing back to human genes is essential. Luckily, there is an online database called Homophila which contains human gene homologues in flies. It is possible to contribute to the society if we could find homologues. If we do find homologues, developing new treatments will be just matter of time!

References

Arking, R., 1998. The Biology of Aging: Observations and Principles, second ed.Sinauer Associates, Sunderland, MA

Taniguchi, Cullen M., Brice Emanuelli, and Ronald Kahn. "Critical Nodes In Signalling Pathways: Insights Into Insulin Action." *Nature Reviews Molecular Cell Biology* 7.2 (2006): 85-96. *Academic Search Complete*. Web. 2 Dec. 2013.

Melanie A. Jones, et al. "A forward genetic screen in Drosophila implicates insulin signaling in age-related locomotor impairment."*Experimental Gerontology*. 44. (2009): 542-540. Web. 16 Oct. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/19481596>.

Grotewiel, Mike, and Melanie A. Jones. "Drosophila as a Model for Age-Related Impairment in Locomotor and other Behaviors." *Experimental Gerontology*. 45(5). (2011): 320-325. Web. 16 Oct. 2013. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3021004/>.

Rodenizer, Devin, Mike Grotewiel, et al. "Genetic and environmental factors impact age-related impairment of negative geotaxis in Drosophila by altering age-dependent climbing speed." *Experimental Gerontology*. 43(8).739-748 (2008): n. page. Web. 16 Oct. 2013. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2591094/>.

Massimo Zeviani, et al. "Mutations In TTC19 Cause Mitochondrial Complex III Deficiency And Neurological Impairment In Humans And Flies." *Nature Genetics* 43.3 (2011): 259-263. *Academic Search Complete*. Web. 18 Oct. 2013.

Andrew G. Davies, Ryan I. Friedberg, Hersh Gupta, Chung-Lung Chan, Keith L. Shelton, Jill C. Bettinger, Different genes influence toluene- and ethanol-induced locomotor impairment in C. elegans, Drug and Alcohol Dependence, Volume 122, Issues 1–2, 1 April 2012, Pages 47-54, ISSN 0376-8716, <http://dx.doi.org/10.1016/j.drugalcdep.2011.08.030>. (http://www.sciencedirect.com/science/article/pii/S0376871611003905)

R. St. Laurent, L.M. O’Brien, S.T. Ahmad, Sodium butyrate improves locomotor impairment and early mortality in a rotenone-induced Drosophila model of Parkinson’s disease, Neuroscience, Volume 246, 29 August 2013, Pages 382-390, ISSN 0306-4522, <http://dx.doi.org/10.1016/j.neuroscience.2013.04.037>. (http://www.sciencedirect.com/science/article/pii/S030645221300362X)

Ian Martin, Melanie A. Jones, Mike Grotewiel, Manipulation of Sod1 expression ubiquitously, but not in the nervous system or muscle, impacts age-related parameters in Drosophila, FEBS Letters, Volume 583, Issue 13, 7 July 2009, Pages 2308-2314, ISSN 0014-5793, <http://dx.doi.org/10.1016/j.febslet.2009.06.023>. (http://www.sciencedirect.com/science/article/pii/S0014579309004712)