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

1. Introduction

Aging affects all organisms. During aging, Age-Related Locomotor Impairment (ARLI) is particularly problematic. 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. Although ARLI is a serious clinical challenge for patients and their caregivers, genes and genetic pathways that influence ARLI are not commonly known.

In one of the ARLI studies, Jones et al implicates that insulin signaling is 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 protein respectively. Insulin signaling is very complex network that controls multiple processes in the body. Although studying insulin signaling from humans is quite a bit challenging, in many studies they used fruit flies called Drosophila instead. Drosophila is a commonly used model organism in biological and genetic studies because the results of those studies could interpret back into human.

How do Jones et al purport that insulin signaling is a key regulator? They conducted an experiment based on fruit fly Drosophila. They performed a forward genetic screen to identify P-element insertions that influences ARLI (Jones et al. 2006). Then, they used the principle of Negative Geotaxis to measure Drosophila’s physical activities and select best transposon lines from genetic screen. Next they those best transposon lines and insert P-elements into specific genes they want to apply. Lastly they used Negative Geotaxis and measured walking speed 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 finding insertion sites, applying to genes Dp110, Akt, and measuring walking speed. Conceivably, the insertion of certain transposon in Dp110 and Akt caused delay in ARLI.

Is there any other insulin signaling genes? based on those genes the experiment could be repeated.

1. Experiment(Still referring to Jones et al. article, I will work on it to modify in terms of what I am going to experiment)

IIA. Identify insulin signaling genes

A forward genetic screen is an approach used to identify genes that are responsible for particular behavior.

IIB. P-element insertion

In order to identify genes that influence ARLI using negative geotaxis, Jones et al performed a forward genetic screen for P-element insertions. P-element insertion is a method used to insert a transposon into an insertion site in order to create genetically modified flies. Transposon is a DNA sequence that could copy its own sequence and insert into a different position of same genome. In this case, Jones et al inserted number of transposons to identify genes that are associated with ARLI.

There are many possible ways to insert transposons, but for Jones et al, they insert in 5’ regions of a target gene they want to mutate. How do they know where to insert transposons? Then they compare the results of negative geotaxis and Identify that which genes are associated with ARLI. For Jones et al, they specify which genes were affective with different insertion site. Genes: PDK1, Pfrx, Dorsocross3, m6, HLHm7, and CG14045. P-element: EP937, Ep3553, BG02759, EP1150, DJ708, c00368, e03435, and c02098. If one of the P-elements, EP937, was applied to a gene, m6, the notation will be m6EP937.

IIC. Negative geotaxis

Negative Geotaxis is a walking behavior that becomes impaired during aging.

Jones et al claims that PDK1EP837 delayed ARLI. PDK1 is one of insulin nodes. This gives us a sense of insulin signaling might influence ARLI. To confirm their claims of PDK1, they ran an experiment of comparing the result of a gene with EP837 insertion and one without it. The negative geotaxis values for PDK1 with the insertion were much higher which means that EP837 insertion in PDK1 causes delay in ARLI.

1. Discussion (soon to be added)

How would that interpret back into humans?

Limitations of this experiment.

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