Insulin/Insulin-like Growth Factor Signaling Pathway’s Effect on the 4 Biomarkers of Aging

Abbay Lisicky, Nutrition Science
Mentor: Rachel Flores, MS, RD
Kellogg-Honors College Capstone Project

Abstract
Throughout history, humans have demonstrated the innate drive to control both their external and internal environment. However, despite tremendous technological advances in several fields, people cannot control one of the basic portions of their life cycle, i.e. aging. This paradox is a major reason I chose to research the human aging process. Commonly, human aging is studied using animal models, such as nematodes, fruit-flies, and mice as the model system to answer questions related to human aging with a focus on metabolic processes. This research was focused on the role of Insulin/Insulin-like growth factor (IIS)-1/IGF-1 signaling in aging and its effects on major organs such as skeletal muscle, skin, liver, and immune system. This pathway utilizes insulin growth factor-1 (IGF-1) to activate other pathways which then leads to measurable effects on four major biomarkers of aging: skin, the reproductive system, muscles, and the immune system. I reviewed dozens of case studies and scientific journals to better understand the role of the IIS pathway and IGF-1 on the four biomarkers of aging. Although researching aging research most likely won’t allow us completely to avert the aging process itself, it might give us more insight into the role of health and disease on aging of the body and the mind.

The IIS pathway’s main role is activating the signaling of transcription factors that then stimulate growth and development. Researchers use worm and flies to study this pathway because instead of the invertebrates’ short lifespan and simpler body structure, the IIS pathway is highly conserved between both invertebrates and mammals. IGF-1 is the initiating step in mammalian IIS; IGF-1 is secreted from the liver and through the activation of the AKT pathway via the IIS pathway, it is then established. The mechanism of action of IGF-1 is that the liver is the primary mediator of growth hormone 1 (GH) is made in the anterior pituitary gland and then is released into the bloodstream which then stimulates the liver’s production of IGF-1. IGF-1 then promotes systemic growth.

Breakdown the specificities of the IIS pathway includes several of the following ligands (molecules that bind to other usually larger molecules), receptors (protein molecules that receive chemical signals from outside the cell), secondary messengers (molecules released by the cell to trigger physiological changes), protein kinases (enzyme molecules that add phosphate groups to other molecules), and transcription factors (proteins involved in the process of converting, transcribing, DNA into RNA).

In mammals there are three distinct insulin ligands (Insulin, IGF-1, and IGF-2) rather than just one (IGF-1-Ins) in invertebrates. There are also two different receptors (IGF-1R and IRS-1) in mammals. After the ligand binds to the receptor, the IIS(1-2) ligand phosphorylates several intracellular receptor substrates (IRS-1, Shc, Grb2, and SOS). IRS-1, Shc, Grb2, and SOS provide docking sites like PI3K (a regulatory subunit) and Ras (a growth factor). Once docked, the pathway splits into two separate components. Starting at PI3K, the IRS proteins and the PI3K enzymes trigger a cascade of events that lead to the activation of AKT (a protein kinase) and then to the growth of the cell.

Going back to the growth factor, the activation of Ras occurs. Ras is a protein kinase whose elevated levels lead to the activation of other kinases. MEK1-2 and ERK1-2. These cause the phosphorylation of ELK1 (another transcription factor). The phosphorylation of FoxOs 1a, 3a, 4, and 6 and ELK1 results in the activation of the AKT pathway, this pathway controls the metabolic and mitogenic effects of IGF-1 signaling.

Insulin/IGF-1 signaling is regulated by C. elegans reproductive aging by modulating multiple aspects of the reproductive process, including embryo integrity (quality of embryos), oocyte fertilization, chromosome segregation fidelity (how sister chromatid pair in DNA replication), DNA damage resistance, and oocyte and germine morphology (the quality of the structures). Systematic studies on C. elegans examine the molecular and cellular mechanisms of reproductive aging process from embryos to eggs to adult worms. Additionally, research has been conducted on how reduced levels of Insulin and IGF-1 are related to aging and human senescence.

As humans age, muscles begin to change. Muscle size and architecture are both altered with advanced adult age. Further changes in myofibers (multinucleated single muscle cells) include impairments in several physiological domains including muscle fiber activation, excitation-contraction coupling, actin-myosin cross-bridge interaction, energy production, repair, and regeneration; all of these affect the structure and function of muscles. As aging occurs, body composition changes; this means there is an increase in body fat percentage and a decrease in muscle mass. With a decrease in muscle mass comes a decrease in strength and mobility. All of these changes are above in factors that play roles in aging and disease.

Local IGF-1’s autocrine and paracrine properties result in it being a major controller of muscle tissue growth. Several studies done on mice have shown that mice without IGF-1 have a decrease in muscle atrophy. Reduced levels of IGF-1 in these studies has been shown to be correlated with a decrease in IGF-1 signaling.

Efficiency:
*Full list of sources is available on request