



세미나 | 제2 세미나실

Exercise and Myokine

송 옥

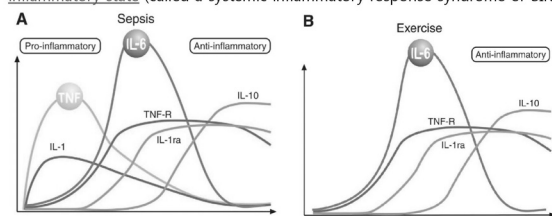
Health and Exercise Science Laboratory Institute of Sports Science Seoul National University

Today's Talk

- Introduction
- IL-6
- IL-15
- BDNF (Brain-derived neurotrophic factor)
- Irisin
- Lab's work regarding myokines

INTRODUCTION

Sepsis is a serious medical condition that is characterized by a whole-body inflammatory state (called a systemic inflammatory response syndrome or SIRS)

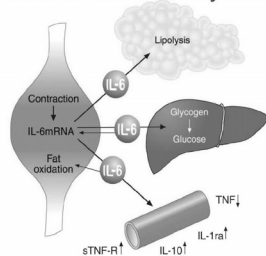


With the discovery that exercise provokes an increase in a number of cytokines, a possible link between skeletal muscle contractile activity and immune changes was established.

INTRODUCTION

Interleukin-6

Cytokines and other peptides that are produced, expressed, and released by muscle fibers and exert either paracrine or endocrine effects should be classified as "myokines."



Contracting **muscle fibers** produce and release IL-6, which induces several metabolic effect.

Interleukin-6 (IL-6)

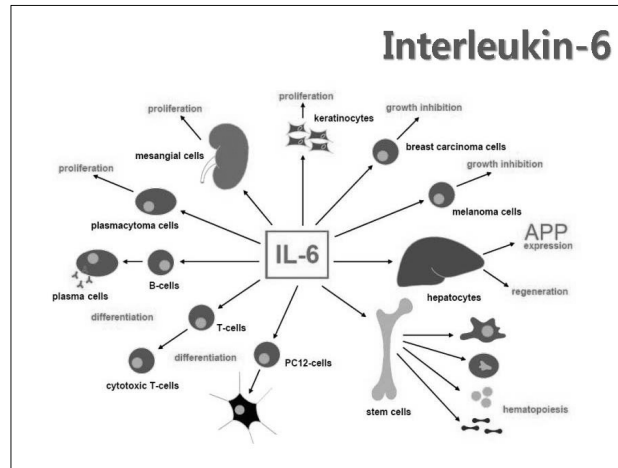
Interleukin-6

IL-6 in health...

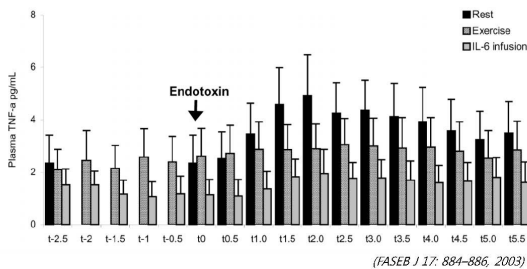
- Major inducer of acute-phase protein synthesis in hepatocytes
- Promotes B-cell differentiation into plasma cells
- T-cell differentiation
- Chemotactic factor for lymphocytes
- Many more less well defined functions...

...and disease

- Chronic inflammatory diseases (rheumatoid arthritis, Morbus Crohn)
- Growth factor for tumor cells
- Acute sepsis
- Coronary heart disease
- Multiple sclerosis
- Etc..

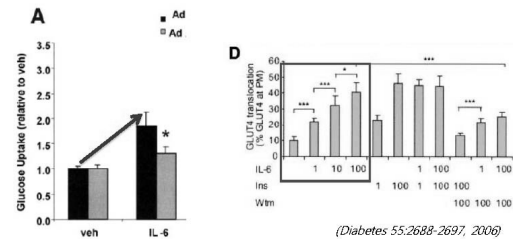


Interleukin-6



Both exercise and IL-6 infusion suppress TNF-α production in humans

Interleukin-6



In vivo, experiments demonstrated that IL-6 may increase basal and insulin-stimulated glucose uptake via an increased GLUT4 translocation

Interleukin-15 (IL-15)

Interleukin-15

IL-15 (14-15 kDa) is a four alpha-helix cytokine with structural similarities to IL-2.

Two isoforms of IL-15 with altered glycosylation have been shown to exist

: a **long signaling peptide form** (48 amino acids) that is secreted from the cell, and a **short signaling peptide** (21 amino acids) form that remains intracellular.

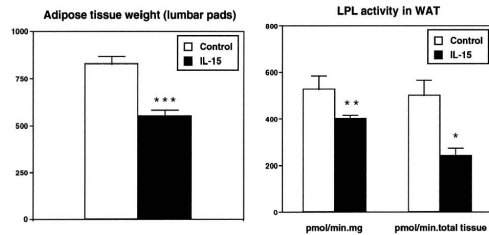
IL-15 functions via a widely distributed **heterotrimeric receptor (IL-15R)**, which consists of a α -chain (shared with IL-2) and common γ -chain, together with a unique β -chain (IL-15) that in turn exists in eight isoforms.

Interleukin-15

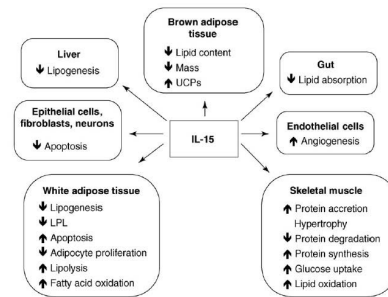
IL-15 seems to play a role in reducing adipose tissue mass

When IL-15 was administered to adult rats for 7 days, it resulted in a 33% decrease in white adipose tissue mass.

(*Biochimica et Biophysica Acta* 1526 (2001) 17–24)



Interleukin-15



Interleukin-15

Exercise-induced IL-15

The regulatory role of muscle contraction with regard to IL-15 is not clear.

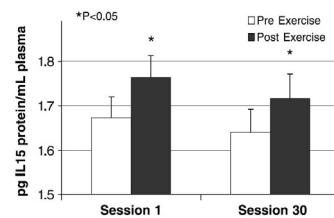
Nieman et al. found that muscle IL-15 mRNA levels were not changed immediately after a 3-h run.

Ostrowski et al. found that plasma IL-15 (measured up to 6 h into recovery) did not change in response to 2.5 h of treadmill running.

Skeletal muscle IL-15 mRNA levels, measured immediately after a 2-h weight training bout, did not differ from baseline.

Whereas plasma **IL-15 protein was increased immediately after acute resistance exercise** in one study

Interleukin-15



Plasma IL-15 protein concentration before and after resistance exercise at the beginning (session 1) and end (session 30) of the resistance exercise training intervention (n = 124).

(*J Appl Physiol.* 2004 Dec 9;97(6):2214-9.

Interleukin-15

In summary, IL-15 is a recently discovered **anabolic factor** that is constitutively expressed by skeletal muscle and regulated by **strength training**.

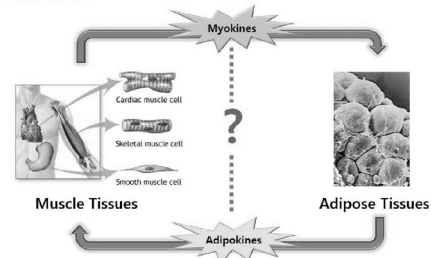
While IL-15 has solid anabolic effects, it also seems to play a role in **reducing adipose tissue mass**, and it is therefore suggested that IL-15 may play a role in **muscle-fat cross talk**.

We suggest that muscle-derived IL-15 should be classified as a potential myokine.

Interleukin-15

IL-15 has been identified as an **anabolic factor**, which is highly expressed in skeletal muscle.

Furthermore, IL-15 has been suggested to play a role in **muscle-adipose tissue interaction**.



BDNF (Brain-derived neurotrophic factor)

BDNF

Brain-derived neurotrophic factor (BDNF)

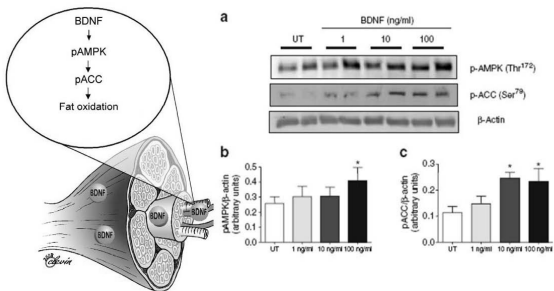
Brain-derived neurotrophic factor (BDNF) has been shown to regulate neuronal development and plasticity and plays a role in learning and memory.



BDNF exerts many of their effects on neurons primarily through Trk receptor tyrosine kinases.

Among these, BDNF and its receptor TrkB are the ones most widely and abundantly expressed in the brain.

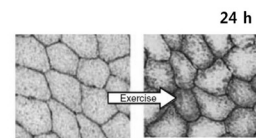
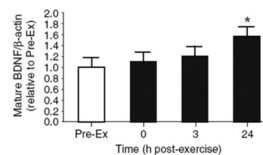
Biological role of contraction-induced BDNF



Matthews et al., 2009

BDNF mRNA and protein expression were increased in human skeletal muscle after exercise; however, muscle derived BDNF appeared **not to be released into the circulation**.

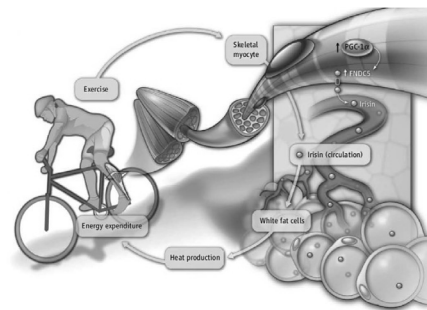
High intensity Cycle exercise



Irisin

Irisin

Irisin is a PGC1-α dependent myokine that drives brown fat like development of white fat.



(Kelly, Science 2012)



Introduction of irisin

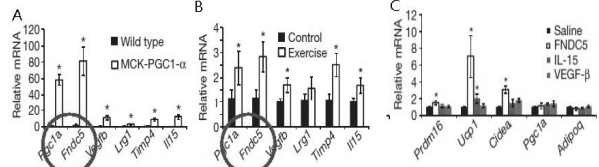
ARTICLE

Nature 2012, Pontus Boström et al

doi:10.1038/nature10777

A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis

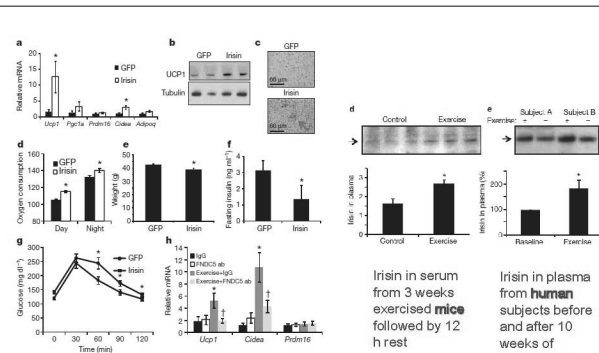
Pontus Boström¹, Jun Wu², Mark P. Jedrychowski³, Anshu Kordik⁴, Li Ye⁵, James C. Lo⁶, Kyle A. Rabuch¹, Elisabeth Almér Boström¹, Jang Hyun Choi⁴, Jonathan Z. Long³, Shingo Kajimura⁴, Maria Cristina Zingales¹, Brigitte F. Vind¹, Hua Tu⁷, Severin Cinti⁸, Kurt Huber⁹, Steven P. Gygi² & Bruce M. Spiegelman¹



Major findings from irisin paper

Nature 2012, Pontus Boström et al

- Muscle-specific PGC1- α transgenic mice have increased brown/beige fat cells in the subcutaneous depot
- FNDC5 is induced with forced PGC1- α expression or exercise, and turns on brown/beige fat gene expression
- FNDC5 is a potent inducer of the brown/beige fat gene program
- FNDC5 is proteolytically cleaved and secreted from cells
- Detection of irisin in mouse and human plasma
- Irisin induces browning of white adipose tissues in vivo and protects against diet-induced obesity and diabetes



Irisin induces browning of white adipose tissues in vivo and protects against diet-induced obesity and diabetes

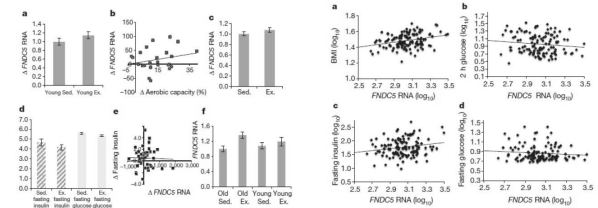
Nature 2012, Pontus Boström et al

BRIEF COMMUNICATIONS ARISING

Controversial report

Is irisin a human exercise gene?

ARISING FROM P. Boström et al. Nature 831, 463–468 (2012)



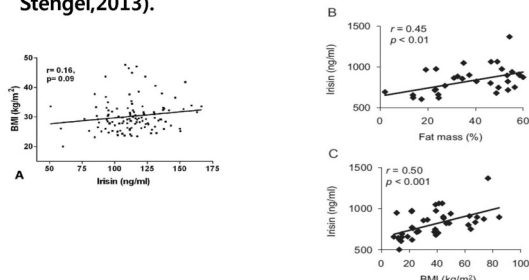
Irisin is not routinely activated by exercise in humans

Irisin expression is not related to diabetes status in humans

Nature 2012, Timmons et al

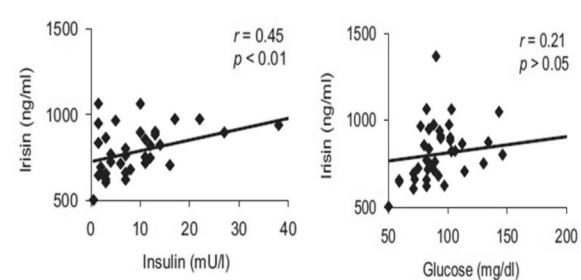
Controversial results regarding irisin and clinical parameters

- Irisin levels showed a positive correlation with body weight and BMI (Joo Young Huh, 2012 ; Andreas Stengel, 2013).



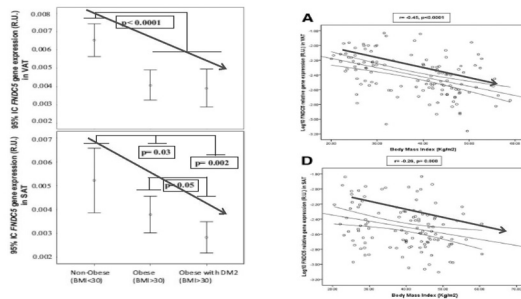
Controversial results regarding irisin and clinical parameters

- Irisin was positively correlated with circulating insulin and glucose (Andreas Stengel, 2013).

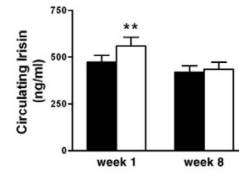


Controversial results regarding irisin and clinical parameters

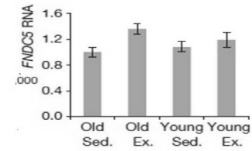
- Irisin levels were negatively associated with obesity (Jose Maria, 2013; Yeon Kyung Choi, 2013).



Circulating irisin level with exercise



(Metabolism, Huh et al., 2012)
8 week training program involving 3 training sessions per week.
2 or 3 set of runs on an indoor track with two 80m sprint runs in each set. A resting period of 20 min between sets.



(Nature, Timmons et al, 2012)
6 week of endurance cycle training program involving four times a week (45min) at 75% of peak aerobic capacity(peak VO₂).