

## **The therapeutic potential of irisin in treatment of obesity and diabetes in humans**

Irisin is an exercise-induced myokine proposed to mediate the beneficial effect of exercise, especially on adipocyte browning. In the initial report in mice, irisin has been shown to induce uncoupling protein 1 expression and increase the energy expenditure. Therefore, the therapeutic potential of irisin in treatment of metabolic disease is of interest. However, the physiology of irisin in humans is not completely understood. In this study, we have examined how irisin is regulated in physiological (exercise) and pathophysiological conditions (metabolic syndrome). In addition, we studied the effect of exogenously treated irisin on human adipocyte and myocyte metabolism. After an acute bout of exercise, irisin was immediately secreted in a transient manner. Through primary human muscle cell culture, we found that exogenous irisin can mimic exercise-induced muscle metabolism through AMPK signalling activation. Similar to reports in mice, irisin induced uncoupling protein 1 levels and reduced lipid accumulation in human adipocytes. Cross-sectional analysis revealed that irisin levels are increased in subjects with metabolic syndrome, implying that irisin may be increased as a protective feedback mechanism to overcome the metabolic dysregulations.

## Curriculum Vitae



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## Education

- ✚ **2002. 3 – 2006. 2** 학사. 이화여자대학교 약학대학 제약학과
- ✚ **2006. 3 – 2011. 8** 석/박사 통합과정. 이화여자대학교 약학대학 약물학 전공  
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**Thesis:** The role of mitochondrial antioxidant peroxiredoxin 3 in regulation of adipocyte function. (Advisor: Professor Hunjoo Ha, Co-advisors: Professors Jae Bum Kim, Hanjoong Jo, Myung-Hee Chung, and Kong-Joo Lee)

- ✚ **2011. 9 – 2012. 6** Postdoctoral fellow. 이화여자대학교 약학대학
- ✚ **2012. 7 – 2014. 8** Postdoctoral research fellow at Division of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA. (Principle Investigator: Dr. Christos S. Mantzoros)

## Peer-reviewed Journal Articles

- ✚ **Huh JY**, Siopi A, Mougios V, Park KH, Mantzoros CS. Irisin in response to exercise in humans with and without metabolic syndrome. *J Clin Endocrinol Metab.* **2014** Dec 16;jc20142416. [Epub ahead of print]
- ✚ **Huh JY**, Mougios V, Kabasakalis A, Fatouros I, Siopi A, Douroudos II, Filippaios A, Panagiotou G, Park KH, Mantzoros CS. Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through AMPK activation. *J Clin Endocrinol Metab.* **2014** Nov;99(11):E2154-61.
- ✚ **Huh JY**, Mougios V, Skraparlis A, Kabasakalis A, Mantzoros CS. Irisin in response to acute and chronic whole-body vibration exercise in humans. *Metabolism.* **2014** Jul;63(7):918-21.

- ✚ **Huh JY**, Dincer F, Mesfum E, Mantzoros CS. Irisin stimulates muscle growth-related genes and regulates adipocyte differentiation and metabolism in humans. *Int J Obes.* **2014** Mar 11. DOI:10.1038/ijo.2014.42 [Epub ahead of print]
- ✚ **Huh JY**, Gouni-Berthold I, Berthold HK, Berman R, Spenrath N, Krone W, Mantzoros CS. Effects of Lipid-Lowering Drugs on Irisin in Human Subjects in Vivo and in Human Skeletal Muscle Cells ex Vivo. *PLoS One.* **2013** Sep 2;8(9):e72858.
- ✚ **Huh JY**, Panagiotou G, Mougios V, Brinkoetter M, Vamvini MT, Schneider BE, Mantzoros CS. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. *Metabolism.* **2012** Dec;61(12):1725-38. 현재 Metabolism – Clinical and Experimental 저널에서 가장 많이 읽은 (most read) 논문 top 5에 속해있으며 이후 발표된 irisin 관련 189편의 논문 중 116편의 논문 (editorial 또는 review paper 포함) 에서 인용됨.
- ✚ Moon HS, **Huh JY**, Dincer F, Schneider BE, Hasselgren PO, Mantzoros CS. Identification, and saturable nature, of signaling pathways induced by metreleptin in humans: comparative evaluation of in vivo, ex vivo and in vitro administration. *Diabetes.* **2014** Sep 23. pii: DB\_140625. [Epub ahead of print]
- ✚ Choi HY, Kim S, Park JW, Lee NS, Hwang SY, **Huh JY**, Hong HC, Yoo HJ, Baik SH, Youn BS, Mantzoros CS, Choi KM. Implication of Circulating Irisin Levels with Brown Adipose Tissue and Sarcopenia in Humans. *J Clin Endocrinol Metab.* **2014** Aug;99(8):2778-85.
- ✚ Peter P, Park KH, **Huh JY**, Wedick NM, Mantzoros CS. Circulating irisin levels are associated with the metabolic profile in humans but are not affected by coffee intake. *PLoS One.* **2014** Apr 11;9(4):e94463.
- ✚ Park KH, Zaichenko L, Tsoukas M, Joung KE, Sahin-Efe A, **Huh JY**, Geladari EV, Davis CR, Crowell JA, and Mantzoros CS. Circulating Irisin in Relation to Insulin Resistance and the Metabolic Syndrome. *J Clin Endocrinol Metab.* **2013** Dec;98(12):4899-907.
- ✚ Matarese G, La Rocca C, Moon HS, **Huh JY**, Brinkoetter MT, Chou S, Perna F, Greco D, Kilim HP, Gao C, Arampatzi K, Wang Z, Mantzoros CS. Selective capacity of metreleptin administration to reconstitute CD4+ T-cell number in females with acquired hypoleptinemia. *Proc Natl Acad Sci U S A.* **2013** Feb 26;110(9):E818-27.
- ✚ Vamvini MT, Aronis KN, Panagiotou G, **Huh JY**, Chamberland JP, Brinkoetter MT, Petrou M, Christophi CA, Kales SN, Christiani DC, Mantzoros CS. Irisin mRNA and circulating levels in relation to other myokines in healthy and morbidly obese humans. *Eur J Endocrinol.* **2013** Oct 21;169(6):829-34.
- ✚ **Huh JY**, Kim Y, Jeong J, Park J, Kim I, Huh KH, Kim YS, Woo HA, Rhee SG, Lee KJ, Ha H. Peroxiredoxin 3 is a key molecule regulating adipocyte oxidative stress, mitochondrial biogenesis, and adipokine expression. *Antioxid Redox Signal.* **2012** Feb 1;16(3):229-43.
- ✚ **Huh JY**, Son D, Lee Y, Lee J, Kim B, Lee HM, Jo H, Choi S, Ha H, Chung MH. 8-

hydroxy-2-deoxyguanosine prevents plaque formation in partially ligated ApoE knockout mouse. *Free Radic Biol Med.* **2012** Jul 1;53(1):109-21.

- ✚ Hwang I, Lee J, **Huh JY**, Park J, Lee HB, Ho YS, Ha H. Catalase deficiency accelerates diabetic renal injury through peroxisomal dysfunction. *Diabetes.* **2012** Mar;61(3):728-38.
- ✚ **Huh JY**, Seo EY, Lee HB, Ha H. Glucose-based peritoneal dialysis solution suppresses adiponectin synthesis through oxidative stress in an experimental model of peritoneal dialysis. *Perit Dial Int.* **2012** Jan;32(1):20-8.
- ✚ Park J, Kwon MK, **Huh JY**, Choi WJ, Jeong LS, Nagai R, Kim WY, Kim J, Lee GT, Lee HB, Ha H. Renoprotective antioxidant effect of alagebrium in experimental diabetes. *Nephrol Dial Transplant.* **2011** Nov;26(11):3474-84.

### Submitted Manuscripts

- ✚ Liu X, **Huh JY**, Gong H, Chamberland J, Brinkoetter M, Hamnvik OP, Mantzoros CS. Lack of mature lymphocytes results in obese but metabolically healthy mice when fed a high fat diet.
- ✚ Ha H, Jung I, **Huh JY**, Miyata T, Nam D. A synthetic PAI-1 inhibitor alleviates obesity and insulin resistance in mice fed a high-fat diet.

### Research Interests

- ✚ **최근 연구 요약:** 하버드 의대 Mantzoros 연구실에서 중개 연구 (translational research)를 통해 irisin이라는 새로운 myokine의 대사질환 및 운동과의 상관관계를 규명. 사람 조직으로부터 배양된 지방 세포와 근육 세포를 이용, irisin 세포 단위에서 지방과 근육의 대사 조절에 관여함을 규명.
- ✚ **향후 연구 계획**
  - 운동 또는 대사에 의하여 변화하는 genomics & epigenetics를 통하여 molecular marker 탐색 및 효능 검색
  - 당뇨 또는 비만 환자 군에서의 운동시 myokine/adipokine 변화 및 그 기전
  - Myokine/adipokine에 의한 근육/지방 세포의 미토콘드리아 대사 조절 및 그 기전
  - Brown fat과 대사 질환의 연관성 및 insulin-sensitive tissue와의 crosstalk
  - Irisin receptor와 co-regulator의 발견