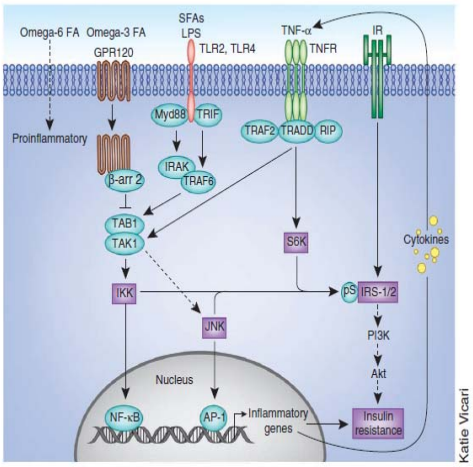
Doctoral College
Metabolic & Cardiovascular Disease

Insulin Resistance & Type 2 Diabetes

GUEST LECTURE by



Inflammatory signaling pathways involved in the development of insulin resistance

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Tuesday, 17.04.2012
17:00h

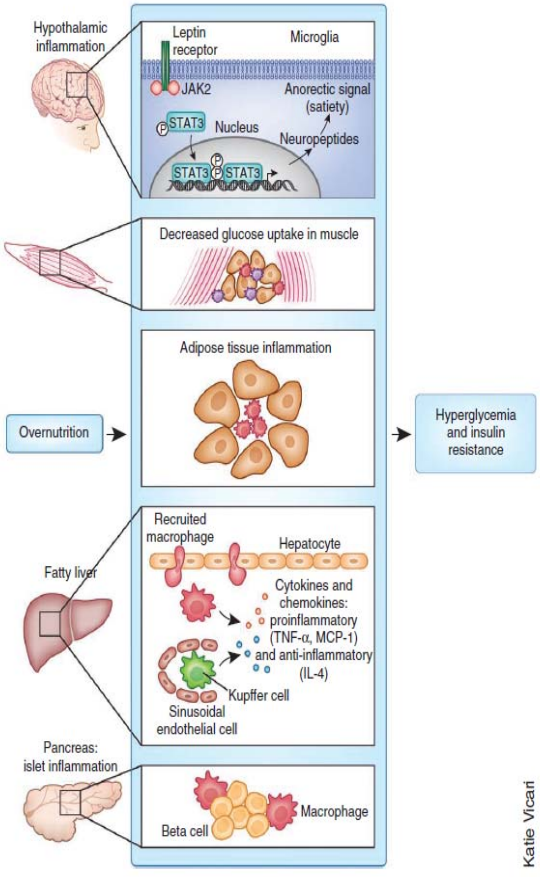
SR 07.12, Preclinics
Harrachgasse 21, 1st floor

Abstract

Obesity-associated chronic tissue inflammation is a key contributing factor to insulin resistance and type 2 diabetes. In the obese state, macrophages accumulate in insulin target tissues and secrete proinflammatory mediators that drive the development of insulin resistance.

GPR21 is an orphan G protein coupled receptor that is highly expressed in macrophages as well as the brain. In adipose tissue, obesity-induced GPR21 expression occurs primarily in the stromal vascular cells. In mice fed a high fat diet, whole body knockout of GPR21 resulted in improved insulin sensitivity and glucose tolerance as well as increased energy expenditure. Macrophage deletion of GPR21 mediates potent insulin sensitizing effects in vivo by repressing chemotaxis as well as reducing adipose tissue and liver tissue inflammation. Hypothalamic knockdown of GPR21 expression results in decreased body weight.

In summary, reduced expression of GPR21 in the hypothalamus or macrophage both contribute to improved insulin sensitivity and suggest that GPR21 is an important target for the development of new therapeutic approaches for the treatment of obesity-induced insulin resistance and type 2 diabetes.



Schematic of integrative physiology. Nutrient overload activates inflammatory responses, contributing to systemic insulin resistance and glucose intolerance.

pictures taken from: Nature Medicine 18(3):363-74

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Education

2011 - present Project Scientist, level III: University of California, San Diego (La Jolla, CA, USA)
Supervisor: Professor Jerrold Olefsky

2009 - 2011 Post Doc: University of California, San Diego (La Jolla, CA, USA)
Supervisor: Professor Jerrold Olefsky

2007 - 2009 Post Doc: The Scripps Research Institute (La Jolla, CA, USA)
Supervisor: Professor Tamas Bartfai
Skaggs Chemical Biology Fellowship (2009, Jan-Sept)
Helen Dorris Research Fellowship (2007-2009)

2003 - 2006 DPhil. Neuroscience & Genetics. (University of Oxford). Completed Dec 2006
Supervisor: Professor Kay E Davies
Sponsorship award from the Medical Research Council

2001 - 2002 Msc Bioinformatics (Manchester University). Completed Oct 2002
Sponsorship award from the Medical Research Council

1997 - 2001 2:1 Bsc (Hons) Genetics with Industrial Experience (Manchester University). Completed Jun 2001.

Degree Projects

DPhil project Identification of the transcriptional targets of Af4

MSc project Prediction of the Dimerisation Properties of the Nuclear Hormone receptors at Pfizer, Sandwich, UK. (Jun-Oct 2002)

BSc projects Identification of a locus for autosomal dominant "pure" hereditary spastic paraplegia maps to chromosome 19q13
Human Genome Mapping Project Resource Centre, Cambridge. (Aug 1999-Sept 2000)

Final Year project Characterising the 8q22 translocation breakpoint in patients with Cleidocranial Dysplasia Dept. of Medical Genetics, St Mary's Hospital. (Nov 2000-Apr 2001)

Work Experience

2009 - present Post doc: University of California, San Diego.

2007 - 2009 The Scripps Research Institute

Roche: Customer Response Group (Feb-Oct 2003). Providing technical support to customers.

Schering: Product Safety Assistant (Jan 2003). Involved setting up a database of drug safety reports.

Grants

Diabetes and Endocrinology Research Center Pilot and Feasibility Award: July 2011-Jun 2012: Deletion of G protein coupled receptor 21 (GPR21) improves insulin sensitivity, PI 100%, $35,000

Pfizer SFP: 2009-2010: IL-1Ra antibody study in T2D, insulin sensitivity and adiposity, Co-investigator, $300,000

Skills

In vivo mouse studies: hyperinsulinemic-euglycemic clamp studies, glucose tolerance tests, insulin tolerance tests, metabolic chamber analysis including CO2, O2, RER, temperature, locomotor activity, telemetry surgical implant of transmitter and analysis.

Molecular Biology: PCR, sequencing, cloning, Real Time PCR, site directed mutagenesis, southern and western blotting, *in vitro* transcription, *in-situ* hybridization, denaturing high performance liquid chromatography (DHPLC), ribonuclease protection assays, immunohistochemisty, immunocytochemistry, tissue culture of mammalian cell lines, chromatin immunoprecipitation, ELISA.

Microarrays: Expression and ChIP chip.

Computational skills: Highly competent in Microsoft Excel, Word & Powerpoint.
Basic programming skills in Java and Perl.
Bioinformatics tools: excellent knowledge of an extensive range of bioinformatics tools including Clustal, BLAST, Bioedit, Ingenuity.

Publications

Osborn, O, Oh DY, McNelis J, Sanchez-Alavez M, Talukdar S, Lu M, Li P, Thiede L, Morinaga H, Heinrichsdorff J, Nalbandian S, Scadeng S, Hadcock J, Bartfai T and Olefsky JM. Deletion of G protein coupled receptor 21 (GPR21) improves insulin sensitivity in diet induced obese mice. (revised and re-sent to J Clin Invest).

Osborn, O and Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nature Medicine, 2012, Mar 6;18(3):363-74.

Schenk S, McCurdy CE, Philp A, Chen MZ, Holliday MJ, Bandyopadhyay GK, Osborn O, Baar K, Olefsky JM. Sirt1 enhances skeletal muscle insulin sensitivity in mice during caloric restriction. J Clin Invest. 2011 Nov 1;121(11):4281-8.

Talukdar S, Olefsky JM, Osborn O. Targeting GPR120 and other fatty acid-sensing GPCRs ameliorates insulin resistance and inflammatory diseases. Trends Pharmacol Sci. 2011, Sep;32(9):543-50.

Sanchez-Alavez M*, Osborn O*, Tabarean IV, Holmberg KH, Eberwine J, Kahn CR, and Bartfai T. Igf-1 mediated hyperthermia involves anterior hypothalamic insulin receptors. JBC, 2011 Apr 29;286(17):14983-90 (*these authors contributed equally).

Osborn O, Sanchez-Alavez M, Dubins JS, Gonzalez AS, Morrison B, Hadcock JR, Bartfai T Ccl22/MDC, is a prostaglandin dependent pyrogen, acting in the anterior hypothalamus to induce hyperthermia via activation of brown adipose tissue. Cytokine. 2010 Dec 20.

Osborn O, Sears DD, Olefsky JM. Fat-induced inflammation unchecked. Cell Metab. 2010 Dec 1;12(6):553-4.

Sanchez-Alavez M*, Tabarean IV*, Osborn O*, Mitsukawa K, Schaefer J, Dubins J, Holmberg KH, Klein I, Klaus J, Gomez LF, Kolb H, Secrest J, Jochems J, Myashiro K, Buckley P, Hadcock JR, Eberwine J, Conti B, Bartfai T. Insulin causes hyperthermia by direct inhibition of warm-sensitive neurons. Diabetes. 2010 Jan;59(1):43-50. (*these authors contributed equally)

Osborn O, Sanchez-Alavez M, Brownell SE, Ross B, Klaus J, Dubins J, Beutler B, Conti B, Bartfai T Metabolic characterization of a mouse deficient in all known leptin receptor isoforms. Cell Mol Neurobiol. 2010 Jan;30(1):23-33.

Osborn O, Gram H, Zorrilla EP, Conti B, Bartfai T. Insights into the roles of the inflammatory mediators IL-1, IL-18 and PGE2 in obesity and insulin resistance. Swiss Med Wkly. 2008 Nov 15;138(45-46):665-73.

Osborn O, Brownell SE, Sanchez-Alavez M, Salomon D, Gram H, Bartfai T. Treatment with an Interleukin 1 beta antibody improves glycemic control in diet□induced obesity. Cytokine. 2008 Oct;44(1):141-8.

Reid E, Dearlove AM, Osborn O, Rogers MT, Rubinsztein DC. A locus for autosomal dominant “pure” hereditary spastic paraplegia maps to chromosome 19q13. Am J Hum Genet. 2000 Feb; 66(2): 728-32.

Book Chapters:

Schenk S, Osborn O, Olefsky, JM. Nutritional Genomics: The Impact of Dietary Regulation of Gene Function on Human Disease. Chapter 11 “Mechanisms Mediating Obesity-induced Inflammation and Insulin Resistance” (Taylor and Francis Group, 2012)

Invited lectures:

Amgen, San Francisco, USA. Title: “Metabolic Characterization of the GPR21 knockout mice” May 2011.

University of Graz, Austria: “The role of inflammation in Type 2 Diabetes”. April 2012.

Professional Presentations:

Osborn, O, Oh DY, McNelis J, Sanchez□Alavez M, Talukdar S, Lu M, Li P, Thiede L, Morinaga H, Heinrichsdorff J, Nalbandian S, Scadeng S, Hadcock J, Bartfai T and Olefsky JM. Deletion of G protein coupled receptor 21 (GPR21) improves insulin sensitivity in diet induced obese mice. Keystone Symposia, Santa Fe, New Mexico. Pathogenesis of Diabetes: Emerging Insights into Molecular Mechanisms (J8), 2012.

Osborn O; Oh D; Thiede L; Lu M; Talukdar S; Brenner M; Hadcock J; Bartfai T; Olefsky JM. Deletion of G protein coupled receptor 21 (GPR21) improves insulin sensitivity in diet induced obese mice. Keystone Symposia, Keystone, Colorado. Type 2 Diabetes, Insulin Resistance and Metabolic Dysfunction (J1), 2011

Osborn O; Oh D; Thiede L; Lu M; Talukdar S; Brenner M; Hadcock J; Bartfai T; Olefsky JM. Deletion of G protein coupled receptor 21 (GPR21) improves insulin sensitivity in diet induced obese mice. UCSD/UCLA/Salk/Cedars Sinai Diabetes Center Retreat, 2011

Osborn O , Tabarean I, Klein I , Hadcock J, Sanchez-Alavez M , Klaus J , Ross B, Schaffer L , Conti B , W. Loging , Gregorsson Lundius E, Jochems J , Miyashiro K , Eberwine J, Bartfai T . Identification of warm sensitive neurons in the anterior hypothalamus. Neuroscience, Washington, 2008.

Klein I, Osborn O , Tabarean I , Hadcock J, Sanchez-Alavez M , Ross B, Klaus J , Schaffer L , Conti B , W. Loging , Gregorsson Lundius E , Jochems J , Miyashiro K , Eberwine J , Bartfai T. Characterization of single warm sensitive hypothalamic neurons. Neuroscience, Washington, 2008.

Bartfai T, Sanchez-Alavez M, Tabarean I , Klein I , Osborn O , Conti B, Hadcock J, Jochems J, Miyashiro K , Eberwine J. Effects of CBT in energy homeostasis, involvement of bombesin and prolactin into the POA. Neuroscience, Washington, 2008.

Osborn O, Brownell SE, Sanchez-Alavez M, Salomon D, Gram H, Bartfai T. Treatment with an Interleukin 1 beta antibody improves glycemic control in diet-induced obesity. Keystone Islet & Beta Cell Biol, keystone, Utah, 2008

Osborn O, Sanchez-Alavez M, Brownell S, Ross B, Conti B, Bartfai T. Metabolic characterization of a mouse deficient in all known leptin receptor isoforms. Neuroscience 2007, San Diego.

Osborn O, Oliver P, Bitoun E, Davies KE. Identification of the transcriptional targets of Af4. Abcam Chromatin Structure and Function 2006, Punta Cana, Dominican Republic.

References

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