ATLAS and Functional Genomics & Metabolism

Distinguished Seminar

Thursday, May 9 from 14.15-15.15
in BMB Seminar room

Principles for Personalizing PPARγ Prescriptions

Mitchell A. Lazar, M.D., PhD

Willard and Rhoda Ware Professor in Diabetes and Metabolic Diseases

Institute for Diabetes, Obesity, and Metabolism, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104 USA

Abstract

Obesity and diabetes are metabolic diseases whose prevalence is rising due to failure of homeostatic mechanisms to counter environmental challenges. Environmental factors such as diet, circadian inputs, and pharmacological agents regulate the output of the genome via transcription factors (TFs). Cell-type specific functions of TFs are largely determined by three factors 1) cell-specific expression of the TF; 2) epigenomic factors that make specific regions of genomic DNA accessible to the TF; and 3) DNA-sequence specificity of the TF. Sequence-specificity is the most proximal regulator of TF interaction with the genome and, while the genome is the same in virtually all cells of a given individual, natural genetic variation in the population is the major determinant of personal traits that distinguish individuals from one another.

Nuclear receptors are a class of TFs whose activities are directly influenced by binding to hormones, metabolites, and drugs that alter their transcriptional activity. The nuclear receptor PPARɣ is expressed most highly in fat cells and is required for adipocyte differentiation as well as differentiated fat cell functions. In humans as well as mice there is strong genetic evidence that PPARɣ activity influences insulin sensitivity. Moreover, thiazolidinedione drugs such as rosiglitazone are potent PPARɣ activators that increase insulin sensitivity in obese mice and humans. However, while their ability to reverse insulin resistance is unique, side effects limit their clinical use. We have explored the role of natural genetic variation in the activity of these

drugs. We find that single-nucleotide polymorphisms (SNPs) control PPARγ binding in adipocytes from different individuals, often by changing the DNA-sequence directly bound by PPARγ or one of its cooperating TFs such as C/EBP□ and NF1. This correlates with individual-specific effects of rosiglitazone on adipocyte gene expression. One highly informative SNP causally determines a site of PPARγ binding that is the gatekeeper for rosiglitazone-dependent gene expression and cholesterol metabolism in human adipocytes. This common SNP is also a major determinant of undesired serum cholesterol increases in rosiglitazone-treated diabetics. These findings highlight human genetic variation as an underlying cause of individual differences in PPAR□ function and patient responses to antidiabetic drugs, with broader implications for the development of personalized therapies for metabolic disorders.

Host: Prof. Susanne Mandrup, Functional Genomics & Metabolism Research Unit, Dept. Biochemistry and Molecular Biology, SDU