Institutionen för molekylär medicin och kirurgi

Epigenetic Influences on Type 2 diabetes and Obesity

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Hillarp Salen, Retzius väg 8

Onsdagen den 25 januari 2012, kl 09.00

av

Jie Yan

Huvudhandledare:
Professor Juleen Zierath
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Bihandledare:
Professor Anna Krook
Karolinska Institutet
Institutionen för fysiologi och farmakologi

Fakultetsopponent:
Associate Prof. Rebecca A. Simmons
Perelman School of Medicine at University of Pennsylvania, Philadelphia, USA
Department of Pediatrics

Betygsnämnd:
Prof. Rachel Fisher
Karolinska Institutet, Stockholm, Sweden
Department of Medicine, Solna

Prof. Peter Stenvinkel
Karolinska Institutet, Stockholm, Sweden
Department of Clinical Science, Intervention and Technology

Associate Prof. Charlotte Ling
Faculty of Medicine at Lund University, Malmö, Sweden
Department of Clinical Sciences, Malmö

Stockholm 2012
ABSTRACT

Type 2 diabetes and obesity are multifactorial diseases involving interactions between genetic and environmental factors. A common feature shared between these two diseases is skeletal muscle insulin resistance. Insulin resistance refers to a state when the normal biological effect is not achieved by a normal amount of insulin. Complicated genetics alone is unlikely to explain the diversity of phenotypes in the general population. Epigenetics provides a mechanism which may explain the etiology of Type 2 diabetes and obesity, as well as other human diseases.

DNA methylation is an epigenetic modification that plays a key role in various biological processes including imprinting, mammalian development and maintaining genomic stability. DNA methylation is believed to be modulated by environmental and nutritional factors, essentially functioning as a molecular switch to turn genes on or off. The research on the role of DNA methylation in metabolic diseases is still in its infancy. This thesis aims at elucidating the role of DNA methylation in regulating expression of genes involved in controlling mitochondrial function and insulin sensitivity. Emphasis has been placed on the role of methylation in a non-CpG context.

Using an adapted Luminometric-based Assay, we detected 7-13% non-CpG methylation in mouse tissues at the genomic level, and similar levels were for specific promoter sequences through different bisulfite sequencing strategies. Mitochondrial dysfunction is associated with skeletal muscle insulin resistance in Type 2 diabetes and obesity. In Paper II, we show that mitochondria number is reduced and mitochondria morphology is altered, in skeletal muscle from Type 2 diabetic patients. The promoter region of PGC1α, a gene involved in mitochondrial biogenesis, was differentially methylated in Type 2 diabetic patients using whole genome promoter methylation analysis. Methylation level of PGC1α was negatively correlated with mRNA expression. Non-CpG methylation of PGC1α promoter was induced in human myotubes by culturing cells in the presence of tumor necrosis factor α or free fatty acids. These changes in methylation could be prevented by silencing DNA methyltransferase 3B.

Many morbidly obese individuals undergo gastric bypass surgery as a means to reduce daily calorie consumption and lose weight, since conventional strategies for obesity treatment are often insufficient. Insulin sensitivity can be dramatically improved after the surgery. In Paper III, we report that concomitant with the weight loss, the expression of genes involved in mitochondrial function and insulin sensitivity in obese subjects was normalized to levels of normal weight controls. Furthermore methylation levels of PGC1α and PDK4 promoter regions are altered in obese subjects, and methylation of these regions is dynamically changed with weight loss.

In conclusion, we identify the existence of non-CpG methylation in mammals and report a functional role in regulating genes associated with skeletal muscle insulin resistance, which is of relevance to the pathogenesis of Type 2 diabetes and obesity. We also provide evidence that DNA methylation is dynamically remodeled, concomitant with alterations in insulin sensitivity. Environmental factors are potential triggers for changes in DNA methylation.