Dietary lipids and gene expression

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Abstract
Nutrition is a key environmental factor that is particularly involved in the pathogenesis and progression of several polygenic, diet-related diseases. Nutrigenomics refers to the interaction between nutrition and the human genome. Dietary fatty acids interact with multiple nutrient-sensitive transcription factors. This explains the molecular basis of some of the health effects associated with altered dietary fatty acid composition. The metabolic syndrome is a very common condition, characterized by insulin resistance, abdominal obesity, dyslipidaemia and hypertension. It often precedes Type 2 diabetes mellitus, and is associated with a greater risk of cardiovascular disease. Several lines of evidence suggest that the interaction between nutrient-derived metabolic stressors and pro-inflammatory signals play an important role in the aetiology of insulin resistance and the development of the metabolic syndrome. This paper will address the interaction between several nutrient-sensitive transcription factors, including SREBP (sterol-regulatory-element-binding protein) and NFκB (nuclear factor κB), demonstrating how this interaction may be altered with dietary fatty acid interventions.

Introduction
Nutritional genomics (nutrigenomics) or molecular nutrition refers to research that investigates the interaction between nutrition and the human genome. It is well recognized that good nutrition promotes health and quality of life. However, the cellular and molecular effects of nutrients on cellular homeostasis are not fully understood. In light of the Human Genome Project and the rapid advances in molecular biology, a wealth of genetic information is being generated, particularly with respect to polygenic, diet-related diseases. Also, it is becoming increasingly obvious that an individual's health or disease status is not only a function of an individual's genetic background. An individual's phenotype represents a complex interaction between the human genome and environmental factors. Nutrition is a key environmental factor that is particularly involved in the pathogenesis and progression of the classical diet-related diseases. Thus the application of novel, high-throughput molecular technologies provides the opportunity to progress our understanding of the role of diet and nutrition in health and disease. Given the rising incidence of diet-related diseases, including obesity, the metabolic syndrome, T2DM (Type 2 diabetes mellitus) and CVD (cardiovascular disease), there is a great sense of urgency to use nutritional genomics approaches to understand the biology of these diseases. A nutritional systems biology approach may enhance our ability to develop effective nutrient-based preventative and therapeutic strategies to combat common polygenic, diet-related diseases.

Nutrigenomics: core concepts
There is a dynamic, two-way interaction between nutrition and the human genome. As illustrated in Figure 1, this interaction determines gene expression and the metabolic response, which ultimately affects an individual's health status and/or predisposition to disease. Firstly, an individual's genetic background can determine nutrient status, metabolic response and predisposition to diet-related diseases [1]. Secondly, nutrients can have a direct effect and interact with transcription factors to regulate gene expression. A number of transcription factors that are sensitive to nutrient and non-nutrient food components have been identified, some of which are detailed in Table 1 [2]. Furthermore, it is becoming increasingly obvious that an individual's genetic background can also determine responsiveness to nutritional therapy and/or diet-related disease progression [3].

It is important to realize that nutrients, in contrast with specific pharmacological ligands, can have a number of direct and indirect effects on gene expression, as illustrated in Figure 2. For example, dietary fatty acids can interact with a number of transcription factors and have direct effects on gene expression, whereby they interact with a number of transcription factors and up- or down-regulate the expression of particular genes [4,5]. In addition, metabolic fatty acid derivatives may mediate the effect of a dietary lipid intervention to alter gene expression. For example, eicosanoids, prostaglandins and leukotrienes are fatty acid derivatives of the cyclo-oxygenase and lipoxygenase metabolic pathways, which mediate the effect of the primary fatty acid intervention on gene expression. Furthermore, fatty acid derivatives may also alter cell signalling cascades which then alter gene transcription. For example, altering the induction of the lipid-derived second messenger diacylglycerol will affect activation of protein kinase C isoforms that mediate many cellular functions, including cell growth, activation, and
Interaction between nutrition and the human genome

Figure 1

Table 1

Lipid-sensitive transcription factors
Adapted from [2]. PPAR, peroxisome-proliferator-activated receptor; LXR, liver X receptor; HNF4, hepatocyte nuclear factor 4; ChREBP, carbohydrate-response-element-binding protein; FXR, farnesoid X receptor; USF, upstream stimulatory factor; C/EBP, CCAAT/enhancer-binding protein; RAR, retinoic acid receptor; RXR, retinoid X receptor; VDR, vitamin D receptor; PXR, pregnane X receptor; NF-AT, nuclear factor of activated T-cells; IRP, iron-regulatory protein; MTF1, metal-responsive transcription factor 1; ER, oestrogen receptor; NF-κB, nuclear factor κB; AP1, activator protein 1; CAR, constitutive androstane receptor.

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Compound</th>
<th>Transcription factor</th>
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</thead>
<tbody>
<tr>
<td>Fat</td>
<td>Fatty acid</td>
<td>PPARs, SREBPs, LXR, HNF4, ChREBP</td>
</tr>
<tr>
<td></td>
<td>Cholesterol</td>
<td>SREBPs, LXR, FXR</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Glucose</td>
<td>USFs, SREBPs, ChREBP</td>
</tr>
<tr>
<td>Protein</td>
<td>Amino acids</td>
<td>C/EBP</td>
</tr>
<tr>
<td>Vitamin</td>
<td>Vitamin A</td>
<td>RAR, RXR</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
<td>VDR</td>
</tr>
<tr>
<td></td>
<td>Vitamin E</td>
<td>PXR</td>
</tr>
<tr>
<td>Mineral</td>
<td>Calcium</td>
<td>Calcineurin/NF-ATs</td>
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<tr>
<td></td>
<td>Iron</td>
<td>IRP1, IRP2</td>
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<tr>
<td></td>
<td>Zinc</td>
<td>MTF1</td>
</tr>
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<td>Non-nutrients</td>
<td>Flavonoids</td>
<td>ER, NF-κB, AP1</td>
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<tr>
<td></td>
<td>Xenobiotics</td>
<td>CAR, PXR</td>
</tr>
</tbody>
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The direct and indirect effects of nutrients on gene expression

Figure 2

The development and progression of the metabolic syndrome

Figure 3

Dietary fatty acids, inflammation and the metabolic syndrome

The metabolic syndrome is a very common condition, characterized by insulin resistance, abdominal obesity, dyslipidaemia and hypertension, which is associated with a high risk of T2DM and CVD [7,8]. This paper will explore the hypothesis that interaction between nutrient-derived metabolic stressors, in particular fatty acids, and pro-inflammatory stressors within the context of obesity leads to the development of the metabolic syndrome. Figure 3 illustrates the concept that the interaction between metabolic stressors and inflammation, in the presence of obesity, leads to insulin resistance. Several lines of evidence suggest that both metabolic stressors [high-fat diet, elevated plasma NEFA (non-esterified fatty acid) levels, etc.] and pro-inflammatory signals induce insulin resistance by inhibiting insulin signalling. The potential pathway between insulin resistance, the metabolic syndrome and T2DM represents a progressive phenotype, which reflects multiple organ dysfunction. Obesity is the key aetiological factor that predisposes to insulin resistance and the development of the metabolic syndrome and T2DM [9]. There are at least two ways in which adipose tissue may influence glucose homeostasis. Firstly, excessive adipose tissue energy storage results in increased fatty acid flux to other tissues and increased TAG (triacylglycerol) storage in peripheral tissues, which promotes insulin resistance. Secondly, adipose tissue is an important endocrine organ that secretes several inflammatory factors, collectively known as adipocytokines or adipokines, which have a direct effect on insulin sensitivity. These adipocytokines include TNF-α (tumour necrosis factor-α), leptin, plasminogen activator protein, IL-6 (interleukin), resistin, angiotensin and adiponectin, also known as Acrp-30 [10]. The insulin-desensitizing effects of TNF-α and its related signalling pathways are probably the best characterized.
TNF-α inhibits autophosphorylation of tyrosine residues of the IR (insulin receptor) and promotes serine phosphorylation of IRS-1 (IR substrate 1), which in turn causes serine phosphorylation of IR in adipocytes and inhibits tyrosine kinase phosphorylation [11]. Interestingly, elevated NEFA levels have been associated with insulin resistance. Also there is evidence to suggest that fatty acids induce insulin resistance through inhibition of IRS-1 signalling [12–14].

A number of *in vivo* animal models have shown the importance of the interaction between dietary fatty acid and a pro-inflammatory state on whole body insulin resistance. In genetic and dietary models of obesity, knocking out the TNF-α and TNF-α receptor genes improved insulin resistance [15–17]. Another group have shown that IKK-β (IkB kinase-β) plays a central role in the interplay between dietary fatty acids and insulin resistance. It was demonstrated that salicylate treatment, a known inhibitor of IKK-β, prevented fat-induced muscle insulin resistance [18]. Also, lipid infusion failed to decrease insulin-stimulated glucose uptake and inhibit activation of IRS-1 in skeletal muscle of IKK-β-knockout mice [18]. More recently, it has been demonstrated that c-Jun N-terminal kinases (JNKs) play a central role in obesity and insulin resistance. Mice with a targeted mutation in *Jnk1* put on less weight and have significantly improved insulin sensitivity and enhanced IR-signalling capacity in both dietary and genetic models of mouse obesity [19]. The improvement in insulin sensitivity was ascribed to enhanced signalling capacity through the insulin receptor, at least in part, through its effects on IRS-1 phosphorylation. These studies suggest that the lack of several components of the inflammatory response results in substantial protection from obesity-induced insulin resistance. Therefore it may be possible to reduce the impact of the nutrient derived metabolic stressors, using nutrient based anti-inflammatory strategies, to improve insulin sensitivity and impede the progression towards the metabolic syndrome and T2DM. Only with a greater understanding of genetic susceptibility and the molecular mechanisms that underlie this progressive disease can evidence-based nutritional therapies be developed to attenuate the impact of obesity-induced insulin resistance.

Several studies have suggested that adipose tissue is the source of the pro-inflammatory molecules that mediate obesity-induced insulin resistance. Nevertheless, adipocytes produce relatively lower cytokine levels compared with the classical inflammatory cells. A recent paper proposed that macrophages are the principal source of adipose tissue pro-inflammatory cytokines, and that obesity-related insulin resistance is, at least in part, a chronic inflammatory disease initiated in adipose tissue [20]. Also, it has been shown that obesity is associated with progressive infiltration of monocytes and macrophages into adipose tissue, and adipose tissue macrophages are the source of inflammatory pathways that are activated in adipose tissue of obese individuals [21]. Expression analysis of macrophage and non-macrophage cell populations isolated from adipose tissue demonstrates that adipose tissue macrophages are responsible for almost all adipose tissue TNF-α expression, and significant amounts of iNOS (inducible nitric oxide synthase) and IL-6 expression. It has been proposed that the obesity-induced inflammatory changes in adipose tissue are initiated by adipocytes that secrete low levels of TNF-α, which in turn stimulate pre-adipocyte and endothelial cell MCP-1 (macrophage chemotactic protein-1), adipocytokine expression and NEFA release, to promote further a pro-inflammatory and pro-oxidative state [22], the ultimate outcome of which is impaired adipocyte function and insulin resistance.

It is important to note that, although the effect of TNF-α in relation to insulin resistance has been studied in detail, the presence and/or absence of other adipocytokines is also important. For example, resistin markedly decreases insulin-mediated glucose uptake [23]. More recently, it has been shown that IL-6 inhibits insulin transduction in hepatocytes and the insulin-desensitizing effect of IL-6 is mediated by suppressor of cytokine signalling-3 (SOCS-3), which associates itself with the IR and IRS-1, impeding insulin signalling [24,25]. In contrast, plasma adiponectin levels are inversely associated with several risk factors for the metabolic syndrome, including adiposity (waist/hip ratio), insulin resistance, diastolic blood pressure, TAG concentrations and TNF-α receptor concentrations [26]. A greater understanding of the interaction between pro-/anti-inflammatory adipocytokines and metabolic stressors in obesity-induced insulin resistance will promote the identification of novel therapeutic strategies to reduce the impact of insulin resistance.

**Nutrient regulation of gene expression: fatty acids, inflammation and adipose tissue**

Serum adipocytokine levels are elevated in obesity, and interventions that reduce fat mass also lower adipocytokine levels [9]. Therefore, in terms of manipulating dietary factors to attenuate the inflammatory response in adipose tissue to improve insulin sensitivity, the most obvious treatment is to reduce adipose tissue mass. Nevertheless, the prevalence of obesity is increasing, and due to poor compliance current therapies are largely ineffective. Therefore other strategies to attenuate the impact of insulin resistance in the presence of obesity are required. Our group have demonstrated that a subgroup of fatty acids, known as CLAs (conjugated linoleic acids), and in particular the *cis*-9,trans-11 CLA isomer (c9,t11-CLA), may have the potential to improve lipid metabolism and insulin sensitivity within the context of obesity [27,28]. This effect was ascribed to differential SREBP-1c (sterol-regulatory-element-binding protein 1c) gene expression, a key regulatory transcription factor involved in lipogenesis and glucose metabolism [29–31]. Feeding a c9,t11-CLA-rich diet had divergent tissue-specific effects on SREBP-1c expression, significantly reducing hepatic SREBP-1c and increasing adipose tissue SREBP-1c expression, both of which could contribute to improved lipid and glucose metabolism [27]. Interestingly, this study also showed that TNF-α regulated SREBP-1c expression in human adipocytes, but not in hepatocytes, thereby
supporting the hypothesis that there is cross-talk between molecular markers of insulin sensitivity and adipocytokines, which in turn can be modified by fatty acids. Further work showed that the insulin-sensitizing effect of the c9, t11-CLA-rich diet was associated with a marked reduction in adipose tissue TNF-α expression, which could be related to lower NF-κB (nuclear factor-κB) DNA binding, which has been attributed to lower nuclear p65 levels and increased cytosolic IκBα (inhibitor of κBα) expression [28]. Further work investigating the cell-specific nature of adipocytokine and adipose tissue SREBP-1c expression is required. This study suggests that the fatty acid composition of the diet can be adjusted to attenuate the pro-inflammatory insulin-desensitizing effect of obesity-induced insulin resistance.

References

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