Type 2 diabetes mellitus (T2DM) is usually caused by insulin resistance, and often combined with progressive defect in insulin secretion. However, the etiology of T2DM remained unknown. Among various factors which lead to the onset of T2DM, host genetics and environmental factors are the focus of discussion. Identification and characterization of specific genes that can result in metabolic abnormalities are helpful for the effective prevention and therapeutic intervention of diabetes mellitus. Accumulating evidences have proved that T2DM is closely correlated with chronic inflammation, with increased levels of circulatory acute response proteins and cytokines in affected subjects. The aim of this article is to provide a general overview on the epidemiology, classification, and roles of cytokines in metabolism and T2DM. In addition to focusing on the cytokines-related literatures of diabetic studies, a summary of our study results concerning the polymorphisms of cytokine genes among diabetic patients is also included. Accomplishments of the immune-related genetic studies in a particular ethnic population can lead not only to the understanding of the interactions between immune responses and T2DM, but also potential clues for the designing of personalized type 2 diabetic treatment in the future.

Key words: cytokines; metabolism; interleukins; diabetes

Epidemiology and Classification of Diabetes Mellitus

Diabetes mellitus (DM) is a syndrome of abnormal metabolism with inappropriate hyperglycemia due either to an absolute deficiency of insulin secretion or a reduction in the biologic effectiveness of insulin, or both. DM patients with long duration have the propensity to develop universal microangiopathy, neuropathy and atherosclerosis.

Traditionally, diabetes is classified according to the patients’ age at onset of symptoms (juvenile-onset versus adult-onset). In 1997, the National Diabetes Data Group of American Diabetes Association recommended that DM be classified into one of two major types according to the correlation of diabetic onset and immune response: T1DM (T1DM; formerly designated as insulin-dependent DM, IDDM) and T2DM (T2DM; formerly designated as non-insulin dependent DM, NIDDM). T1DM is a severe form of DM and is associated with ketosis in the untreated state. It is a catabolic disorder in which circulating insulin is virtually absent, plasma glucagon is elevated, and the pancreatic $\beta$ cells fail to respond to all known insulinogenic stimuli. T2DM is characterized by abnormally high blood glucose resulting from a relative deficiency of insulin [1]. Insulin secretion in T2DM patients is preserved, and such cases can be treated with dietary changes combined with oral antidiabetic drugs [2]. Therefore, patients are not necessarily dependent on exogenous insulin therapy to sustain life. Genetic factors are important in the aetiology of T2DM, and linkage studies have localized some of the genes that influence the development of this disorder [3, 4]. T2DM, in fact, comprises a heterogeneous group of the milder forms of diabetes, occurs predominantly in adults but may occa-

Mini Review

Cytokines, Metabolism, and Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (T2DM) is usually caused by insulin resistance, and often combined with progressive defect in insulin secretion. However, the etiology of T2DM remained unknown. Among various factors which lead to the onset of T2DM, host genetics and environmental factors are the focus of discussion. Identification and characterization of specific genes that can result in metabolic abnormalities are helpful for the effective prevention and therapeutic intervention of diabetes mellitus. Accumulating evidences have proved that T2DM is closely correlated with chronic inflammation, with increased levels of circulatory acute response proteins and cytokines in affected subjects. The aim of this article is to provide a general overview on the epidemiology, classification, and roles of cytokines in metabolism and T2DM. In addition to focusing on the cytokines-related literatures of diabetic studies, a summary of our study results concerning the polymorphisms of cytokine genes among diabetic patients is also included. Accomplishments of the immune-related genetic studies in a particular ethnic population can lead not only to the understanding of the interactions between immune responses and T2DM, but also potential clues for the designing of personalized type 2 diabetic treatment in the future.

Key words: cytokines; metabolism; interleukins; diabetes
sionally have its onset in childhood. Treatment of diabetest and its complications are an increasing health-care burden in our society [5].

Diabetic patients worldwide are estimated to be approximately 200 million, among which approximately 60–80% are obese [6]. The global prevalence of diabetes in year 2000 is about 2.8%, however, this prevalence is estimated to reach 4.4% in year 2030. Number of the diabetic patients is rapidly increasing globally. The population of global diabetic patients was 151 million in year 2000 and predicted to be 221 million in year 2010, with the increased rate of 46% within a single decade [5]. The prevalence of T2DM varies among different ethnic populations, with the highest rate found in Pima Indians (as high as ~50%) [7]. Accompanied with the more and more westernized food-uptake habits, the living standard of people in Taiwan has been continuously elevated. Unfortunately, the prevalence of chronic metabolic diseases such as cardiovascular diseases and diabetes are also increasing. In Taiwan, more than 98% of DM patients are characterized as T2DM [8], affecting more than 1 million individuals. Type 2 diabetic prevalence in Taiwanese population is much lower than that of Caucasians (4–16%) [9]. The discrepancy indicates that unique genetic characteristics and possibly distinct etiological/environmental factors may be involved in the pathogenesis of T2DM in Taiwan.

T2DM, Acute-phase Response and Immune Responses

The etiology of T2DM is still an enigma. Though insulin resistance seems to be a central abnormality, the origin of the impaired insulin action and how it explains the many other abnormalities of T2DM await to be investigated. Pickup et al. first discovered that blood concentrations of acute-phase response markers, such as C-reactive protein and cortisol, as well as the cytokine mediators, such as interleukin-6 (IL-6), in circulation of type 2 diabetic patients are increased [8]. Since then, accumulating evidences have shown that T2DM is an acute-phase disease in which increased concentrations of cytokines are secreted from many cells under the influence of various stimuli such as overnutrition, increasing age, genetic or fetal metabolic preprogramming[10,11]. Their study implicated that acute inflammatory phenomena will result in glucose intolerance and diabetes, and many of the clinical biochemical features and the complications of T2DM may be explained by the augmented acute-phase response. Cytokines, mainly IL-1, IL-6 and tumor necrosis factor-alpha (TNF-α), act on the liver to produce the characteristic dyslipidaemia of T2DM (increased very low density lipoprotein [VLDL] and decreased high density lipoprotein [HDL]) and may contribute to obesity, hypertension and insulin resistance. Treating animals and humans with cytokine can induce hypertriglyceridaemia and insulin resistance [12,13]. For example, TNF-α is a potent inhibitor of the tyrosine kinase activity of the insulin receptor and has been implicated in the insulin resistance of T2DM and obesity [14]. Repeatedly giving IL-1β, in vivo to normal rats would result in reduced glucose-stimulated first-phase insulin release from the isolated islets, without altering the islet insulin content or ultrastructure [15]. Moreover, many observations suggest that diabetes may be associated with enhanced cytokine production, raising the possibility that some of the metabolic abnormalities associated with diabetes may be due to or exacerbated by cytokine overproduction [16-19].

Polymorphisms of Cytokine Genes and T2DM in Taiwan

Accordingly, immune responses and inflammation are suggested to play certain roles in the development and complications of T2DM[10,11]. Among the elevated cytokines in T2DM subjects, IL-6 is one of the type 2 T helper cell (Th2) cytokines that contribute to the exquisite regulation of balance between Th1 and Th2 cells [reviewed in ref. 20]. In addition to IL-6, other cytokines that affect the Th1/Th2 balance include IL-4, IL-10, etc. Because proinflammatory cytokine production is increased in T2DM, it is intriguing to investigate if other Th2 cytokines are also involved in the pathogenesis of T2DM. Additionally, cytokine production ability is tightly controlled at the level of gene transcription [20], that is, the promoter activity. Therefore, it is tempting for us to identify whether the promoter polymorphisms that influence the transcription activity and the resulting cytokine secretion ability contribute to Taiwanese T2DM pathogenesis.

For verifying the above hypothesis that cytokines and immune response are involved in T2DM pathogenesis, genomic DNA was extracted from peripheral blood cells of T2DM patients and control subjects, with their information of body height, weight, body mass index (BMI), age, clinical biochemical parameters including fasting blood glucose level, renal function index (creatinine [CRE] and blood urea nitrogen [BUN]), and lipid profile filed and analyzed. Ten polymorphisms of 4
cytokine genes (IL-4: -34T>C, -81A>G, -285C>T and -589T>C [manuscript revised in submission]; IL-6: -174G>C [7]; IL-10: -592A>C and -819T>C [21]; and TNF-α: G-238A and G-308A [22]) and the α chain of IL-4 receptor (IL-4Rα E400A [manuscript in submission]) were subsequently investigated by polymerase chain reaction and restriction fragment length polymorphism. Several significant associations between these cytokine genes and T2DM and/or the clinical biochemical parameters were found using multiple linear regression analysis with adjustment for subjects’ age, sex and diabetic status (Table 1). First of all, polymorphisms in IL-4 (-34T>C and -589T>C) and IL-10 (-592A>C and -819T>C) were found to be associated with T2DM. Second, several polymorphisms, including IL-4 -589T>C, IL-4Rα E400A and TNF-α -238G>A were associated with circulatory HDL-C levels. Third, TNF-α -308G>A polymorphisms was associated with fasting glucose concentrations. Fourth, significant correlations between IL-4Rα E400A genotypes with blood pressure, as well as with BUN, were also observed in lean control subjects.

Our observations suggested that while TNF-α polymorphisms are not associated with the prevalence of Taiwanese T2DM, its secretion levels might be linked to insulin resistance and diabetic complications. On the contrary, IL-10 polymorphisms may play certain roles in determining susceptibility to diabetes, but do not seem to be important in the clinical manifestations of T2DM. Notably, significant associations between IL-4 polymorphisms and HDL-C levels, as well as between polymorphisms in IL-4Rα and HDL-C levels, are identified. The correlation between IL-4Rα and the HDL-C levels is observed both in non-obese control individuals and the obese T2DM patients, which further implies that IL-4 might be involved in HDL-C and lipid metabolism. It might be premature to make solid conclusion regarding the role of cytokines in lipid metabolism, nevertheless, in addition to the external environmental factors such as food intake and lifestyle, we hypothesize that genotypes of cytokine genes might be one of the internal factors which affect lipid metabolism.

**Possible role of IL-4 and IL-4α in Lipid Metabolism**

It is intriguing to explain the correlation between IL-4 and lipid metabolism. In hypercholesterolemia, the accumulated low density lipoproteins (LDL) in the artery wall would be oxidized to release oxidation products that lead to activation of inflammatory responses. In mice model, severe hypercholesterolemia is associated with a switch to Th2 immune response, with increased IL-4 expression in the atherosclerotic lesions [23]. IL-4 mRNA can also be detected in atherosclerotic lesions in human body [24]. The microenvironmental IL-4 in the atherosclerotic lesions has multiple effects on atherogenesis, such as the augmentation of LDL cholesterol esterification by a concentration- and time- dependent manner [25]. In addition, IL-4 can regulate the expression of 15-lipoxygenase (15-LO), a key enzyme in LDL oxidation [26, 27]. Elbe-Burger et al. further demonstrated that the adipocyte layer in the dermis is reduced in IL-4 transgenic mice [28]. Accordingly, local microenvironmental expression of IL-4 is suggested to be involved in the atherogenic process.

**Table 1. Association between cytokines polymorphisms and T2DM in Taiwan**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>T2DM Association</th>
<th>Clinical Parameter</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-34T&gt;C</td>
<td>+</td>
<td>-</td>
<td>[Manuscript revised in submission]</td>
</tr>
<tr>
<td>-81A&gt;G</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>-285C&gt;T</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>-589T&gt;C</td>
<td>+</td>
<td>HDL-C</td>
<td></td>
</tr>
<tr>
<td>IL-4Rα</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E400A</td>
<td>-</td>
<td>blood pressure</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>BUN</td>
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<tr>
<td></td>
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<td>HDL-C</td>
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</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-174G&gt;C</td>
<td>-</td>
<td>-</td>
<td>[7]</td>
</tr>
<tr>
<td>IL-10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-592A&gt;C</td>
<td>+</td>
<td>-</td>
<td>[21]</td>
</tr>
<tr>
<td>-819T&gt;C</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>TNF-α</td>
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<td></td>
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<tr>
<td>-238G&gt;A</td>
<td>+</td>
<td>HDL-C</td>
<td>[22]</td>
</tr>
<tr>
<td>-308G&gt;A</td>
<td>-</td>
<td>Fasting glucose</td>
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</table>
IL-4Rα is a crucial component for binding and signal transduction of IL-4 [29]. It is reasonable that polymorphisms located in IL-4Rα, which alter the binding affinity to IL-4 or downstream signaling pathways and thus contribute to the fine tune of IL-4 responsive phenotypes, would also be linked to disease development. Several studies have reported that genetic polymorphisms of IL-4 and IL-4Rα are associated with genetic predisposition to diseases, possibly through their influences on the activity of these genes or their products [30-33]. Georgea et al. studied the influence of IL-4 to fatty streak formation using IL-4 knockout mice and found that HDL and triglycerides in the IL-4-deficient mice were higher [34]. In support of the previous studies, our observations provide further evidence that IL-4 may be involved in lipid metabolism. We hypothesize that the contribution of IL-4Rα to HDL-C and lipid metabolism is likely due to influencing the strength of both IL-4:IL-4R interaction and the downstream IL-4 signaling, then eventually the lipid metabolism and the resulting diabetic incidence. Nevertheless, this speculation awaits further study.

**Inter-ethnic Differences in T2DM**

While more and more evidences regarding the investigation of cytokine genotypes in patients with T2DM are documented, some reported correlations are still controversial because discrepancies among different studies exist. Ethnic differences may play a role in these conflicting results, as the distribution of genetic polymorphisms in a certain gene is diverse among study subjects with different racial origins.

For example, the prevalence of IL-6 -174 C allele is reported to be ranged from 4.45% in Afro Caribbean [35], 13.85% in Gujarati Indians [35], 40-50% in Caucasians [36] to 62% in Spanish Caucasians [37]. Studies demonstrated that individuals carrying IL-6 -174C/C genotype have an increased insulin sensitivity index than carriers of the G allele with similar age and body composition [38, 39]. Study from Vozarova et al. [40] also demonstrated that the IL-6 -174G/G genotypes are associated with T2DM in Spanish Caucasian subjects and American Indian subjects with non-Pima admixture. The above results demonstrated that individuals carrying IL-6 -174G allele would be more susceptible to develop insulin resistance and T2DM. However, contradictory results existed. Insulin sensitivity, glucose oxidation rates and nonoxidative glucose disposal are decreased in healthy Finnish normoglycemic subjects with IL-6 -174 C/C genotype, compared with the subjects carrying the heterologous C/G and homologous G/G genotypes [41].

Our previous report showed that the IL-6 -174G>C polymorphisms, which affects insulin sensitivity in Caucasians [40], is unlikely to play a role in development of T2DM in Taiwanese, because no polymorphism has been identified at this position in our population [7]. Taken the results of IL-6 in diabetic studies together, it reflects the unique genetic characteristics and possible distinct etiological/environmental factors may be involved in pathogenesis of Taiwanese T2DM.

**Conclusions**

Although the initiation and etiology of T2DM still await to be identified, accumulating evidences have proved the hypothesis that T2DM is a state of chronic inflammation, with increased acute phase proteins and various cytokines. Genetic studies regarding the exploration of susceptible or resistant genes for T2DM could provide clues for understanding the mystery of diabetic pathogenesis and for future designing of diabetic treatment. Particularly, the achievements of genetic studies in Taiwanese diabetic population should be able to echo the needs for the development of personalized medicine based on the contribution of distinct genetic heterogeneity to diabetic development and complications. Hopefully, this article can provide valuable references to this metabolic tragedy.

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the IL-6 gene are associated with hyperandrogenism. J Clin Endocrinol Metab 2002; 87: 1134-41.
細胞激素、新陳代謝與第二型糖尿病

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第二型糖尿病(type 2 diabetes mellitus, T2DM)為常見的內分泌疾病，其致病機轉仍然未知。T2DM病患雖然可自行分泌胰島素，但其細胞無法有效接收或傳遞胰島素的訊息而產生胰島素阻抗性(insulin resistance); 長期罹病患者的胰島素分泌能力也可能受損。許多因素可能會導致T2DM，其中以遺傳因子和環境因素最受矚目。研究可引起代謝異常的遺傳基因有助於了解糖尿病的致病因素及發展嶄新的治療與預防策略。許多研究已證實T2DM與慢性發炎反應有密切相關性，患者體內的急性發炎蛋白與細胞激素濃度都會增高。本文的宗旨為討論糖尿病的流行病學與分類，以及細胞激素在T2DM和新陳代謝中的角色。此外，本文亦納入本實驗室近年來有關T2DM病患細胞激素基因型的研究結果，提供參考。特定族群的糖尿病免疫基因學研究結果不僅有助於釐清免疫反應與T2DM的相關性，也可供發展個人化醫療與疾病預防的參考資訊。

關鍵詞：細胞激素、新陳代謝、介白素、糖尿病

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