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Review

The linkage between inflammation and Type 2 diabetes mellitus

Nathália G. Cruz [a], *Lirlândia P. Sousa* [a], *Marinez O. Sousa* [a], *Nathalia T. Pietrani* [b], *Ana P. Fernandes* [a], *Karina B. Gomes* [a,b,*]

[a] *Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*
[b] *Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*

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ABSTRACT

The Type 2 diabetes mellitus (DM2) is considered nowadays as one of the most important chronic disturbances because of the significant number of people with diabetes and its severe complications, responsible for elevated indexes of morbidity and mortality. DM2 is characterized by several degrees of insulin resistance and relative deficiency in its secretion. Genetic and environmental factors have been described as of major importance in the DM2 development as obesity, which is directly correlated with development of resistance in peripheral tissues and inflammatory state in metabolic activated adipose tissue. Inflammatory responses may have a dual role in DM2, since it may have either a causal relationship leading to resistance to insulin or may be intensified by the hyperglycemic state, resulting in DM2 complications. In this review, we discuss the association of polymorphisms in genes encoding inflammatory cytokines and the increased level of these pro-inflammatory markers, associated to chronic pathologic conditions in DM2.

Contents

* *Corresponding author at*: Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Av. Antônio Carlos, 6627, Pampulha, 31270-901 Belo Horizonte, MG, Brazil. Tel.: +55 31 3409 6895; fax: +55 31 3409 6985.
E-mail address: karinabgb@gmail.com (K.B. Gomes).
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1. Introduction

The Type 2 diabetes mellitus is considered nowadays as a worldwide epidemic. It is one of the most important chronic disturbances because of the significant number of people with diabetes and its severe chronic complications, responsible for elevated indexes of morbidity and mortality.

The most prevalent form of diabetes mellitus corresponds to Type 2 (DM2), responsible for approximately 90% of all cases of diabetes in the world. According to World Health Organization (WHO) [1] the number of people with this metabolic disturbances tends to increase during the fore coming years. The global forward estimative is that in the year 2030, 366 million people will present the disease. In the past, adults represented the main target segment of the population, but nowadays the number of children and teenagers with DM2 is growing remarkably [1,2].

The clinical manifestations usually found in DM2 patients can be defined considering the associated metabolic disorders and complications of the clinical outcome. The metabolic disorders are consequences of a framework hyperglycemia, resulting from glucose underutilization in tissues. The chronic complications also are important results of hyperglycemic state and include vascular, neuropathic and visual disturbances [3,4].

The DM2 is characterized by several degrees of insulin resistance and relative deficiency in its secretion. In most people with this form of diabetes, insulin action is impaired. The insulin resistance can be a consequence of a decrease on insulin receptor numbers or failure in insulin-receptor binding. Also, this resistance can happen due to a failure in glucose transportation into the cell by a specific protein carrier as the glucose transporter (GLUT 4) [5].

Genetic and environmental factors have been described as of major importance in the DM2 development and its complications. Among environmental factors obesity, mainly abdominal fat accumulation, is one factor that stands out and that is often present in individuals with diabetes. Obesity is directly correlated with elevated levels of insulin and consequently the development of resistance in peripheral tissues [6].

Insulin resistance has been attributed to adipose tissue activation associated with an increased release of inflammatory cytokines such as TNF-α, IL-6 and decreasing production of IL-10, an anti-inflammatory cytokine, by macrophages and lymphocytes. High levels of other inflammatory factors such as PAI-1 (plasminogen activator inhibitor), C-reactive protein and monocytes activation also are associated with increased insulin resistance [7]. Other factors have been positively associated as hypertension, sedentary lifestyle, age over 40 years, previous gestational diabetes, medications and hyperglycemic family history [4].

This review will explore the main studies that describe the association of inflammatory cytokines and other inflammatory markers, associated to chronic pathologic conditions in DM2.

2. The signaling through insulin receptor

Cell insulin signaling starts when insulin binds in to its specific receptor in several tissues, inducing a complex intracellular cascade.

The family of insulin receptor substrates (IRSs) is an important regulatory key in the insulin signaling pathway and includes at least four distinct IRS proteins, among IRS-1 and IRS-2 which are found in several human tissues. They are considered the most important proteins of the family linked to actions of insulin on peripheral lipid and carbohydrate and β-cell function. The other two IRS proteins of the family are less well characterized and have apparently a reduced distribution and importance. The IRS-3 is restricted to adipose tissue, β cells and possibly liver. IRS-4 also has a restricted distribution, being primarily located at the thymus, brain and kidneys. Therefore, the specific expression of IRS proteins in distinct tissues can be associated to the mechanism for tissue specific responses to insulin [8,9].

Insulin receptor-mediated tyrosine phosphorylation of IRS leads to activation of two major pathways: the PI3K/AKT and MAPK. The phosphatidylinositol 3-kinase (PI3K)-AKT pathway is largely responsible for insulin action on glucose uptake and suppression of gluconeogenesis, whereas the MAPK pathway regulates gene expression and additionally interacts with the PI3K-AKT pathway to control cell growth and differentiation (Fig. 1) [10].

The PI3K/AKT pathway is required for insulin-dependent regulation of systemic and cellular metabolism. The PI3K/AKT pathway is activated downstream of the IR. PI3K catalyzes the addition of a phosphate molecule to the three positions of the inositol ring of phosphoinositides (PtdIns), converting membrane phosphatidylinositol into phosphatidylinositol-3-phosphate (PIP), phosphatidylinositol-4,5-bisphosphate (PIP2) and phosphatidylinositol-3,4,5-triphosphate (PIP3). AKT binds to PIP3, which facilitates activation of AKT by upstream kinases (PDK1 and PDK2). Once activated, AKT is released from the plasma membrane and translocates to cellular compartments, such as the cytoplasm, mitochondria and nucleus, where it regulates several substrates by phosphorylation events. Some of them are related to regulation of glycogen synthesis, gluconeogenesis and glucose uptake, respectively. PDK1 also activates isoforms of protein kinase C (PKC), which are required for GLUT 4-dependent regulation of glucose uptake. Moreover, AKT and PKC control *de novo* lipogenesis by regulating lipogenic genes, such as sterol regulatory element-binding transcription factor 1 (SREBF1 and SREBP1c) and peroxisome proliferator-activated receptor γ (PPARγ) [10].

MAP kinases (MAPKs) constitute a family of serine/threonine kinases. The four well-characterized subfamilies of MAPKs include: the extracellular signal-regulated kinases (ERK1/2), c-Jun terminal kinases (JNK-1/2/3), p38 (p38α/β/γ/δ) and ERK5. The JNK and p38 can be activated by cellular stresses and are collectively known as stress-activated MAPKs. Phosphorylation of both the threonine and tyrosine within this signature sequence is required for MAPK activation. Upon activation, MAPKs regulate key cellular events in the cytoplasm by phosphorylation of membrane-associated and cytoplasmic proteins, including other kinases and cytoskeletal