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Metabolic syndrome and risk of cancer: Which link?

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ABSTRACT

Metabolic syndrome (MS) is characterized by a group of metabolic disturbances which lead to an enhanced risk of cardiovascular diseases and type 2 diabetes mellitus. MS constitutes a preoccupant issue with elevated prevalence in the western countries and is often related with cancer development. Elucidating the mechanisms linking these two pathologies is, therefore, essential to identify potential therapeutic molecular targets for cancer treatment in MS patients. The main goals of this review are, to identify the relation between MS and cancer development, handling specifically each one of the main players on this process: insulin and IGF system, estrogen, pro-inflammatory cytokines and others; and, given that colorectal cancer is one of the most prevalent types of cancer in MS patients, we intend to particularly highlight the mechanisms that promote colorectal cancer development in MS individuals. Finally, we will also focus on the clinical implications of the presented mechanisms on cancer therapy and care.

1. Introduction

Metabolic syndrome (MS) is a group of risk factors for type 2 diabetes mellitus and cardiovascular disease development [1]. MS and its concomitant complications are a serious health problem worldwide and, probably, will gain even more importance in the future, given the fact that obesity prevalence, sedentary lifestyle and unbalanced diets are increasing [2–4]. In USA, it is estimated that MS prevalence is already at over 23.7% without significant statistic evidence between both sexes [5]. In Europe, various studies suggest the existence of significant geographic variation, and it is expected that MS prevalence between non-diabetic population reaches 25.9% in men and 23.4% in women (DECODE Study Group) [6]. MS prevalence in Portugal determined by VALSIM study was high (27.5%), being in line with that observed in NHANES III study (Third National Health and Nutrition Examination Survey) [5]. Emerging evidence supports that MS may be an important etiological factor for development and progression of certain types of cancer [7], particularly colorectal cancer [8,9]. According to GLOBOCAN 2008 report of International Agency for Research on Cancer (IARC), colorectal cancer is the third more common type of cancer in men and second more common in women around the world. In Portugal, it is the second more frequent type of cancer [10]. Recent studies also suggest an increased incidence and mortality due to colorectal cancer in MS individuals [1,11]. Biological plausibility of this association may be justified by growth hormone deregulation (including insulin, IGF-1, several intracellular signaling pathways and

Abbreviations: IGF, insulin-like growth factor; IGFR1, IGF receptor-1; IGFBP, IGF binding proteins; IR, insulin resistance; MS, metabolic syndrome; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; MCP-1, monocyte chemotactic protein-1; PAI-1, plasminogen activator inhibitor; RBP-4, retinal binding protein-4.

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adipokines), cytokines and cellular crosstalk, and vascular integrity factors [2].

The main objective of this paper is to present a clarifying approach to the pathological mechanisms that link MS and its components to carcinogenesis in general and, in a second phase, to colorectal cancer. Understanding these mechanisms has a huge clinical and economic impact in health systems worldwide, because cancer represents one of the main causes of death around the world.

2. Metabolic syndrome

This cluster of metabolic disorders that confer an increased risk of cardiovascular disease and type 2 diabetes mellitus includes central obesity, dyslipidemia, hyperglycemia, insulin resistance and hypertension [12]. However, there are other additional criteria that may aid diagnosis, like the presence of increased levels of inflammatory/pro-thrombotic markers and reduced anti-inflammatory molecules [13], markers that are related with excessive adiposity [3].

2.1. *Pathophysiology of metabolic syndrome*

Adipose tissue plays a key role in the pathophysiology of metabolic syndrome. Traditionally, it has been considered an organ of storage and mobilization of lipids. However, as it was earning a growing scientific interest, it has recently been considered an active endocrine organ, to play a primordial role in the integration of systemic metabolism, due to its ability to secrete a large amount of bioactive mediators that modulate various signaling cascades: the so-called adipokines [14]. Being a secretory organ, adipose tissue exhibits several important features. For instances, the various fatty deposits (visceral and subcutaneous) exhibit different metabolic capabilities and secrete distinct adipocytokines [15]. The distinct adipose tissue depots are composed of different types of cells (structural support, functional and immunological). Further, blood vessels display a double function: to supply nutrients and oxygen and to spread inflammatory mediators to distant tissues [14]. Table 1 shows a list of adipocytokines mainly involved in visceral obesity and their established deleterious effects.

Obesity can be characterized by a low-grade chronic inflammatory state, mediated by cytokines and bioactive molecules [16]. The increased lipid storage and the weight gain processes that characterize obesity require anabolism. In contrast, inflammation associates with catabolic pathways, such as lipolysis. Thus, the homeostatic mechanism of catabolism activation via inflammation and resistance to anabolic signals, can be viewed as a last attempt from the organism to control the growing adiposity. However, these effects involve a worsening in the inflammatory state and insulin resistance [3,16]. In the expanded adipose tissue, lipolysis is stimulated, resulting in abundant free fatty acids (FFA) release into the portal vein. In turn, reaching the liver, FFA increase glucose and triglyceride synthesis, a well as very low density lipoproteins (VLDL). Dyslipidemias that are associated with this condition consist in reduction of HDL-cholesterol and increase in LDL [17]. Furthermore, FFA also reduce insulin sensitivity in muscle, inhibiting thus, glucose uptake. An increase in circulating glucose and, to some extent, FFA, results in augmented pancreatic insulin secretion, leading to hyperinsulinemia, which can result in augmented sodium resorption and of the sympathetic nervous system activity, which may contribute to hypertension [18]. The pro-inflammatory state overlaps and contributes to insulin resistance produced by excessive FFA. The increased adipocyte and macrophage secretion of TNF-α and IL-6 further enhance insulin resistance and lipolysis in adipose tissue. On other hand, IL-6 and other cytokines also stimulate hepatic gluconeogenesis, VLDL production and insulin resistance in muscle [3]. In addition, the increased production of fibrinogen and C-reactive protein by the liver and plasminogen activator inhibitor (PAI-1) by adipocytes leads to a pro-thrombotic state, also characteristic of this syndrome.

Several studies hypothesize that each component of the metabolic syndrome contributes to the development of various processes, such as angiogenesis, insulin resistance, adipocytokines production, oxidative stress, which potentiate the risk of chronic diseases development such as cancer, or cause of a worse prognosis of these same complications [2,4,19].

3. Metabolic syndrome and cancer risk

The adipose tissue in MS patients is characterized by deregulation of cytokine production, which can unleash a chronic inflammatory state. This inflammation and its mediators may be involved in tumor development [2]. Experimental and epidemiological data emphasize a connection between metabolic syndrome and increased cancer risk

Table 1 – Summary description of the deleterious effects of cytokines released by adipose tissue, particularly visceral fat and immune cells.

Adipocytokines	Effects
Tumor necrosis factor α (TNF-α)	Remodeling of adipose tissue Insulin resistance Increased levels in cardiovascular diseases Decreased insulin signaling and leptin
Interleukin-6 (IL-6)	Stimulation of lipolysis and release of C-reactive protein
Monocyte chemotactic protein-1 (MCP-1)	Chemotactic and maintenance of inflammation
Plasminogen activator inhibitor (PAI-1)	Hypofibrinolysis and promotion of pro-thrombotic state
Angiotensinogen	Elevated blood pressure
Retinal binding protein-4 (RBP-4)	Insulin resistance
Leptin	Increased angiogenesis, increased cell proliferation
Visfatin	Chemotactic effects; pro-inflammatory cytokines
Resistin	Hepatic insulin resistance, hyperglycemia, overexpression of adhesion molecules and pro-inflammatory cytokines