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GUIDELINES FOR BASIC RESEARCH

Diabetes and cancer: Looking at the multiligand/RAGE axis

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Abstract

The association between diabetes and hyperglycemia and the associated increased risk of several solid and hematologic malignancies has been the subject of investigation for many years. Although the association is not fully understood, current knowledge clearly indicates that diabetes may influence malignant cell transformation by several mechanisms, including hyperinsulinemia, hyperglycemia and chronic inflammation. In this context, the receptor for advanced glycation end-products (RAGE) has emerged as a focal point in its contribution to malignant transformation and tumor growth. We highlight how RAGE, once activated, as it manifests itself in conditions such as diabetes or hyperglycemia, is able to continuously bring about an inflammatory milieu, thus supporting the contribution of chronic inflammation to the development of malignancies.

Key words: Diabetes; Cancer; Inflammation; Receptor for advanced glycation end-products; Malignant transformation

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INTRODUCTION

The association between diabetes and hyperglycemia and cancer, has been investigated extensively. Most studies, but not all, have found that both conditions are associated with an increased risk of several solid and hematologic malignancies. Currently, more than 250 million people live with diabetes; hence any impact derived even in smaller increases in the risk of cancer may have important consequences at world population level, and on associated costs to healthcare systems worldwide[1]. Although this association has been consistently reported for the most common cancer, more research efforts are needed, particularly in connection with the less common cancers, where data are limited or absent[2].

From the biological point of view, an essential question is raised when the association is analyzed: What are the mechanistic links between diabetes and cancer risk? Obviously, the answer to this question is not easy to find. However, and based on current knowledge, diabetes may influence malignant cell transformation by several mechanisms, including hyperinsulinemia, hyperglycemia and chronic inflammation. These three mechanisms are closely related to the receptor for advanced glycation end-products (RAGE), which may represent a focal point in their respective contri-

butions to malignant transformation.

In 1927, Otto Warburg and co-workers reported the increased uptake of glucose and production of lactate by tumors. At present, resurgent research interest in the Warburg effect, as it is now known, have brought about a growing body of evidence supporting the dependence of many tumors on glycolysis for energy production. One consequence of the rise of glycolysis is the non-enzymatic glycation of proteins, leading to the formation of advanced glycation end-products (AGEs)[3,4]. AGEs were the first identified RAGE ligands, particularly N-carboxymethyllysine [CML]-modified proteins[5].

The formation of AGEs is based on the non-enzymatic reaction of the reactive aldehyde moiety of glucose with the amino groups of proteins, forming slowly reversible Amadori products. Rearrangement reactions then occur to produce a chemically related group of moieties, termed AGEs, which remain irreversibly bound to proteins[6].

The major AGEs *in vivo* appear to be formed from highly reactive intermediate carbonyl groups, known as α-dicarbonyls or oxoaldehydes, including 3-deoxyglucosone, glyoxal, and methylglyoxal[7,8].

There is considerable evidence linking hyperglycemia with the accelerated formation of irreversible AGEs, which subsequently accumulate in different tissue locations[9,10,11]. Of note, the presence of AGEs has been detected in human cancer tissues, and their expression is markedly varied between different types of tumors[12].

It has been demonstrated by different authors that the circulating level of AGEs is associated with insulin resistance even in non-obese, non-diabetic subjects, independent of adiponectin levels[13,14,15].

How AGEs can impact insulin actions has been recently reviewed by Schalkwijk and co-workers[16]. Experimental data, obtained from both animal and isolated muscle and adipose tissue, suggest that glycation of insulin significantly impairs its biological activity[17].

It is also known that the increase of endogenous methylglyoxal accumulation impairs the insulin-signaling pathway and decreases insulin-stimulated glucose uptake in adipose tissue, which, in turn, may contribute to the development of insulin resistance[18,19].

Reduced intake of dietary AGEs has been shown to decrease the incidence of type 1 diabetes in non-obese diabetic mice[20], as well as the formation of atherosclerotic lesions in diabetic apolipoprotein E-deficient mice[21]. Vlassara and co-workers[22] have also shown that reduced AGE intake leads to lower levels of circulating AGEs and to improved insulin sensitivity in *db/db* mice. Furthermore, AGEs are reported to impair insulin action in muscle tissue by the formation of a multi-molecular complex, including RAGE/IRS-1/Src and PKCα[23].

RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS

The receptor for advanced glycation end-products (RAGE) is a member of the immunoglobulin protein family of cell surface molecules[24] and shares structural homology with other immunoglobulin-like receptors. Firstly described in 1992, RAGE has attracted increasing attention, due to its diverse ligand repertoire and its involvement in several pathophysiological processes associated with inflammation, such as diabetes, cancer, renal and heart failure, as well as neurodegenerative diseases[25,26].

The RAGE gene is localized on chromosome 6 in the vicinity of the MHC class Ⅲ complex region in humans and mice, and in close proximity to the homeobox gene HOX12 and the human counterpart of the mouse mammary tumor gene int-3[27,28].

RAGE is highly expressed during development, especially in the brain, but its expression level decreases in adult tissues. However, RAGE expression is also markedly augmented by increased levels of ligands, as observed in some pathologic states[29]. The mature 382 amino-acid long RAGE is composed of an extracellular domain (85 aa), a single transmembrane spanning helix (27 aa) and a short cytosolic region (41 aa)[30]. The extracellular domain of RAGE contains one variable, like V-domain, and two constants, like C type domains, which are frequently referred to as C1 and C2 domains. Recent studies suggest that RAGE forms oligomers at the cell surface[31]. RAGE possesses two N-glycosylation sites, one adjacent to the V-domain and the second one located within the V-domain[32].

Recently, RAGE splice variants have been classified and renamed according to the Human Gene Nomenclature Committee[33], and many of them appear to be more abundant under various pathological conditions. At DNA level, the RAGE gene consists of 11 introns/exons that can alternatively be spliced into different variants. In terms of prevalence, the three major isoforms appear to be the full-length RAGE, a secreted form RAGE_v1 (previously named as sRAGE, secretory C-truncated RAGE, esRAGE, hRAGEsec or sRAGE1/2/3) and a N-terminally truncated isoform RAGE_v2 (previously named Nt-RAGE, N-RAGE or N-truncated RAGE). It is important to point out that RAGE_v1 is released into the extracellular compartment, where it can interact with free RAGE ligands, then working as a "decoy receptor", thereby preventing ligands from interacting with cell surface RAGE[34].

RAGE AS A MULTILIGAND RECEPTOR

In addition to AGEs, other molecules have been identified as RAGE ligands, as has been demonstrated for S100/calgranulins; high-mobility group box 1 (HMGB1) have also been identified as ligands of this promiscuous receptor. The S100/calgranulin protein family comprises several members of non-ubiquitous Ca-binding proteins of the EF-hand type that have both intracellular and extracellular functions. At intracellular level, S100 proteins are responsible for different roles in the cell cycle, cell differentiation and cell motility. However, some members of the family have additional relevant extracellular roles, particularly

at sites of chronic inflammation, where they are able to activate, *via* RAGE, endothelial cells, macrophages and peripheral blood mononuclear cells, including T lymphocytes[35].

The DNA binding protein HMGB1 stabilizes nucleosome function, and acts as a transcription factor that regulates the expression of several genes[36]. HMGB1 belongs to the so-called "damage associated molecular pattern molecules" or alarmins, which are released in response to infection or inflammatory stimuli, especially during tissue damage[37].

Although glucose may be the triggering stimulus to draw RAGE into diabetes pathology, consequent cellular stress results in the release of pro-inflammatory RAGE ligands S100/calgranulins and HMGB1. Thus, RAGE engagement in diabetic tissue produces a vicious cycle of ligand-RAGE perturbation, leading not only to chronic tissue injury, but also suppression of repair mechanisms[38]. RAGE engagement activates multiple signaling pathways (Figure 1), including reactive oxygen species, p21ras, erk1/2 (p44/p42) mitogen-activated protein kinases, p38 and SAPK/JNK mitogen-activated protein kinases, rhoGTPases, phosphoinositol-3 kinase and JAK/STAT pathway, with important downstream inflammatory consequences, such as the activation of nuclear factor-kappaB (NFκB), AP-1 and STATs, which are involved in the inflammatory process seen in both diabetes and cancer.

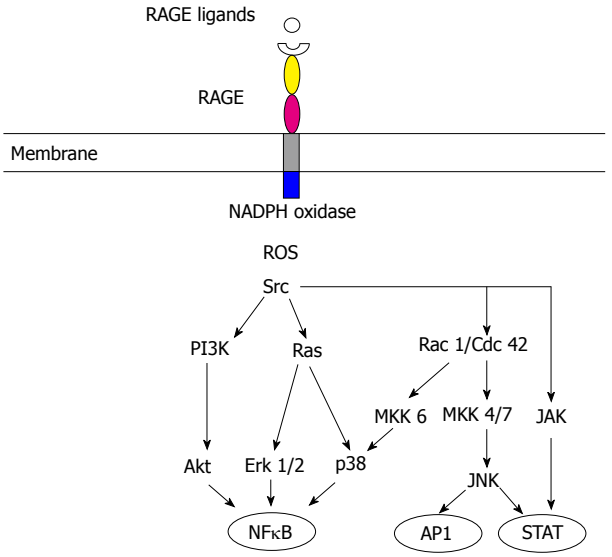

Figure 1 RAGE engagement activates many signaling pathways which are involved in both diabetes-associated vascular complications and tissue damage, and as well as in the tumor microenvironment-associated inflammatory milieu. RAGE: Receptor of advanced glycation end-products.

RAGE, CHRONIC INFLAMMATION AND CANCER

In the nineteenth century, Rudolph Virchow first launched the idea about a putative connection between inflammation and cancer. At present, resurgent research interest in this topic has raised a growing body of evidence supporting the contribution of chronic inflammation to the development of malignancies, as well as an association between the usage of non-steroidal anti-inflammatory agents, and protection against various tumor types[39,40,41,42].

For many years, the relationship between the expression of the receptor of advanced glycation end-products (RAGE) and cancer has been well-documented, as reported in gastric, prostate, lung, pancreas, and liver malignancies. However, the contribution of RAGE to cancer biology seems to be much more functional than initially thought, because it has now emerged as a relevant element that can continuously fuel an inflammatory milieu at the tumor microenvironment[43].

Most of the cancer-promoting effects of RAGE ligands are the result of their interaction with RAGE. Signals downstream of RAGE, drive the strength and maintenance of an inflammatory reaction during tumor promotion in a mouse model of skin cancer, as well as a marked reduction in the number of infiltrating immune cells and the levels of proinflammatory mediators in RAGE$^{-/-}$ animals[44]. In addition, the interaction of the ligands S100A8/A9 with RAGE involve carboxylated glycans; the transition from acute to chronic inflammatory conditions in the study cited did not occur in RAGE$^{-/-}$ mice, which in turn, produced fewer tumors in a colitis-associated cancer model[45].

The consequences of RAGE activation to tumor biology also reach key processes, such as the acquisition of an hypoxia–resistant phenotype in carcinoma cells[46]. Recently, it has been reported that S100A8/A9 proteins contribute to the recruitment and retention of myeloid suppressor cells through a mechanism mediated, at least in part, by the binding to carboxylated N-glycans expressed on the receptor for advanced glycation end-products, and the subsequent activation of the NFκB signaling pathway[47]. AGEs can also down-regulate in vitro the ability of dendritic cells (DCs) to express co-stimulatory signals and to activate T cells[48]. Similar results have been described after a blockade of the autocrine secretion of HMGB1, and of RAGE activation[49,50].

In recent years, a growing body of evidence supports the role of ligands/RAGE axis in angiogenesis. Upon RAGE engagement, profound effects are reported in endothelial cells, including up-regulation of VEGF and metalloproteinase-2, as well as the disruption of the VE-cadherine/catenins complex, thus favoring capillary tube formation[51,52]. Additionally, RAGE activation also increases endothelial permeability to macromolecules, a condition very common in tumor microvasculature[53].

Although many aspects of differentiation, mobilization and recruitment of endothelial progenitor cells (EPCs) remain controversial, it has been reported that the levels of peripheral blood EPCs have been shown to be increased in certain malignant states[54].

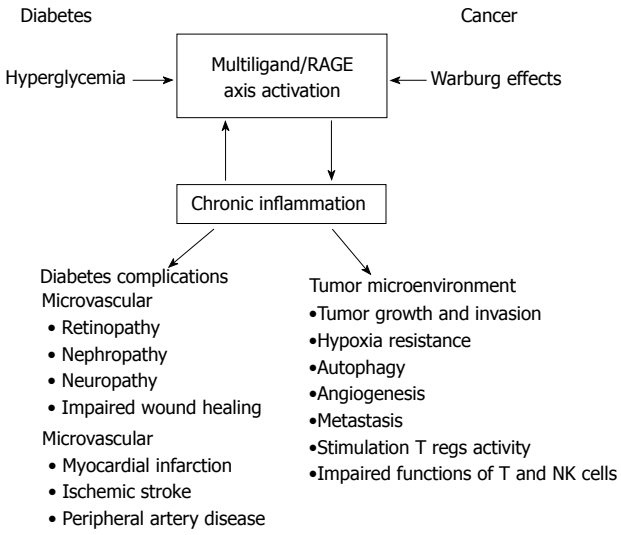

Figure 2 Schematic depiction of consequences of RAGE activation in both diabetes and cancer. A common focal point is the onset and perpetuation of inflammatory conditions.

HMGB1 increased EPCs adhesion to the immobilized integrin ligands intercellular adhesion molecule-1 and fibronectin in a RAGE-dependent manner, thus stimulating EPC homing to ischemic tissues[55].

In 2000, a seminal report on the contribution of multiligand/RAGE axis on invasion and metastasis demonstrated that a blockade of RAGE-HGMB1-derived signaling decreased growth and metastases of both implanted tumors, and tumors developing spontaneously in susceptible mice[56].

CONCLUSION

During the last decade, relevant advances in our understanding of the pathophysiologic role of the multiligand/RAGE axis have lead to a substantial knowledge of how this promiscuous receptor, once activated, is able to continuously bring about an inflammatory milieu (Figure 2). The current relevance of Virchow´s postulate about the role of chronic inflammation in cancer development highlights the facts associated with the presence of an activated RAGE axis, smoldering inflammation such as that occurring in diabetes, and thus its contribution towards the understanding of the mechanistic scenario supporting the link between diabetes and cancer.

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