Journal of
Tumor Medicine & Prevention
ISSN: 2575-890X

Juniper Publishers
key to the Researchers

Mini Review
Volume 1 Issue 2 - May 2017
DOI: 10.19080/JTMP.2017.01.555558

J Tumor Med Prev

Advanced Glycation End Products and Tumorigenesis

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Submission: April 13, 2017; **Published:** May 26, 2017

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Abstract

Advanced glycation end products (AGE) have gained interest in recent decades and in particular over recent years within the realm of cancer development and progression. This stems from the interaction between AGEs, their receptor (RAGE) and chronic inflammatory pathways which could play a pivotal role tumorigenesis. Of late, treatments have been interrogated as possible methods by which RAGE progression could be curtailed and thus possible treatments or preventative measures for cancer disease. This brief review aims to highlight the most recent thoughts on the AGE-RAGE axis, how it imparts on cancers and where these beliefs originate.

Introduction

Advanced glycation end products (AGE), previously described as glycotoxins, are the resultant products of non-enzymic reactions between reducing sugars and proteins [1,2]. These AGEs have been attracting continued interest in the realms of inflammatory driven disease especially in the setting of hyperglycemic states, such as diabetes [3]. The excess of AGE either by exogenous dietary intake or endogenous development, has been associated with detrimental effects via its interaction with its receptor (AGER or RAGE) initially described in 1992 [4,5]. The mechanisms of function of RAGE are continually attracting interest as they may hold the key in altering the progression of tumourigenesis via therapeutic blockade or prevention [6].

Implication in Neoplasia

In recent years, the AGE-RAGE axis has been implicated in the development of many cancers including lung, colorectal, hepatocellular, pancreatic, renal, ovarian, prostate, breast, haematological and skin cancer, both by ligand/AGE association or RAGE presence and up regulation [7-16]. RAGE is generally present in low levels within most non-pathological tissue apart from lung parenchyma where it is raised at homeostasis [17]. RAGE ligands include not only AGEs but also pro-inflammatory ligands such as S100 proteins and high-mobility group box 1 (HMGB1) have been extensively studied and associated with cancer states and tumor microenvironment [18-20]. The ligand-RAGE axis has also been associated with metastasis or micrometastasis [21-25].

Up regulation of the RAGE is evident and may not only help to prove the association of AGE/RAGE in neoplasia and cancer progression but there have been suggestions for its use as a biomarker of disease alone or possibly in combination with its ligands [21,26-28].

Participation in Tumorigenesis

Reactive oxygen species are produced by a number of methods, one of which being the AGE-RAGE axis [29]. This itself is the process by which many of the non-neoplastic complications of hyperglycemia and diabetes are believed to arise [30]. The recent association of inflammatory and carcinogenic processes [31] is where AGEs and RAGE activation may hold roles in tumorigenesis. When activated, RAGE activates pro-inflammatory pathways namely NF-κB and mitogen activated protein kinase (MAPK) pathways [3] to release pro-inflammatory cytokines. The association between inflammation and cancer is not a new one [32].

Upregulation of RAGE is determined by the increased presence of its ligands [33]. AGEs are certainly found to be increased in metabolic syndrome [34-37] and thus will lead to increased RAGE expression hinting the causative link between chronic hyperglycemic states and neoplasia.

RAGE activation aids in the progression of cancerous states by cancer cell survival, limitation of apoptosis and cellular autophagy [14,38]. This RAGE assisted survival of tumor

cells may offer a window of opportunity for interrupting the progressive nature of cancer.

Possible Therapeutics and Practical Dietary AGEs

Very recently a sharp increase in interest toward the therapeutics and prevention of RAGE driven carcinogenesis can be seen. Blockage of the RAGE pathway can occur at the AGE formation, RAGE blockade and RAGE downstream signaling pathways [39]. Therapeutic inhibition of AGEs such as cross-link breakage or reactive carbonyl trapping precursors, have yet to yield clinically viable therapeutics. A promising therapeutic strategy is the use of soluble RAGE or sRAGE to act as a decoy receptor to mop up circulatory AGEs and other RAGE ligands [40,41]. The use of low molecular weight heparin has been shown to act by ligation with RAGE thus blocking its pro-inflammatory ligands [42]. Anti-RAGE antibodies have been seldom ventured thus far but could be produced in altered form to provide a blockade assisting to curtail the disruptive tumor microenvironment [43].

In the era of greater focus on preventative medicine some focus needs to shift toward dietary AGE reduction and decreased endogenous AGE formation. Association between hyperglycemia and RAGE or its inflammatory products is evident [44-46]. There are some promising effects upon the inflammatory processes seen with the restriction of dietary AGE or calorific restriction [47,48] however practical applications have yet to be proven. Currently, simple application of dietary restriction, dietary awareness and glycemic index may be useful in restricting exogenous and endogenous AGEs [49,50]. Uribarri et al. [49] have produced a practical guide to the AGE content in foods however even the quality of food production at industrial level will play an important role and presents another avenue of research for prevention [51].

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How to cite this article: Niall D K,Des C W. Advanced Glycation End Products and Tumorigenesis. J Tumor Med Prev. 2017; 1(2): 555558.
DOI: 10.19080/JTMP.2017.01.555558

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DOI: 10.19080/JTMP.2017.01.555558

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