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Review

AGEs, RAGEs and s-RAGE; friend or foe for cancer

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ABSTRACT

Impaired awareness of glycation biology in cancer initiation and progression is one of the fundamental reasons for its meticulous investigation of the molecules involved in signalling pathway. Glycation of biological macromolecules results in the progression of advanced glycation end-products (AGEs) that proliferates the process of carcinogenesis by activation of transcription factors and release of cytokines. The receptor for advanced glycation end-products (RAGEs) with the binding of its different ligands like; AGEs, HMGB1 and S100 activate the signalling arrays. The activation of downstream signalling pathway ultimately leads to the pathophysiological conditions of diabetes, ageing, neurological disorders and cancers as well as a result of the activation of transcription factors which is discussed in the main body text of this review. However, there might be a likelihood of the positive effect of the HMGB1 and S100 proteins in cancer. Still, some untouched mechanisms might be responsible for the establishment of the function of AGE-RAGE or AGE-sRAGE axis activation that leads to the friend-foe association with the cancers. The levels of RAGE and s-RAGE may be a useful biomarker of ligand-RAGE pathway activation and cancer. Thus, the possibility of providing a potential complement to carcinogenesis is very high which might be an interesting target for therapeutic interventions. This article is an insightful assessment on AGE, RAGE and s-RAGE for its possible role in cancer onset and progression. The novel therapeutic targets for cancer prevention or inhibition are also explained in brief in relation to AGE and RAGE.

1. Introduction

The real story of most forms of tumours or cancers starts with an uncontrolled growth and division of cells and is life threatening at many a time when the timely diagnosis is not done at an early stage of this threatening disease. The chief culprit behind most of the cancer is the accumulation of reactive oxygen species (ROS) leading to oxidative stress within the cells where antioxidant defence system gets depleted over the period of time [1]. This may lead to the oxidative burst which inexorably results in excess of free radicals accumulation that causes the cellular machinery of the cells to malfunction like, glutathione (GSH) which is one of the most potent antioxidant component of defence system. Thus, the accumulation of free radicals exceeds the threshold value which might have been checked and quenched by the body's antioxidant defence system, including GSH, glutathione peroxidases (GPx), and superoxide dismutase etc. When such circumstances arises, the free radicals that are in enormous amount may smash up proteins, nucleic acids and lipids and dent their biological properties which might instigate the process of tumourigenesis. Thereafter, the story goes on and may lead to cancer if it is unchecked at very early stage. There are a number of other aspects which may initiate tumour and show the way to cancer state of the disease. Genetic predisposition combined with the environmental factors is one of the other rationales for cancer development which is based on the genetic makeup of an individual. Benzopyrene, 4-aminobiphenyl, and several other polycyclic aromatic hydrocarbons are responsible for damage to the DNA and consequentially forming adducts with DNA leading to mutation and thus results in tumourigenesis and cancer [2–4]. Moreover, several interrelated lifestyle parameters such as poor diet, lack of exercise, cigarette smoking, obesity and low income have been proposed to affect cancer disparity [5].

However, there are several other means of which there could be an initiation and progression of cancer state of the disease. One such important reason is 'glycative stress' which is by and large less studied

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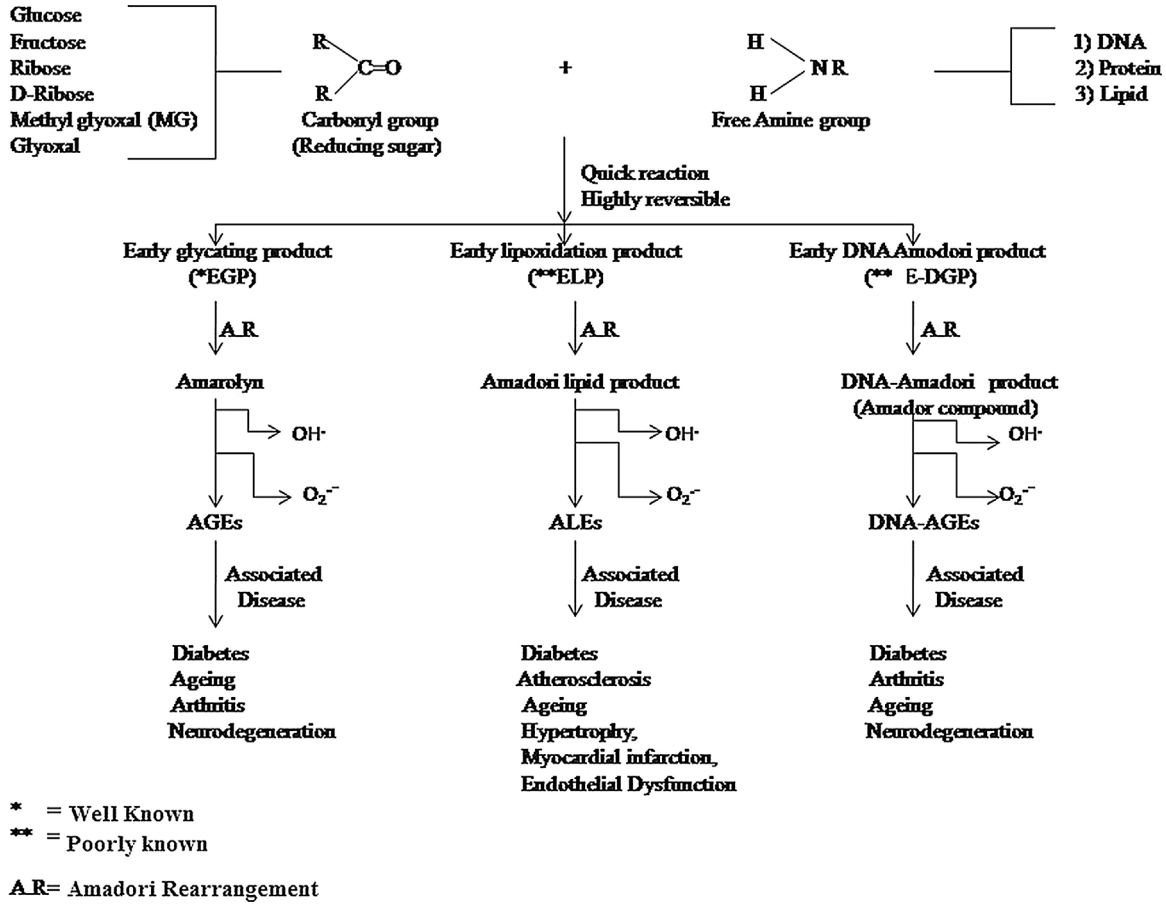

Scheme 1. Schematic representation of probable pathway of macromolecules reacting with reducing sugars to form AGEs/ALEs and DNA-AGEs, respectively. This Figure was adapted from our published research paper in the Elsevier journal International Journal of Biological Macromolecules" (2013), 58:206–210. The permission is automatically granted to the authors/corresponding authors of the paper as per Elsevier STM Permission Guidelines (2012).

research question by the researchers all across the globe. This is a non-enzymatic reaction in which free amino groups of proteins and amino acids like, lysine and arginine react swiftly with the free carbonyl groups of reducing sugar or with the reactive carbonyl species and results in the formation of Schiff's base. The Schiff's base is then converted into the more stable product, an early glycation product (EGP) also known as 'Amadori product'. This EGP then undergoes dehydration, cyclisation and isomerisation to form advanced glycation end products (AGE) [6–9] (Scheme 1). As per our pubmed search with keywords; Glycation, Cancer, AGE, RAGE and sRAGE, only 17 articles were found, out of which merely five articles were relevant to the keywords searched for. (the pubmed search was done in March; 2017).

The AGEs thus formed in and outside of the cells have a strong affinity for the receptor for advanced glycation end-products (RAGEs) [10]. The interaction of AGEs with the RAGE affect the initiation and activation of downstream signalling pathways leading to the commencement of several inflammatory cytokines, leading to a wide spectrum of diseases; like diabetes, nephropathy, rheumatoid arthritis, neurodegeneration, and cancer. Apart from AGE, there are several other ligands for RAGEs, like, HMGB1, and S-100 (calgranulins) etc., for this reason, it is also known as a multi-ligand receptor. Apart from RAGE, there are few other variants, like soluble receptor for advanced glycation end-products (s-RAGE) and endogenous secretory RAGE (es-RAGE) which affects the metabolic pathways of the cellular system. s-RAGE are the curtailed structure of complete RAGE in which cytoplasmic tail has gone astray and splice variant es-RAGE secretion, may counteract RAGE-mediated pathogenesis, by acting as a decoy. Therefore, it is hypothesised that when the concentration of s-RAGE is increased, it could bind more ligands (AGEs) which might prevent the activation of downstream signalling thus may reduce the inflammatory and tumourigenic state of the disease. The detailed AGE-RAGE interaction and other ligands for RAGEs are discussed in later part of the review and will spotlight on the AGE, RAGE and s-RAGE in the context of tumour and cancer state of the disease.

The neoplasia initiation where the cellular genome undergoes neoplastic development and that leads to carcinogenesis, a process by which normal cells are transformed into cancer cells [11]. Presently, cancer is the leading cause of death worldwide; its mortality can be reduced by its early diagnosis and treatment [12]. The International Agency for Research on Cancer (IARC) suggests that the new cancer cases are expected to grow to 21.7 million as well as 13 million cancer deaths simply due to the growth and ageing of the population. In India, the threat of the total number of new cancer cases expected to be around 2.5 million and the figure is likely to reach nearly 1.73 million new cases in 2020 as per the estimates of the Indian Council of Medical Research (ICMR), 2016 [13]. To overcome the difficulty of abundantly escalating neoplasia, it is must to take an intense insight into the mechanism and the progression of cancer and its complications and/or manifestations.

1.1. Link and blink of glycation: the flickering biomolecules

The link of glycation with the bio-macromolecules is one of the weird reasons for the blinking of DNA and proteins that result in the initiation and the development of cancer [14]. The advanced glycation end products (AGEs) is the non-enzymatic reactions between sugars and proteins or nucleic acids which have become the trending research in the mediation of cancer progression [15]. The general aspects of AGEs