

Low-Glycotoxin Diets and Spirulina may have Potential for Slowing the Growth and Spread of RAGE-expressing Cancers

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Abstract

A number of recent studies indicate that many cancers express receptors for advanced glycation end products (RAGEs), and that stimulation of these receptors make these cancers more invasive and, in some cases, boosts their proliferation. In some of these cancers, autocrine production of protein agonists for RAGE (HMGB1, S1100A) promotes their spread; the typically aggressive growth of cancers in diabetics may reflect activation of RAGE by endogenously produced advanced glycation end products (AGEs). But RAGE can also be activated by dietary “glycotoxins” – compounds produced by Maillard reactions in highly heated foods that are structurally and functionally similar to AGEs produced in diabetics. In rodents, dietary glycotoxins promote oxidative stress and pathologies linked to oxidative stress, presumably via RAGE activation. These considerations suggest that low-glycotoxin diets may have potential for slowing the spread of certain cancers expressing RAGE, a proposition that can readily be tested in rodent tumor models. Guidelines for achieving such diets have been published; low-fat foods of plant origin are typically low in glycotoxins, and the glycotoxin content of animal products and fatty plant products can be minimized by cooking at low heat (e.g. boiling, steaming). It may also be feasible to suppress the downstream signaling of RAGE in cancers by inhibiting the activity of NADPH oxidase, which appears to be the chief source of the oxidative stress triggered by RAGE; a role for NADPH oxidase in the aggressive growth of many cancers has been established. By mimicking the physiological antioxidant role of free bilirubin, the phycocyanobilin richly supplied by spirulina has the potential to down-regulate NADPH oxidase activity, and thereby impede RAGE signaling.

Keywords: Advanced glycation end products; RAGE; Glycotoxins; Cancer; Diet; Cooking; NADPH oxidase; Spirulina

A Role for RAGE Signaling in Cancer Aggressiveness

Recent studies have demonstrated that a wide range of cancers can express RAGE receptors (receptors for advanced glycation products), and that stimulation of these receptors renders the cancer more aggressive – more invasive and, in some cases, more proliferative [1-13]. Many of these cancers produce endogenous proteins – HMGB1 or S100A8 for example – that function to stimulate these receptors; hence, an autocrine loop can promote RAGE activation in these cancers [1,2,8,11,12,14]. In such cancers, knock-down of RAGE expression, or administration of a soluble RAGE receptor (which opposes RAGE signaling by acting as a decoy) or of a RAGE antagonist, can slow cancer growth and spread [1,5,7,9,10]. When chemotherapy kills cancer cells by necrosis, the resultant release of HMGB1 into the circulation may stimulate the growth of surviving cancer cells which express RAGE receptors [15].

Dietary Glycotoxin Content may Modulate the Growth of RAGE-Expressing Cancers

But it stands to reason that advanced glycation end-products (AGEs) of endogenous origin, or absorbed from the diet, should also promote the aggressiveness of such cancers. Indeed, as has recently been suggested, this may help to explain why cancers tend to progress more rapidly in diabetic patients, and why poorer diabetic control

(high HbA1c) is associated with poorer prognosis [13,16-22]. With respect to dietary impacts on RAGE activity, studies by Vlassara and colleagues have established that cooked foods often contain absorbable “glycotoxins” capable of activating RAGE [23-25]. These compounds typically arise from heat-catalyzed Maillard reactions which are initiated when an amine group, usually from protein or nucleic acid, forms a Schiff base with an aldehyde or ketone from a metabolite of a sugar or fatty acid. When a fatty acid metabolite is involved in this reaction – as when 4-hydroxynonenal reacts with an amine – the resulting product is called an “advanced lipoxidation end product” [26]. The term “glycotoxin” is a bit of a misnomer, as the highest content of these toxins is typically found in low-carbohydrate foods that are high in both fat and protein, and subjected to high heat – most notably, cooked flesh foods [24]. Remarkably, cooked diets rich in absorbable glycotoxins have been shown to promote oxidative stress, renal damage, atherosclerosis, metabolic syndrome, fatty liver disease, and cognitive dysfunction in rodents, to delay wound healing, and to shorten lifespan [27-32]. Clinically, ingestion of glycotoxin-rich diets boosts the level of AGEs measured in plasma, increases C-reactive protein, and impairs endothelial function [25,33,34]. In one provocative study, type 2 diabetics advised to decrease the glycotoxin content of their usual diet by using lower heat in food preparation for a 4 month period, achieved improvements in insulin sensitivity and markers of inflammation and oxidative stress [35]. Epidemiologically, habitual consumption of high-glycotoxin diets has been linked to increased risk for early cognitive decline, Alzheimer’s disease, and pancreatic cancer [36-39].

In light of these considerations, it is reasonable to predict that diets high in glycotoxins will tend to boost the growth and spread of cancers that express functional RAGE receptors. Conversely, low-glycotoxin diets would seem likely to slow the spread of such cancers to some degree. In RAGE-expressing cancers that also make their own RAGE agonists, a low-glycotoxin diet will evidently only partially dampen RAGE signaling, but this benefit still might be worthwhile in some cases. This hypothesis could be readily tested in nude mice bearing RAGE-expressing tumors; the impact of high-glycotoxin vs. low-glycotoxin diets on the growth and spread of such cancers could be assessed.

Plant-based raw food diets would be expected to be exceptionally low in glycotoxins. It is curious to note that such diets have been recommended for cancer control by various “alternative” practitioners whose views have usually been accorded little respect by orthodox medical scientists [40]. Of course, the dubious rationales typically given for use of raw food diets in cancer treatment (live enzymes!) tend to invite ridicule. Such diets also might be expected to slow the growth of some cancers by down-regulating systemic levels of free IGF-I and promoting good insulin sensitivity [41,42].

However, a low-glycotoxin diet need not be composed solely of raw foods. Uribarri and colleagues have measured the glycotoxin content of a wide range of common foods, prepared in various ways, and have summarized their findings in a monograph [24]. By and large, low-fat plant-derived foods are low in glycotoxins even if cooked. The highest glycotoxin content is typically seen in foods high in both fat and protein – meat, poultry, fish, cheese, nuts and nut butters, tofu – which have been subjected to high heat during preparation. When cooking such foods, their glycotoxin content can be mitigated to some degree by the use of lower-temperature cooking methods (boiling, poaching, stewing, steaming), shorter cooking times, and the addition of lemon juice or vinegar [24]. So the glycotoxin content of almost any characteristic diet can be reduced by appropriate modification of cooking techniques. Minimal glycotoxin content will be found in low-fat plant-based diets that are raw or cooked with moderate heat.

Alternate Strategies for Impeding RAGE Signaling in Cancer – Focus on Spirulina

As noted, low-glycotoxin diets could not be expected to abrogate RAGE signaling in cancers which make their own RAGE agonist proteins. Evidently, agents which either impede the interaction of RAGE receptors with their agonists, or which intervene downstream in RAGE signaling, could be useful in the control of RAGE-expressing cancers. In mice bearing RAGE-expressing human tumors, injection of soluble RAGE receptors, or of modified forms of the RAGE-agonist protein S100P which block RAGE activation, slowed cancer growth and metastasis [1,7].

With respect to intervening in RAGE signaling, a number of studies examining a range of cells types have concluded that activation of NADPH complexes is the chief source of the oxidative stress induced by RAGE activation; moreover, some of these studies demonstrate that inhibition of NADPH oxidase abrogates other key downstream effects of RAGE signaling [43-57]. The role of NADPH oxidase in RAGE signaling in cancer cells has so far received little study, although RAGE activation has been shown to potently activate NADPH oxidase in a human neuroblastoma cell line [58]. If indeed NADPH oxidase is a key mediator of the impact of RAGE signaling on cancer aggressiveness, then safe strategies for down-regulating NADPH

oxidase activation may prove useful for reducing the aggressiveness of cancers expressing RAGE. It should be noted that many cancers express constitutive NADPH oxidase activity, and that the oxidants generated by this complex often promote cancer proliferation and invasiveness, in part by reversibly inhibiting tyrosine phosphatases which oppose growth factor signaling; up-regulation of NF-kappaB and AP-1 signaling may also play a role in this regard [59-63].

In this regard, free bilirubin functions physiologically to inhibit certain NADPH [64-67]. Moreover, the biliverdin homolog phycocyanobilin, a major constituent of cyanobacteria such as the food spirulina, can be reduced intracellularly to the bilirubin homolog phycocyanorubin, which mimics bilirubin’s inhibitory impact on NADPH oxidase activity [68-70]. This effect seems likely to explain the versatile anti-inflammatory and antioxidant effects of orally administered spirulina or phycocyanin (the spirulina protein which contains phycocyanobilin as a chromophore) observed in rodent studies [68,71]. Although the effects of oral administration of spirulina or of phycocyanobilin on cancer growth have so far received little research attention, one recent study found that dietary spirulina slowed the growth of a human pancreatic adenocarcinoma implanted in nude mice by about 60% [72]. The impact of phycocyanobilin or its homolog biliverdin on RAGE signaling in cancer cells lines could readily be studied.

If indeed bilirubin and phycocyanobilin can suppress RAGE signaling, this will likely have implications for the prevention of diabetic complications, in which RAGE is believed to play a key mediating role [73]. In this regard, there is epidemiological evidence that diabetics who also have Gilbert syndrome – a genetic variant in which plasma levels of free bilirubin are constitutively elevated – are at greatly lower risk for developing diabetic complications (nephropathy, retinopathy, and coronary disease) [74]. Moreover, rodent studies demonstrate that NADPH oxidase overactivity is a key mediator of such complications [75-77]. And oral administration of either biliverdin or phycocyanobilin has been reported to prevent nephrosclerosis in diabetic mice [78,79]. Hence, examining the impact of these compounds on RAGE signaling should be a high priority.

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