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Human Risk of Diseases Associated with Red Meat Intake: Analysis of Current Theories and Proposed Role for Metabolic Incorporation of a Non-Human Sialic Acid

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Abstract

One of the most consistent epidemiological associations between diet and human disease risk is the impact of red meat consumption (beef, pork, and lamb, particularly in processed forms). While risk estimates vary, associations are reported with all-cause mortality, colorectal and other carcinomas, atherosclerotic cardiovascular disease, type II diabetes, and possibly other inflammatory processes. There are many proposed explanations for these associations, some long discussed in the literature. Attempts to explain the effects of red meat consumption have invoked various red meat-associated agents, including saturated fat, high salt intake, Trimethylamine–N-oxide (TMAO) generation by microbiota, and environmental pollutants contaminating red meat, none of which are specific for red meat. Even the frequently mentioned polycyclic aromatic carcinogens arising from high temperature cooking methods are not red meat specific, as these are also generated by grilling poultry or fish, as well as by other forms of cooking. The traditional explanations that appear to be more red meat specific invoke the impact of *N*-nitroso compounds, heme iron, and the potential of heme to catalyze endogenous nitrosation. However, heme can be denatured by cooking, high levels of plasma hemopexin will block its tissue delivery, and much higher amounts of heme likely originate from red blood cell breakdown *in vivo*. Therefore, red meat-derived heme could only contribute to colorectal carcinoma risk, via direct local effects. Also, none of these mechanisms explain the apparent human propensity i.e., other carnivores have not been reported at high risk for all these diseases. A more recently proposed hypothesis involves infectious agents in beef from specific dairy cattle as agents of colorectal cancer. We have also described another mechanistic explanation for the human propensity for risk of red-meat associated diseases that is consistent with most observations: metabolic incorporation of a non-human sialic acid *N*-glycolylneuraminic acid (Neu5Gc) into the tissues of red meat consumers and the subsequent interaction with inflammation-provoking antibodies against this "xenoautoantigen". Overall, we conclude that while multiple mechanisms are likely operative, many proposed theories to date are not specific for red meat, and that the viral and

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xenoautoantigen theories deserve further consideration. Importantly, there are potential non-toxic dietary antidotes, if the xenoautoantigen is indeed correct.

Keywords

Red meat; Disease Risk; Epidemiology; Inflammation; Carcinomas; Atherosclerosis; Diabetes

1.0. Introduction

1.1. Background Information and Scope of this Review

A recent World Health Organization-International Agency for Research on Cancer (WHO-IARC) monograph summary emphasized the carcinogenicity of consumption of red meat and processed red meat (Bouvard et al., 2015). By definition, red meat refers to all types of mammalian muscle meat, such as beef, veal, pork, lamb, mutton, horse, and goat. The term “processed meat” refers to meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavor or improve preservation (Bouvard et al., 2015). Long-term consumption of red meat (and even more clearly processed meat) is associated with significant increase in all-cause mortality (Larsson and Orsini, 2014; Pan et al., 2012; Sinha et al., 2009a), likely contributing to the current epidemic of cardiovascular diseases (Micha et al., 2010; Micha et al., 2012), type 2 diabetes (Pan et al., 2011; Micha et al., 2010; Aune et al., 2009), and to increased risk of certain kinds of adenocarcinomas (cancers of mucosal epithelial origin), particularly colorectal cancer (Aune et al., 2013; Cross et al., 2010; Cross and Sinha, 2004). Aggravation of age-dependent macular degeneration (Ersoy et al., 2014; Chong et al., 2009) and of rheumatoid arthritis (Benito-Garcia et al., 2007; Choi, 2004; Oliver and Silman, 2006) have also been reported as being associated with red meat consumption. Corroborating with these facts, Seventh-Day Adventists consuming a vegetarian diet are at lower risks of cancer, diabetes mellitus, hypertension, and arthritis when compared to non-vegetarians from the same community (Fraser, 1999; Phillips et al., 1980). In fact, follow up studies show that a lifestyle pattern that includes a very low meat intake is associated with greater longevity (Singh et al., 2003; Singh et al., 2003).

There are many proposed mechanisms for the disease-promoting effects of red meat. These include DNA damage due to N-nitroso compounds (NOCs) and mutagens generation by high temperature grilling; high dietary intake of salt and saturated fat; pro-oxidant effects of heme and iron; and production of Trimethylamine–N-oxide (TMAO) by the gut microbiome. Here, we summarize and compare the major mechanistic hypotheses proposed to date. We will also outline a new theory regarding a virus present in beef, and then discuss a recent “xenoglycan” theory, which seems most consistent with available data, and is the one that could best explain the apparent human propensity of the risk.

1.2. Red Meat Consumption in Human Evolution and Reproductive Success

The evolution of the human species was much influenced by dietary changes, especially during the last two million years (Milton, 2003; Ye and Gu, 2011). With the improvement of stone tools, sustained running ability, scavenging and hunting, hominin ancestors in the genus *Homo* (Antón et al., 2014) began to access more animal-derived foods during the Pliocene period (Bramble and Lieberman, 2004; Domínguez-Rodrigo et al., 2005; Schoeninger, 2012). Diverging from other primates and earlier hominins whose diets mainly consisted of fruits and plants, the genus *Homo* appears to have transitioned to one rich in animal sources (particularly large game animals, i.e. "red meats") which are energy dense and easily digestible foods that can provide all essential amino acids and micronutrients (Millward, 1999). Some writers have proposed that this dietary transition supported evolutionary selection for significant physiologic and anatomic changes in *Homo*, such as increase of the brain size and reduced gut volume (Aiello and Wheeler, 1995; Mann, 2000; Milton, 2003). In addition, emerging evidence indicates that human dietary habits contribute to microbiome diversity and its effects on human health (He et al., 2013b).

Although the introduction of animal products into ancestral human diet had many benefits, large-scale red meat consumption by modern society has contributed to epidemics of diseases such as zoonotic infections (Diaz-Sanchez et al., 2013), cardiovascular diseases and cancer, while also contributing to major environmental degradation, and even to global climate disruption (McMichael et al., 2007; Eshel et al., 2014; Springmann et al., 2016). Here, we focus on the impact of red meat consumption on current human diseases.

2. Existing Theories to Explain Increased Disease Risks of Red Meat Consumption

2.1. Theories That Are Not Specific to Red Meat

2.1.1. Carcinogenic compounds produced by cooking methods—Known mutagens found in red meat are heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), which are generated by cooking meat at high temperatures and for long durations (Skog et al., 1998; Knize et al., 1999; Turesky, 2007; Turesky and Le Marchand, 2011). In fact, PAHs are generated at various concentrations by a variety of cooking methods, including baking and grilling (Phillips, 1999; Turesky, 2007; Rose et al., 2015). Similar levels of PAHs are also generated in grilling chicken or fish (Sugimura et al., 2004; Yano et al., 1988), making dietary exposure of non-vegetarian humans to PAHs essentially unavoidable. In addition, PAHs are also generated during smoking of processed foods (Olatunji et al., 2014).

The formation of HCAs is induced by the endogenous reaction between creatine and amino acids or carbohydrates when muscle meat is cooked at high temperature (>150°C) (Jägerstad et al., 1991). Although the most common HCAs found in human diets have been shown to be carcinogenic in rodents (Shirai et al., 1995; Ito et al., 1997), epidemiologic studies have produced inconsistent data regarding associations of HCAs with human cancer (Augustsson et al., 1999; Joshi et al., 2015). In fact, while many authors have found a positive association between HCA's and breast, prostate, lung, and renal cancer (Ferrucci et al., 2009; Cross et al., 2005; Tasevska et al., 2009; Daniel et al., 2012), a recent prospective analysis revealed that intake of these meat-derived mutagens was not significantly associated with colorectal cancer risk (Le et al., 2016). Although studies have shown carcinogenic effects of both HCA and PAH mutagens in animal models, these experiments typically used doses higher than usual human exposure (Ohgaki et al., 1986; Magee, 1989). Regardless, compounds derived from metabolism of dietary aromatic amines have been suggested as biomarkers, to monitor carcinogenic effects in humans (Guo et al., 2016; Turesky and Le Marchand, 2011).

While HCAs and PAHs are also present in processed or high temperature cooked fish, grilled or fried chicken actually contain higher levels of heterocyclic amines than does beef meat (Heddle et al., 2001). However, consumption of poultry or fish are generally not associated with cancer risk (Wiseman, 2008; Norat et al., 2002; Larsson and Wolk, 2006; Huxley et al., 2009; Cross et al., 2007; English et al., 2004). Based on all these facts, it seems reasonable to suggest that, while these mutagens may indeed be carcinogenic in humans, they do not provide a specific explanation for the carcinogenic effects of either processed or non-processed red meat *per se*.

2.1.2. Environmental Pollutants—Red meat also contains contaminating inorganic toxins, such as arsenic (As), cadmium (Cd), mercury (Hg), lead (Pb), pesticides among many others (Domingo and Nadal, 2016). These toxins can be derived from cooking processes, or from industrial sources during meat processing. These compounds are also found in comparable amounts in many dietary products, including fish, poultry, and vegetables, and may represent a general risk for human health. But again, they cannot explain the increased risk of disease specifically associated with red meat.

2.1.3. High Content of Saturated Fat—The fat content of red meat varies depending on animal species, age, sex, breed, feed, and the cut of the meat. Some have proposed that high intake of saturated fat (for which red meats can be a major source) contributes to obesity and general inflammation, insulin resistance, and intestinal dysbiosis (Calle and Kaaks, 2004; Schulz et al., 2014). In addition, oxidation of red meat derived fat leads to the formation of oxyesterols and aldehydes that may alter transforming growth factor beta (TGF-β)-mediated signal and cell proliferation (Biasi et al., 2008). Although all these factors together might contribute to the carcinogenic properties of red meat, they are not specific to red meat, as high content of saturated fats occur in other sources such as whole milk, cheeses, eggs and even certain vegetable sources e.g., coconut and palm oils. Moreover, recent epidemiological studies show inconsistent associations between saturated fat intake and the risk of prostate and breast carcinomas (Pelser et al., 2013; Xia et al., 2015).

2.1.4. High Salt Content of Processed Meats—Excessive salt intake can contribute to increased blood pressure (Weinberger, 1996; Weinberger, 2006) and thus secondarily to the development of cardiovascular and renal disease (Whelton et al., 2012; He et al., 2013a; Kotchen et al., 2013; Mozaffarian et al., 2014). High salt content would be particularly prominent in some kinds of processed meats. Highly salted foods have also been associated with some kinds of cancer risk (Tsugane et al., 2004). However, there are many alternative sources of salt in the diet, and there is no evidence that red meat represents a primary or even major culprit.

2.1.5. Production of Trimethylamine–*N*-oxide (TMAO) by the Gut Microbiome—Recent studies revealed the role of microbiota in generating compounds that affect the human host (Tremaroli and Bäckhed, 2012). Trimethylamine–N-oxide (TMAO) had been shown to arise from bacterial metabolism of choline or L-carnitine via an intermediate, trimethylamine (TMA), and subsequent hepatic oxidation to TMAO via flavin monooxygenase 3 (FMO3) (Wang et al., 2011; Koeth et al., 2013). Elevated levels of TMAO in the plasma have also been associated with increased risk of cardiovascular disease (CVD) (Wang et al., 2011; Koeth et al., 2013; Tang et al., 2013). The proposed mechanism involves inhibition of reverse cholesterol transport from the macrophages promoting foam cell formation in atherosclerosis lesion, as well as the alteration of bile acids pool size (Koeth et al., 2013). Recent studies also showed that TMAO has a direct effect on platelet function *in vitro* and *in vivo* – leading to enhanced thrombosis risk (Zhu et al., 2016) and that TMAO directly promotes enhanced arterial endothelial cell inflammatory gene expression changes *in vivo* (Seldin et al., 2016). Positive associations of plasma TMAO levels and colorectal cancer were recently reported as well (Bae et al., 2014; Xu et al., 2015). High plasma levels of carnitine were also reported to be significantly associated with incident risks for myocardial infarction, stroke, or death over a follow-up period of 3 years, but only in subjects with concurrently high TMAO levels (Koeth et al., 2013).

However, although the TMAO precursor L-carnitine is indeed found at higher levels in red meat (~100 mg in 100 g of beef) than in fish or chicken (~5 mg in 100 g codfish or chicken) (Traber et al., 1999), the much more abundant TMAO precursor choline is an essential nutrient present in most animal and some plant products; e.g., in egg yolk (250 mg in 100 g), meats and fish (~75 mg in 100 g), whole grains (~70 mg in 100 g), vegetable and fruits (~ 25mg in 100 g) (Patterson et al., 2008). Furthermore, some fish are significantly rich in TMAO (around 20 to 120 mg TMAO in 100 g) (Seibel and Walsh, 2002). Adults eating mixed diets that include red meat and other animal products ingest about 60–180 mg of carnitine per day (Rebouche, 2004), and about 300–400 mg of choline per day (Chiuve et al., 2007; Wallace and Fulgoni, 2016).

Meanwhile, supplementation with carnitine (approximately 3–6 g/day) has been reported to have potential benefits in some studies e.g., it has been claimed to improve mental dysfunction in older adults with early Alzheimer's disease (Montgomery et al., 2003); to improve walking in patients with claudication (Brass et al., 2013); and to relieve nerve pain associated with diabetic neuropathy (Sima et al., 2005). Moreover, combinations of intravenous loading and oral ingestion of L-carnitine seems to have the potential to reduce short-term mortality following acute myocardial infarction (Tarantini et al., 2006). However, recent meta-analysis studies revealed conflicting effects for the secondary prevention of cardiovascular disease (CVD) by L-carnitine administration (DiNicolantonio et al., 2013; Shang et al., 2014).

Normal renal function maintains a narrow L-carnitine concentration in the circulation in the range of 40–60 μmol/L (Rebouche, 2004). Chronic kidney disease (CKD) patients who undergo hemodialysis are at risk for secondary carnitine deficiency because hemodialysis removes carnitine from the blood. While CVD is known as one of the major cause of death in CKD patients, the association between plasma TMAO level and CVD risk in CKD is debated (Kim et al., 2016; Stubbs et al., 2016; Tang et al., 2015). Overall, while TMAO derived from endogenous and exogenous sources of choline and carnitine may contribute to increased atherosclerotic vascular disease, red meat does not appear to be a major source of this compound, relative to other foods.

2.2. Theories That Appear More Specific to Red Meat

2.2.1. N-Nitroso-Compounds (NOCs) as Mutagens—One of the proposed mechanisms for the cancer-promoting effects of red meat is DNA damage due to the conversion of nitrates and nitrites in processed meat into NOCs, multi-site carcinogens that can proceed to form covalent adducts with DNA bases and potentially contribute to a wide range of malignancies (Mirvish, 1995; Bingham et al., 1996; Knekt et al., 1999; Parnaud et al., 2000; Santarelli et al., 2008; Kim et al., 2013; Dellavalle et al., 2014; Catsburg et al., 2014). *In vitro* exposure of human colorectal cells to NOCs can indeed induce DNA alkylation (Povey et al., 2002) and consequent mutation in genes involved in DNA damage control and in cell proliferation and differentiation such as *K*-RAS (Hebels et al., 2009; Hebels et al., 2010). In addition, endogenous formation of NOCs can be catalyzed by red meat-derived heme iron (Cross et al., 2002; Cross et al., 2003) and promote carcinogenesis in rats fed with low calcium diets. Thus, calcium present at physiologic concentrations is hypothesized to trap heme iron and thereby inhibit nitrosation as discussed below (Pierre et al., 2003).

In fact, human volunteers fed with diets rich in red meat have shown increased levels of fecal NOCs and NOC-specific DNA adducts in exfoliated colonic cells when compared to volunteers fed vegetarian diets (Lewin et al., 2006). Corroborating these data, a recent study has shown that high red meat intake is associated with increased levels of the O6-Methyl-2′-deoxyguanosine mutagenic adduct in rectal epithelial cells and that a concomitant intake of fiber-derived products, such as butyrylated high-amylose, prevented this red meat-induced adduct formation (Le Leu et al., 2015). Gastrointestinal diseases, such as inflammatory bowel disease (IBD), can also induce the production of NOCs and thus potentially increase the risk of cancer (de Kok et al., 2005).

While studies have shown a positive dose response in the levels of apparent total NOCs in the fecal samples of human volunteers given different quantities of red meat (Hughes et al., 2001; Bingham et al., 2002), many epidemiological studies found modest or no association between dietary NOCs and several types of cancer, including esophagus (Keszei et al., 2013; González et al., 2006), stomach (Keszei et al., 2013; Song et al., 2015), colorectal (Knekt et al., 1999; Dellavalle et al., 2014), and bladder cancer (Catsburg et al., 2014; Ferrucci et al., 2010; Zeegers et al., 2006). Of course, the absence of a biomarker for NOC long-term exposure as well as methods for distinguishing endogenous nitrosation from dietary intake of nitrate/nitrite limit our ability to validate the proposed association of NOC exposure with the risk of colorectal cancer. Thus, studies have also examined the role of nitrate and nitrite in relation to cancer incidence (Cross et al., 2010; Dubrow et al., 2010).

2.2.2. Oxidative and Chemical Transformative Properties of Heme Iron—The iron-carrying pigment heme is non-covalently associated with hemoglobin and myoglobin and gives red meat its distinctive color (Balla et al., 2007; Nagy et al., 2010; Livingston and Brown, 1981; Suman and Joseph, 2013). In light of the cytotoxic and potentially DNAdamaging oxidative properties of heme iron (Sesink et al., 2000), various epidemiological analyses have studied the association between intake of red meat-derived heme and development of carcinoma risk and found associations between these processes (Tasevska et al., 2009; Sinha et al., 2009b; Jakszyn et al., 2013), with the strongest association being found with colorectal cancer risk (Suman and Joseph, 2013; Bastide et al., 2011; Kim et al., 2013; Sesink et al., 1999). In fact, studies in rodents showed that a diet rich in heme increases proliferation and incidence of colon tumors, possibly due to increased levels of peroxyl radicals (Pierre et al., 2003). Yet another study showed a correlation between different levels of dietary heme and the promotion of colon carcinogenesis in rats (Pierre et al., 2004). More recently, additional *in vivo* studies showed that heme-induced oxidative stress and generation of free radicals can cause hyperproliferation and hyperplasia of mouse colon cells that eventually develop into colorectal cancer (IJssennagger et al., 2012b). Of note, heme is also bioavailable at high levels in the colon – more than 90% of heme reaches the colon since it is poorly absorbed in the small intestine (Young et al., 1989).

Nonetheless, it is very likely that any effects of dietary heme are limited to the gastrointestinal tract. This is because the vast stoichiometric excess of the high affinity heme scavenger protein hemopexin that is present in the plasma (Schaer et al., 2013) would quickly sequester any heme that enters the blood stream from the gut. In addition, heme derivatives released locally from damaged red blood cells within the abnormal neovasculature of cancers (Yin et al., 2015) and atheromas (Balla et al., 2007) seem much more likely to serve as the main sources of heme oxidant compounds in tissues throughout the body. Indeed, it is reported that the interior of advanced atheromatous lesions functions as a pro-oxidant environment in which erythrocytes breakdown and release both heme and iron to promote further lipid oxidation, thereby amplifying endothelial cell cytotoxicity (Balla et al., 1991; Balla et al., 1993; Belcher et al., 1993; Nagy et al., 2010). Likewise, neovascularization and hemorrhage are common features of malignant tumors and hemoglobin derived from extravasated RBC deposits heme iron within the tumor (Cermak et al., 1993). Overall, the relative contribution of dietary heme to disease risk via direct toxicity should be minimal, except by direct exposure in the gastrointestinal tract.

Dietary heme can also provoke changes in the gut microbiota that favor the hyperproliferation of colonic enterocytes and disturb the mucus barrier in the colon epithelia, amplifying the potential carcinogenic properties (IJssennagger et al., 2012b; IJssennagger et al., 2012a; Ijssennagger et al., 2015). Additional studies show that red meat-derived heme can promote fat peroxidation and generation of the carcinogenic compounds malondialdehyde, 4-hydroxyl-noneal and NOCs, providing plausible mechanisms underlying the role of heme iron in the promotion of colon cancer by processed red meat (Pierre et al., 2013; Bastide et al., 2015). The authors propose that this is a red meat-specific mechanism for the promotion of colorectal cancer since dietary intake of “white meat” as chicken did not induce the generation of the same carcinogenic compounds (Cross et al., 2003; Bastide et al., 2011).

One confounding issue is that exposure of heme-containing proteins to temperatures as high as 90°C leads to denaturation and drastic reduction of its pro-oxidative properties (Bou et al., 2008; Bou et al., 2010). An early study claimed that heating had no apparent effect on the heme content in fecal samples, but this was measured by a color detection test that is at best semi-quantitative (Schwartz and Ellefson, 1985). In fact, since many cuisines tend to cook their meat at high temperatures (turning the color of red meat to brown) much of the ingested heme may already be denatured prior to its consumption (Knöbel et al., 2007; Pierre et al., 2010).

Elemental iron released from heme is also considered toxic (Belcher et al., 2010). However, while subjects with hereditary hemochromatosis or acquired systemic iron overload are known to have a higher risk of developing colorectal (Shaheen et al., 2003) and liver cancer, the risk for the latter is specifically associated with chronic hepatocyte damage progressing to cirrhosis (Fonseca-Nunes et al., 2014). Such patients also do not show an obviously overall increased incidence of other tumors (Vinchi et al., 2014). Last but not least, red meat is also defined by its heme-derived red color, making heme intake already a direct proxy for overall red meat intake. Considering all these facts we can conclude that while dietary heme and iron from red meat may contribute to colorectal (and possibly esophageal) carcinoma risk, it plays a minor role if any in other cancers. Moreover, since patients with high iron burden do not exhibit an obviously increased incidence of atherosclerosis (Vinchi et al., 2014), it is also unlikely that red meat-derived iron aggravates the development of atherosclerosis.

2.3. Theories that Appear Specific to Red Meat, and Appear to be Human-specific

2.3.1. Species-specific Infectious Agent Found in Dairy Cattle Red Meat—The classic studies of zur Hausen (Boshart et al., 1984; Schwarz et al., 1985) eventually prevailed against the widespread skepticism of an etiologic role of viruses in human cancer development by showing that human cervical cancer is primarily caused by human papilloma virus infections, with the resulting introduction of effective vaccines and the awarding of the Nobel Prize in 2008 (zur Hausen, 2009). Zur Hausen has now suggested the possibility that consumption of red meat specifically derived from the species *Bos taurus* may best explain the global patterns of colorectal cancer risk (Zur Hausen, 2012). He has hypothesized that the intriguing epidemiological variance in the incidence of colorectal cancer between countries that consume high amounts of red meat can be explained by the fact that red meat-derived products from mammals of different species across the world are associated with greatly differing levels of contaminating cancer-causing viruses (zur Hausen and de Villiers, 2015). Thus, countries like Mongolia and Bolivia consume high levels of red meat derived from Yaks (*Bos grunniens* and *Bos mutus*) and several sub-species of Taurines (*Bos taurus turano-mongolicus*) (Maytsetseg, 2006) but nevertheless exhibit relatively low incidence rates of colorectal cancer. In contrast, the red meat and dairy products in regions with high risk for colorectal cancer are derived mostly from cattle of *Bos taurus* species (Zur Hausen, 2012).

Based on these epidemiological observations, the authors propose that *Bos taurus* could carry and transmit a factor involved in colon cancer etiology (Zur Hausen, 2012). Although not yet formally identified, they propose that single-stranded circular DNAs isolated from milk and serum of healthy cattle (Funk et al., 2014; Lamberto et al., 2014) might signal the presence of such factors. The authors postulate that these species-specific infectious agents could be potentially carcinogenic when transmitted to humans and act synergistically with compounds originated during processing or cooking of beef (zur Hausen and de Villiers, 2015). In fact, there is still no experimental evidence showing a direct correlation of these infectious agents with development of colorectal cancer. Nonetheless, this new hypothesis deserves more attention.

2.3.2. Human-Specific Mechanism Involving a Non-human glycan in Red Meat

2.3.2.1. Historical Background and Discovery: Besides being enriched in saturated fat and heme iron, red meats are also enriched (beef > pork & lamb) in glycans containing a particular variant of sialic acid called *N*-glycolylneuraminic acid (Neu5Gc) (Tangvoranuntakul et al., 2003; Samraj et al., 2014b) Samraj et al., 2014, #53932}. This Neu5Gc molecule is not naturally found in human tissues, due to a specific exon deletion mutation that occurred around 2–3 million years ago in the germ line of one of our hominin ancestors. The affected gene encodes the enzyme, cytidine monophospho-*N*-acetylneuraminic acid hydroxylase (CMAH), which is responsible for the generation of Neu5Gc from the precursor sialic acid *N*-acetylneuraminic acid (Neu5Ac) (Figure 1), (Chou et al., 1998; Chou et al., 2002; Hayakawa et al., 2006; Hayakawa et al., 2006), and the pseudogene state is now fixed in the genomes of all humans. Despite the inability of humans to produce Neu5Gc endogenously, this non-human isoform of sialic acid can be detected in small amounts in human epithelial and endothelial cells (Tangvoranuntakul et al., 2003) and also in human carcinomas (Malykh et al., 2001a; Samraj et al., 2014a) (Figure 1). Mice engineered to have a human-like mutation in the *Cmah* gene, which encodes the murine enzyme that generates Neu5Gc, show no evidence of any alternate pathway for Neu5Gc biosynthesis (Hedlund et al., 2007). Thus, metabolic incorporation via dietary consumption is the only possible source of the Neu5Gc that is found in human tissues.

In keeping with this conclusion, human volunteer studies (Tangvoranuntakul et al., 2003) suggested that humans can metabolically incorporate and express Neu5Gc into cell surface glycoconjugates. Feeding of human epithelial cells with Neu5Gc leads to its incorporation (Bardor et al., 2005), with enrichment in mucins (Inoue et al., 2010). However, further studies are required to understand specific glycoconjugates on which Neu5Gc can be found in human tissues, and the nature of the associated underlying glycan structures. Regardless, taken together with the metabolic incorporation of Neu5Gc, Neu5Gc-containing glycans appear to act as “xenoautoantigens” that can be targeted by naturally circulating anti-Neu5Gc “xenoautoantibodies”, leading to an inflammatory process termed “xenosialitis” (Hedlund et al., 2008; Padler-Karavani et al., 2011; Pearce et al., 2014).

Xenosialitis can potentially affect both cancer initiation and progression. In fact, the tumor-promoting properties of auto-reactive antibodies are well described in other systems (Andreu et al., 2010; Wu et al., 2013). Indeed, such a process could be demonstrated in human-like *Cmah* null mice fed with Neu5Gc and infused with anti-Neu5Gc antibodies for other null mice that had been preimmunized (Samraj et al., 2014b). Moreover, when such Neu5Gc-fed mice were immunized to express anti-Neu5Gc antibodies and followed for over one year on a Neu5Gc-rich diet, they showed a markedly increased risk of adenoma-to-carcinoma progression in the liver, in association with Neu5Gc incorporation into the tumors (Samraj et al., 2014b) (see further discussion below). Taken together, these data indicate that the inflammatory xenosialitis triggered by red meat-derived Neu5Gc and anti-Neu5Gc antibodies represents a mechanism that is unique to humans and could be involved both in carcinogenesis and in promoting carcinoma progression. Overall, as argued below, we suggest that red meat-derived Neu5Gc-induced xenosialitis may be the only mechanism that provides an internally consistent explanation for human-specific aggravation of carcinoma risk associated with red meat consumption.

2.3.2.2. Complexities and Diversity of Human Anti-Neu5Gc Antibodies: Although their target was then unknown, anti-Neu5Gc antibodies were actually described almost a century ago, when Hanganutziu and Deicher observed that serum from patients that received animal antisera during therapy, could agglutinate animal red blood cells (Hanganutziu, 1924; Hanganutziu, 1924; Beer, 1936). Many years later, similar antibodies were also found in patients with autoimmune diseases, such as rheumatoid arthritis and Kawasaki disease and various types of cancer (Nishimaki et al., 1978a; Nishimaki et al., 1978b; Arita et al., 1982; Ikuta et al., 1982; Hokke et al., 1990; Gathuru et al., 1989; Higashihara et al., 1991). Subsequent studies then showed that these antibodies were directed against Neu5Gc and could target carcinoma antigens such as the monosialoganglioside (Neu5Gc)GM3 (Higashi et al., 1977; Asaoka et al., 1992; Malykh et al., 2001b). Because (Neu5Gc)GM3 was a well-known target for anti-Neu5Gc antibodies, it was used as capture antigen to detect anti-Neu5Gc antibodies in human individuals. ELISA assays using (Neu5Gc)GM3 revealed that less than (<1–2%) of total IgG were anti-Neu5Gc antibodies in healthy subjects (Merrick et al., 1978; Morito et al., 1982; Higashihara et al., 1991).

Sialic acids like Neu5Gc are terminal monosaccharides on both glycolipids and glycoproteins, generally attached to underlying glycans in an α2-3-linkage to Gal, an α2-6-linkage to Gal and GalNAc, or an α2-8 linkage to another sialic acid. Additionally, monosaccharides attached to Neu5Gc can also be part of the epitope recognized. Overall, there are hundreds of possible alternative Neu5Gc-containing epitopes. Thus, the use of (Neu5Gc)GM3 as the only target to detect anti-Neu5Gc led, for a long time, to the under-detection of the presence and diversity of these human antibodies. Using a more precise method that included glycans with α2-3 or α2-6-linkage to different underlying structures, we demonstrated that human anti-Neu5Gc antibodies are of broad and variable specificities (Padler-Karavani et al., 2008). In fact, while some individuals express high levels of anti-Neu5Gc IgGs that are reactive to most of the glycans structures tested, others showed no reactivity whatsoever. Comparisons of the presence of IgG, IgM or IgA subclasses of anti-Neu5Gc antibodies revealed a broad diversity between the individuals tested. In addition, this study showed that anti-Neu5Gc antibodies could be found in higher levels than some xenoreactive and natural blood group antibodies in some individuals (Padler-Karavani et al., 2008).

Precise serum analysis for anti-Neu5Gc antibodies requires the use of glycan arrays with multiple alternative molecular structures as capture antigens. However, not all possible structures are available for inclusion in such arrays, and there are only limited data available about the levels of specific anti-Neu5Gc antibodies in patients with inflammatory diseases related to red meat consumption. Also, there are no studies showing a correlation between the levels of anti-Neu5Gc antibodies and amounts of red meat consumed.

2.3.2.3. Role of Neu5Gc: Anti-Neu5Gc Antibody Interaction in Carcinoma Risk: Epidemiological studies have demonstrated that high consumption of red meat correlates with increased levels of a variety of inflammatory markers measured throughout the body (Azadbakht and Esmaillzadeh, 2009; van Woudenbergh et al., 2012; Ley et al., 2014; Montonen et al., 2013; Schulze et al., 2005). However, the precise mechanisms involved in the induction of this systemic response are not well understood, beyond the potential pro-inflammatory effects of saturated fat. We have found that red meat-derived Neu5Gc can be incorporated into the glycoconjugates present in various human tissues where they could encounter circulating anti-Neu5Gc antibodies. We have also demonstrated that Neu5Gc incorporation and interaction with anti-Neu5Gc antibodies contributes towards one of the hallmarks of cancer, tumor-promoting inflammation (Samraj et al., 2014b; Pearce et al., 2014).

Previous studies from our group demonstrated that congenic *Cmah*-wild-type murine tumors show accelerated growth in syngeneic *Cmah−/−* mice, after induction of anti-Neu5Gc antibodies (Hedlund et al., 2008). In addition, when *Cmah−/−* mice expressing anti-Neu5Gc antibodies were fed with a diet rich in Neu5Gc, high levels of plasma inflammatory markers were detected, which was associated with a marked increase in the incidence of hepatocellular carcinomas (Samraj et al., 2014b). These results suggest that anti-Neu5Gc antibodies have tumor-stimulating properties through induction of inflammatory processes. Importantly, we noted that the *in vivo* expression of diet-derived Neu5Gc in multiple epithelial cell types may serve to explain the well-documented association of red meat-associated increased risk of carcinomas in diverse epithelial tissues, such as the prostate (Amin et al., 2008; Bosetti et al., 2004; Hori et al., 2011; Kolonel, 2001), breast (Blackburn and Wang, 2007; Cho et al., 2006; Kabat et al., 2009; Linos et al., 2008; Pierce et al., 2007; Pierce, 2009; Taylor et al., 2007; Xia et al., 2015), pancreas (Larsson and Wolk, 2012; Rohrmann et al., 2013); Rohrmann et al., 2013, #82827}, esophagus (Jakszyn et al., 2013), and ovary (Kolahdooz et al., 2010; Wallin et al., 2011).

2.3.2.4. Potential Role of Neu5Gc/anti-Neu5Gc Antibodies in Aggravation of Atherosclerosis: Atherosclerotic CVD is the primary cause of myocardial infarction, ischemic heart failure, strokes, and peripheral vascular disease in humans (Grundy et al., 1999), but apparently not in other mammals (Varki et al., 2009). Indeed, while heart disease is common in great apes like chimpanzees, it results from processes that are distinct from those operating in humans (Varki et al., 2009). Chimpanzee “heart attacks” arise from arrhythmias due to diffuse interstitial myocardial fibrosis of unknown cause. In contrast, most human heart disease results from coronary artery atherosclerosis, which occludes blood supply. Accordingly, human-like myocardial infarction is very rare in the closely related great apes in captivity, despite the fact that apes have many of the major risk factors, including high LDL levels, sedentary conditions, stress, hypertension etc. (Varki et al., 2009).

Consumption of red meats and processed red meats is clearly associated with increased risk of CVD (Micha et al., 2012). As discussed earlier, current explanations include the impact of cholesterol and saturated fat (Swirski and Nahrendorf, 2013), conversion of choline and carnitine into proatherogenic TMAO (Wang et al., 2011; Wang et al., 2011; Koeth et al., 2013; Tang et al., 2013), and oxidant damage due to heme iron (Balla et al., 1991; Balla et al., 1993; Belcher et al., 1993; Nagy et al., 2010). Notably, some of these TMAO studies in mice used a dose of far higher L-carnitine dose – approximately 1700 mg/kg/day (Koeth et al., 2013) – than that typically encountered in a red meat-consuming human. Moreover, another study with doses of 87 or 352 mg/kg showed that TMAO actually had a protective effect against atherosclerosis (Collins et al., 2016). Regardless, as discussed earlier, most of these mechanisms are not specific to red meat, and dietary heme would be neutralized by hemopexin upon entering the circulation, and before it could reach the vasculature.

In contrast to these etiologic hypotheses, the process of xenosialitis can help both explain the association of red meat consumption with atherosclerosis and the human specificity of the risk. Thus, earlier studies from our group demonstrated that red meat-derived Neu5Gc can be detected in endothelium overlying atherosclerotic plaques as well as in subendothelial regions (Pham et al., 2009). In addition, incubation of human endothelial cells expressing Neu5Gc due to feeding, with human serum containing anti-Neu5Gc antibodies led to IgG and complement deposition. This in turn resulted in endothelial activation, selectin expression and increased cytokine secretion (Pham et al., 2009), the types of events common in early stages of atherogenesis. Importantly, these effects were blocked by Neu5Gc-alpha-methyl glycoside, a specific competitor of anti-Neu5Gc antibodies. Neu5Gc was also detected in the endothelium of *Cmah*−/− mice fed with a Neu5Gc-enriched diet (Banda et al., 2012). Overall, the data are consistent with the theory that Neu5Gc incorporation from red meat can induce xenosialitis in vascular endothelium, and may contribute to red meat-induced aggravation of atherosclerosis and CVD. Despite all this circumstantial evidence, further research is needed to confirm that this process is actually pro-atherogenic *in vivo* and thus a major causative factor in the development of CVD in humans.

2.3.2.6. Potential Role of Neu5Gc-induced Xenosialitis in Other Diseases Aggravated by Red Meat: While a strong epidemiological association between red meat intake and adult onset (type 2) diabetes (Pan et al., 2011; Micha et al., 2010; Aune et al., 2009) has been reported, the underlying mechanisms are less clear. However, it is notable that systemic inflammation aggravates type 2 diabetes via a variety of etiologic mechanisms (McNelis and Olefsky, 2014).

ELISA assays to detect anti-Neu5Gc antibodies were confirmed by sialoglycan microarrays (Padler-Karavani et al., 2013), and recently applied to kidney transplant recipients associated with rabbit-generated Neu5Gc-containing anti-thymocyte globulin therapy (Couvrat-Desvergnes et al., 2015). In addition, preliminary evidence suggests that Neu5Gc incorporation occurs at sites of tissue damage in muscular dystrophy (Chandrasekharan et al., 2010). Associations of red meat consumption with rheumatoid arthritis occurrence and progression have also been suggested (Grant, 2000; Grant, 2000; Choi, 2004; Oliver and Silman, 2006; Benito-Garcia et al., 2007). Although the association between xenosialitis and pathogenesis of these diseases is not well studied, it is reasonable to suggest that the inflammation induced by red meat-derived Neu5Gc and anti-Neu5Gc antibodies might aggravate some events during the progression of diseases. Studies have even shown that a diet restricted in red meat can reduce rates of recurrence in patients diagnosed with early stage colon cancer (Meyerhardt et al., 2007), perhaps by minimizing further inflammation that could stimulate growth of micrometastases (Weinberg, 2014).

The percentage of Neu5Gc versus Neu5Ac varies in red meats (beef > pork & lamb) (Samraj et al., 2014b), while being essentially absent in poultry and in fish steaks of various kinds. Neu5Gc is also present in significant amounts in goat and sheep milk (unlike cow milk), as well as in certain fish egg products such as caviar (Samraj et al., 2014b). However, since only small amounts of goat cheese and caviar are usually consumed in meals, it is unlikely that they represent important sources of dietary Neu5Gc. Also, what is called "cow's milk" in some countries may be actually derived from other species such as buffalo, which have not been studied. Further studies of the distribution of Neu5Gc in various products of animal origin, as well as the bioavailability for metabolic incorporation are needed.

3. Potential Approaches to Addressing the Human-Specific Red Meat Risk

The most obvious approach to reduce the risk of diseases associated with red meat is to reduce or completely avoid ingestion of beef, pork, or lamb. However, especially for young healthy females of childbearing age, this would represent a loss of high quality protein as well as important micronutrients such as iron, zinc and vitamins, all of which are enriched in red meat (Mann, 2000). Also, despite increasing evidence and information regarding elevated disease risk resulting from red meat consumption, suggestions that everyone in every society should completely stop eating traditional red meat-based diets and specialty foods are highly unlikely to succeed. Instead, approaches to reduce the risks associated with this dietary habit are more reasonable. Such approaches that have been suggested to date that are designed to reduce the harmful effects of red meat include: A moderate increase in dietary intake of calcium, which could "trap" heme iron and potentially reduce endogenous fat peroxidation (Pierre et al., 2013; Allam et al., 2011; Santarelli et al., 2013) and a diet rich in fiber and/or fiber-derived products could reduce NOC-induced adducts in colonic cells (Le Leu et al., 2015). Although both approaches showed promising effects in reducing colorectal cancer incidence, little is known about the role of these dietary interventions for the other types of cancer or for other diseases associated with red meat intake.

If the xenosialitis hypothesis is validated, another possible approach would involve the use of genetically modified livestock as source of red meat. Pigs that do not endogenously express Neu5Gc ($Cmah-/-$ pigs) are already available (Lutz et al., 2013; Burlak et al., 2013; Burlak et al., 2014; Wang et al., 2014) and have been used in studies related to xenotransplantation (Lutz et al., 2013). However, further studies are required for the public acceptance of meat derived from genetically modified animals, and there is also a theoretical possibility that such animals may be susceptible to new diseases, involving pathogens that recognize their altered sialic acid-containing receptors. Overall, this approach may be also impractical, at least in the near future.

Given all these considerations, the use of methods to eliminate pre-existing diet-derived Neu5Gc from human tissues seems worth investigating. In this regard, studies from our group showed that Neu5Gc could be eliminated from human cells *in vitro* by metabolic competition with Neu5Ac, the isoform of sialic acid predominantly expressed by human cells (Ghaderi et al., 2010). Thus, feeding Neu5Ac to the cells prevents Neu5Gc recycling in lysosomes and its reutilization during glycan biosynthesis. Also, adding excess Neu5Ac is thought to compete with any further incorporation of Neu5Gc derived from the culture medium (Bardor et al., 2005). The flushing out of preexisting Neu5Gc could thus be a useful approach to reduce inflammation induced by red meat and thus slow disease progression. At first glance, this approach would suggest the ingestion of a Neu5Gc competitor Neu5Ac along with red meat. In practice, it would be hard to arrange for such an antidote to be easily available as part of every meal in which red meat is consumed. However, it could be incorporated into processed meat products rich in Neu5Gc. An alternative would be to investigate the effects of periodic "flushing" with a bolus of oral Neu5Ac.

Genetically modified mice that spontaneously develop colorectal tumors that closely resemble human colon cancer have been developed (Hinoi et al., 2007). These can now be backcrossed into the human-like *Cmah−/−* background, as an important tool to evaluate not only the contribution of Neu5Gc/anti-Neu5Gc antibodies to colon cancer progression, but also the proposed protection by competition with Neu5Ac.

4. Conclusions and Future Perspectives

We have proposed that all traditional theories explaining disease risks associated with red meat consumption need to be further examined, with regard to their specificity for red meat consumption and human disease development. This does not negate the potential importance of any of these theories for general effects on disease, but it does indicate that new theories deserve attention. The beef-derived virus theory of Zur Hausen merits further research, as does the theory of Neu5Gc-induced xenosialitis. Based on the potential importance of Neu5Gc incorporation for the biology of human carcinomas, analytical methods for detection and quantification of Neu5Gc have been already been used (Samraj et al., 2014a; Wang et al., 2015). Although it is unquestionable that colon cancer is the type of cancer that has the strongest association with red meat consumption, quantitative analysis of the percentage of Neu5Gc in colorectal tumors still needs to be determined, to ascertain if this value correlates with cancer progression. Although not yet studied, it is also possible that meat processing improves the digestibility, absorption, and metabolic incorporation of Neu5Gc. Similarly, although not yet studied, we believe that xenosialitis may represent the missing link that connects red meat consumption to other inflammatory diseases such as atherosclerosis (Pham et al., 2009), type 2 diabetes (Pan et al., 2011), rheumatoid arthritis (Pan et al., 2011), macular degeneration (Ersoy et al., 2014; Chong et al., 2009) and possibly certain forms of infertility (Sroga et al., 2015). Interventional studies using animal models could be used to address these hypotheses further, eventually leading to potential solutions to this problem.

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Abbreviations

CKD	chronic kidney disease
CMAH	cytidine monophospho-*N*-acetylneuraminic acid hydroxylase
CVD	cardiovascular disease
FMO3	flavin monooxygenase 3
GM3	monosialodihexosylganglioside
HCAs	heterocyclic amines
Neu5Ac	*N*-acetylneuraminic acid
Neu5Gc	*N*-glycolylneuraminic acid
NOCs	N-nitroso compounds
PAHs	polycyclic aromatic hydrocarbons
TGF-β	transforming growth factor beta
TMA	trimethylamine
TMAO	trimethylamine–N-oxide
WHO-IARC	World Health Organization-International Agency for Research on Cancer

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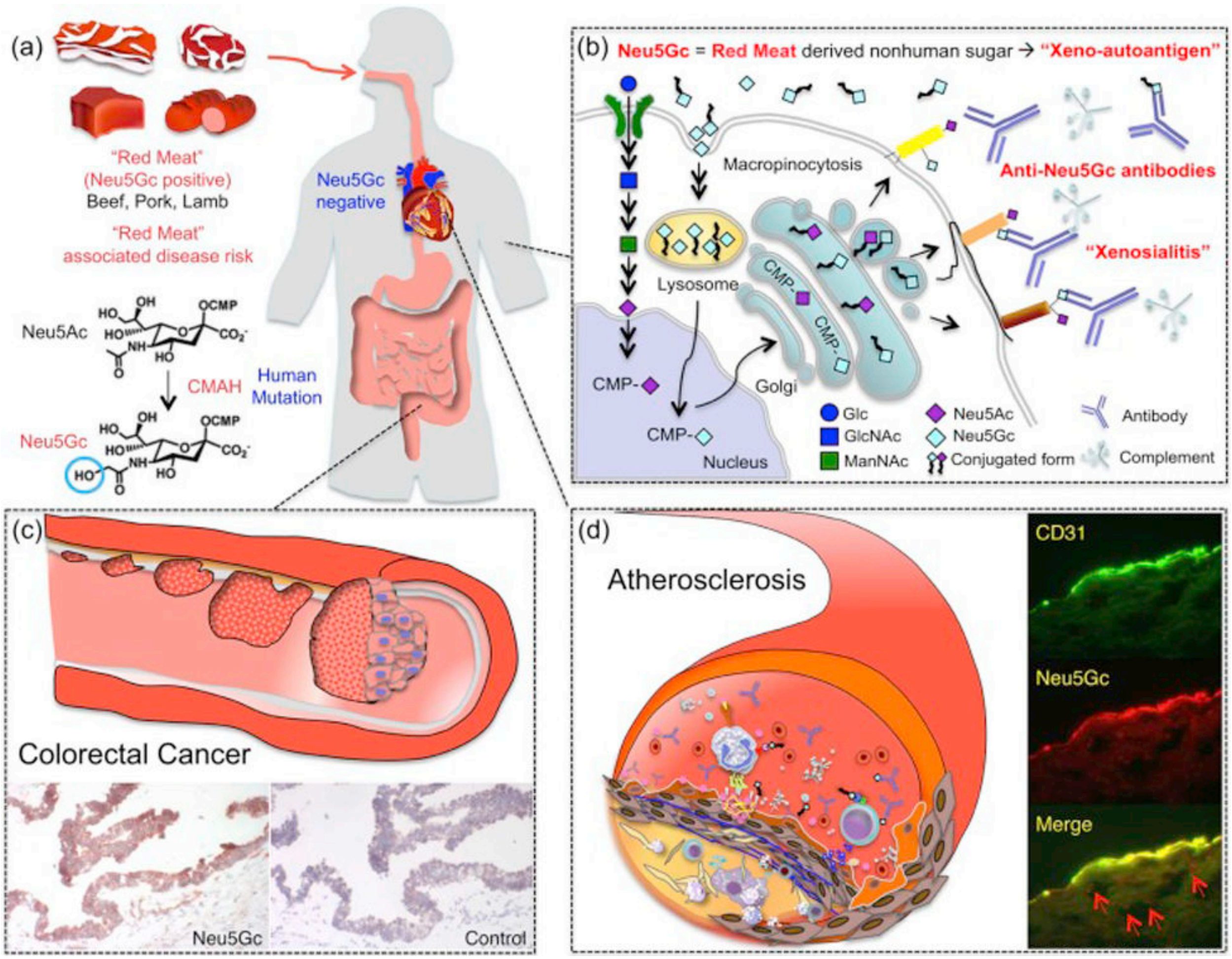

Figure 1. Potential Disease Risks associated with Metabolic incorporation of the Red meat-derived Non-human Sialic Acid *N*-glycolylneuraminic acid (Neu5Gc)

a) Red meat is a dietary source rich in (Neu5Gc) (beef, pork, lamb). Humans cannot synthesize Neu5Gc, due to a specific exon deletion in the gene encoding the enzyme cytidine monophospho-N-acetylneuraminic acid hydroxylase (CMAH), responsible for the generation of Neu5Gc from the precursor sialic acid *N*-acetylneuraminic acid (Neu5Ac). b) Neu5Gc can be incorporated into human cells through the same pathway used for Neu5Ac recycling. Endocytosed Neu5Gc is used as substrate for the synthesis of sialylated glycans in the Golgi. Cell surface glycans containing Neu5Gc may be targeted by circulating anti-Neu5Gc antibodies and complement, leading to a human specific inflammation, termed xenosialitis. c) Neu5Gc incorporation in human epithelia or endothelia and subsequent xenosialitis may be a risk factor for the promotion of colorectal tumor growth, atherosclerosis (d), and other inflammatory diseases associated with red meat consumption. Neu5Gc is detected in human colorectal cancer cells (c), in endothelial cells (CD31 positive) and subendothelial components (red arrow) in human atherosclerotic lesions (d). A part of (d) was originally published in Pham et al., 2009, Blood, 114: 5225–35. © by the American Society of Hematology.)