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Review

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

Frederico Alisson-Silva, Kunio Kawanishi, Ajit Varki *

Glycobiology Research and Training Center (GRTC), Center for Academic Research and Training in Anthropogeny (CARTA), Departments of Medicine and Cellular & Molecular Medicine, UC San Diego, La Jolla, CA 92093-0687, USA

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

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.

* Corresponding author. University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0687, USA. Fax: +1 (858) 534 5611.
E-mail address: a1varki@ucsd.edu (A. Varki).

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Contents

1. 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, 2012), type 2 diabetes (Aune et al., 2009; Micha et al., 2010; Pan et al., 2011), and to increased risk of certain kinds of adenocarcinomas (cancers of mucosal epithelial origin), particularly colorectal cancer (Aune et al., 2013; Cross and Sinha, 2004; Cross et al., 2010). Aggravation of age-dependent macular degeneration (Chong et al., 2009; Ersoy et al., 2014) 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).

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).