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REVIEW

The Role of Meat Protein in Generation of Oxidative Stress and Pathophysiology of Metabolic Syndromes

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Abstract Various processing methods have a great impact on the physiochemical and nutritional properties of meat that are of health concern. Hence, the postmortem processing of meat by different methods is likely to intensify the potential effects on protein oxidation. The influence of meat protein oxidation on the modulation of the systemic redox status and underlying mechanism is well known. However, the effects of processed meat proteins isolated from different sources on gut microbiota, oxidative stress biomarkers, and metabolomic markers associated with metabolic syndromes are of growing interest. The application of advanced methodological approaches based on OMICS, and mass spectrometric technologies has enabled to better understand the molecular basis of the effect of processed meat oxidation on human health and the aging process. Animal studies indicate the involvement of dietary proteins isolated from different sources on health disorders, which emphasizes the impact of processed meat protein on the richness of bacterial taxa such as (*Mucispirillum*, *Oscillibacter*), accompanied by increased expression of lipogenic genes. This review explores the most recent evidences on meat processing techniques, meat protein oxidation, underlying mechanisms, and their potential effects on nutritional value, gut microbiota composition and possible implications on human health.

Keywords diet, processed meat protein, oxidative stress, metabolic syndromes

Introduction

Meat and meat products do not only contain valuable nutrients for human health including vitamins (niacin, thiamin, riboflavin, vitamin B_6 and vitamin B_{12}), but also contain sodium, heme iron, advanced glycation end products, cholesterol and saturated fatty acids that may be harmful for patients with non-alcoholic fatty liver disease

(NAFLD) (Miele et al., 2014; Oddy et al., 2013). Excess consumption of red meat is associated with type 2 diabetes (T2D), insulin resistance (IR) and NAFLD (Hernandez et al., 2017; Zelber-Sagi et al., 2018). Meat products go through many processing steps either industrially or in households, most of which may trigger protein oxidation (Estevez, 2011). Physiochemical and functional changes such as aggregation, fragmentation and modification of structure during processing of meat may cause protein oxidation (Kaur et al., 2014; Sayd et al., 2016). Aging and age-related diseases have been associated with the biological consequences of such chemical changes (Shacter, 2000; Stadtman, 2006). Recent reports have hypothesized whether the occurrence of protein oxidation may not only affect sensory and technological attributes of the meat but also the health and well-being of the consumers (Estevez, 2011). Although more challenging and novel advances have recently been accomplished by food scientists in this field to better understand the effects of protein oxidation on the biomarkers associated with human health. Succeeding studies have been conducted to understand the various effects of protein oxidation on food quality, including altered texture and impaired digestibility (Sante-Lhoutellier et al., 2007).

Oxidized proteins are involved in the onset and severity of different diseases. And it is reasonable to hypothesize that the intake of oxidized proteins may be associated with certain pathological conditions and *in vivo* oxidative stress. This is supported by the growing concern about the impact of animal source proteins on human health, given that such proteins are particularly susceptible to oxidation (Estevez, 2015; Estradaetal et al., 2018). Studies have reported that aging related oxidation of protein is reduced by dietary protein restriction, which clearly emphasizes the link between protein intake and *in vivo* protein oxidation (Youngman et al., 1992). Owing to high levels of protein carbonyls, processed meat proteins are probably the most remarkable sources of the dietary protein oxidation (Jiang and Xiong, 2016; Soladoye et al., 2015). Higher intake of red meat has been found to increase inflammatory markers and systemic oxidative damage to lipids and proteins in experimental animals (Jakobsen et al., 2017; Turner et al., 2017). Recently, a study has shown that proteins isolated from meat sources have different impacts from soy and casein proteins on muscle anti-oxidation, liver metabolism and gut microbiota composition (Zhu et al., 2017). On the contrary, intake of soy protein has negligible effects on blood lipids and oxidative stress biomarkers (Engelman et al., 2005). It is worth recalling that epidemiological studies and reports from health authorities claim on the connection between red and processed meat with obesity and other serious pathologies (Chan et al., 2011; IARC, 2015). Recent studies have revealed that processed meat proteins isolated from different sources exhibited different impact on the intestinal gut microbiota and NAFLD (Ahmad et al., 2019; Ijaz et al., 2018). The bacterial taxa such as *Tenericutes*, *Christensenellaceae*, and *Akkermansia* have been reported to be associated with lipid metabolism and high-density lipoproteins (HDL) (Everard et al., 2013; Fu et al., 2015). Also, *Akkermansia muciniphila* can reduce the level of liver triglyceride and gonadal fat mass (Org et al., 2015). In a recent study, carnitine is an abundant nutrient in red meat, produces trimethylamine-N-oxide via gut microbiota metabolism of L-carnitine, which has been shown to promote cardiovascular disease risks in host (Koeth et al., 2013). However, the effects of dietary proteins isolated from different sources on oxidative stress biomarkers, gut microbiota composition, NAFLD, and metabolic risk markers remains to be established.

Hence, this paper concisely collects recent advances on the effects of dietary processed meat proteins isolated from different sources on the host microbial balance, gut-liver axis and NAFLD. In addition, we have also discussed the underlying mechanisms on the associations between the protein oxidation and oxidative stress. We suggest reasonable hypotheses and future challenges intended to stimulate further investigation in this emerging field of research.

Mechanism Underlying the Protein Oxidation

Proteins are recognized as major targets of oxidative modification owing to a variety of mechanisms (Dean et al., 1997). It

has been well known that oxidation products and oxidation pathways are dependent on how and where the oxidation is initiated on proteins (Xiong et al., 2009; Xiong et al., 2000). Both physical (UV light and fluorescent) and chemical (reducing sugars, Millard reaction, dicarbonyls from lipid oxidation, and ROS) agents trigger protein oxidation in food system (Estevez et al., 2015; Soladoye et al., 2015). In theory, peptide scission, covalent interactions between amino acids chains, and formation of crosslinks collectively lead to the formation of specific oxidation derivatives (Lund et al., 2011). In practice, protein carbonylation is a well-used marker for oxidative damage to food proteins, together with the crosslinks formation, namely, dityrosines and disulphide bonds (Estevez et al., 2015). Furthermore, carbonylation has been observed in assorted muscle foods such as beef patties, fermented sausages, bacon, and milk and dairy proteins (Berardo et al., 2016; Rysman et al., 2016; Soladoye et al., 2017; Utrera et al., 2015). More sensitive and high throughput mass spectrometric technology has been applied to identify and locate protein carbonylation in dairy and pork products (Milkovska-Stamenova et al., 2017; Mitra et al., 2018). In fresh meat, protein carbonylation has been widely accepted as oxidative stress biomarkers, and can vary with species, muscle type and aging time. For example, carbonyl content in meat myofibrils varies from 0.2 nmol/mg to 4.8 nmol/mg protein in lamb *longissimus dorsi* muscle and bovine diaphragm pedialis muscle respectively (Martinaud et al., 1997; Sante-Lhoutellier et al., 2008).

Postmortem meat processing is usually done to alter or enhance the nutritional composition of meat. The loss of sulfhydryl (SH) group is detected as another marker of oxidative modification of proteins. Methionine loss in meat systems, which is very sensitive amino acid to ROS, is a major cause of oxidation of meat proteins. The observed consequences during cooking are loss of SH groups and increased surface hydrophobicity (Gatellier et al., 2010). In addition to cooking conditions, studies have shown that a high ionic strength environment increased oxidation of muscle proteins (Liu et al., 2011). Also, cooked pork showed significantly higher β-sheet, β-turn and random coil contents, and lower α-helix content than emulsion type sausage (He et al., 2018). In that study, Raman spectroscopy was used to determine the protein conformation, and moreover, the digestion products were identified by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The results showed that stewed pork, cooked pork, and emulsion-type sausage pork had significantly lower levels of SH contents compared to raw pork, but did not show significant differences in dry-cured pork. Several factors may cause differences in the SH contents. The structure of protein is affected by cooking temperature. Heating meat protein at 70°C causes oligomers formation and protein unfolding, while at 100°C or higher, the proteins are further modified by oxidation, which promotes aggregation (Liu et al., 2011). Protein aggregation is a long-lasting problem induced by cooking time and temperature (Philo et al., 2009). In a study, dry-cured pork had different SH contents compared to cooked pork, although both types of proteins were heated under the same conditions. Similarly, the SH contents of dry-cured pork were significantly higher than those of other pork products. This mechanism might be attributed to a looser or more disrupted myofibril structure caused by electrostatic repulsion in the high-ionic strength salty environment (Bax et al 2012; Philo et al., 2009). These results indicated that during cooking moderate unfolding and denaturation occurred in meat protein.

Protein digestibility and particle size of pork products is affected by method of processing (Soladoye et al., 2015). Also, methods of cooking affect *in vitro* protein digestibility and availability (Li et al., 2017). Chopping and drying affect the digestibility of protein (Wen et al., 2015). The processing methods not only affect the protein digestibility of meat products but also the peptide fractions released after digestion, and these changes in protein structure and surface hydrophobicity can be attributed to protein oxidation and aggregation (Berardo et al., 2017; Sun et al., 2011). In a study, emulsion-type sausage showed significantly higher protein digestibility, while the lowest protein digestibility was obtained after pepsin digestion alone or with subsequent trypsin digestion or under both these conditions (Li et al., 2017). However, it is not clear how

protein digestibility was affected by different cooking conditions such as time and temperature. In a study, the authors compared the effects of four kinds of processed pork products (dry-cured pork, cooked pork, stewed pork and emulsion-type sausage) on the protein digestibility and digested products (Li et al., 2017). The lowest protein digestibility and the highest particle size were observed in stewed pork, while the opposite for emulsion-type sausage. These results indicated that *in vitro* protein digestibility of pork products can be affected by different processing methods.

The mechanism of lipid peroxidation is a chain reaction and created by a free radical chain reaction (Lund et al., 2011). In a complex matrix such as meat, the associations between protein oxidation and lipid peroxidation are still unclear. The process of protein oxidation leads to the onset of lipid oxidation (Kaur et al., 2014). Moreover, lipid peroxidation products are more susceptible to reacting with amino acids having reactive side chains. Though lipid peroxides are detected earlier than those from the protein oxidation, the oxidation of lipids, specifically hydroxyl radical would react faster with certain amino acid residues (thiols, tryptophan) than with unsaturated fatty acids (Aalhus et al., 2014).

The importance of heme iron in the co-oxidation of lipids and proteins in meat system using pork homogenate has been reviewed (Jongberg et al., 2011; Skibsted, 2011). Fe^{2+} promotes the oxidation of lipids and proteins in a dose-dependent manner and highlights the pro-oxidant role of oxymyoglobin in such reactions. The functionality and digestibility of food proteins such as soy, meat, fish, milk, and myoglobin were shown to be affected by formation of 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA) via covalent modification (Gurbuz and Heinonen, 2015; Hu et al., 2017; Suman et al., 2014; Zhang et al., 2017; Zhou et al., 2015).

Protein Oxidation and Metabolic Disorders

Animal-based protein is an important dietary source for human nutritional requirements. Meat protein distinguishes itself for its richness in all the essential amino acids (Smith et al., 2009). However, except for their differences in amino acid composition, the impact of dietary proteins isolated from different sources on metabolic disorders needs further investigation. Recently, Song et al. (2016) compared the effects of soy and meat proteins on hepatic transcriptomic and metabolic syndrome associated with physiological markers. Functional classification revealed that soy and meat proteins differentially regulate pathways involving amino acid metabolism, energy metabolism, lipid metabolism and insulin signaling. Rictor, Srebf1, NFE2L2, and ATF4 were recognized as potential key upstream regulators. In another study, Song et al. (2018) observed that meat proteins showed beneficial impacts on growth and metabolism in young rats compared to soy and casein proteins.

The pathophysiology and progression of NAFLD is influenced by multiple factors in which oxidative stress plays a key role in the hepatic injury (Oliveira et al., 2002; Wruck and Adjaye, 2017). Another factor associated with hepatic inflammation and lipotoxicity is the stimulation of ROS in fatty liver via mitochondrial dysfunction (Roskams et al., 2003). Intracellular ROS generation and redox homeostasis is regulated by the balance between antioxidant enzymes and ROS generating enzymes, including catalase, glutathione peroxidases (GPX), glutathione (GSH), superoxide dismutase (SOD), and oxidoreductase protein families: glutaredoxin (Glrx) and thioredoxin (Mann et al., 2017). Glrx is a multi-effect cytokine that takes part in cell signaling, protection of cell against oxidative stress, cytoskeletal regulation, and inflammation (Aesif et al., 2011; Shelton et al., 2007). Quantitative metabolomics and proteomics analyses highlighted that cellular depletion of Glrx1 activates p53 and associated signaling pathways but decreased the level of GSH (Yang et al., 2018). Glrx1 is also a potential biomarker and key factor involved in the pathogenesis of diabetes and chronic kidney disease (Du et al., 2013). In a study, Glrx1 knockdown increased the levels of GPX, SOD and catalase, but decreased the levels of ROS and MDA compared with

the wild-type mice (Ahmad et al., 2019). A previous study shows that depletion of Glrx1 results in higher level of ROS and lower level of antioxidant enzymes (Catalase, SOD, and GPX) activities in mice (Liu et al., 2016). This might be because liver contains abundant Glrx and more significantly, has two reactive cysteines (Ley et al., 2016) and explain why mice shows increased hepatic antioxidant defense.

Dietary Protein and Gut-liver Axis

The gut is a complex ecosystem that harbors a diverse bacterial community. Recent studies have revealed that *Bacteroidetes* and *Firmicutes* phyla are the most abundant in gut (Moschen et al., 2013). Significant progress has been made in recent years in elucidating the association of gut microbiota composition with severity of NAFLD (Backhed, 2004; Tremaroli et al., 2012). Alterations of gut microbiota have been thought to be associated with a decrease in the ratio of *Bacteriodetes* to *Firmicutes*, gut bacterial richness and increased expression of genes related to bacterial metabolic activity (Ley, 2006; Le Roy, 2013). In a study, male rats fed casein and soy protein diets showed differences in the biochemical markers associated with hepatic antioxidant enzyme activities and metabolism, accompanied with an increase in the abundances of several taxa such as *Ruminococcus* and *Lactobacillus* (Zhu et al., 2017). However, associations among dietary intakes of processed meat proteins as a result of protein oxidation, host health and gut microbiota composition are still unclear. Our studies highlighted that intake of processed meat protein significantly increased the richness of bacterial taxa (*Mucispirillum*, *Oscillibacter*) associated with obesity and NAFLD, which were also accompanied by an increase in the lipogenic gene expression (Ahmad et al., 2019; Ijaz et al., 2018). Still, the effects of dietary proteins isolated from different sources at different levels incorporated with low or high fat is a matter of further discussion.

Studies showed positive associations among processed meat proteins, oxidative stress, and NAFLD (Kirpich et al., 2015). Excess consumption of processed and red meat increases the risk of a serious liver condition and IR. A study revealed that people who ate the maximum amount of red and processed meats had almost a 50% increased risk to NAFLD, and a higher risk to progressing IR (Zelber-sagi et al., 2018). It was also observed that meat cooked at high temperature for a long duration such as grilling, broiling, or frying was related to about twice the risk of IR. Consequently, levels of serum and hepatic inflammatory mediators (TNF-α, MCP-1) have been found to elevate with both steatosis and NAFLD (Ijaz et al., 2018). More recently, consumption of simple carbohydrate has been pointed out as another possible contributory factor. Multiple diet-induced animal models have been developed for the study of NAFLD. Our previous study demonstrated that high fat beef protein diets increased hepatic triglycerides, total cholesterol, LDL-cholesterol, serum inflammatory markers, hepatic lipid accumulation and upregulated lipogenesis genes (Ahmad et al., 2019). As a result, mice fed high fat beef protein exhibited signs of impaired glucose metabolism and IR compared to high fat diets incorporated with soy and casein protein.

Conclusion

There is a growing interest in processed meat proteins and impact of processing methods on nutrition and health. A full understanding of the chemistry behind the meat protein oxidation is paramount in terms of food quality and consumer health. Oxidative and nitrosative modification of proteins in muscle is a topic to be further explored. The identification of chemistry fundamentals of protein oxidation products in processed meat is required to assess their potential toxicity. Although the effects of isolated dietary protein from different sources by our group open a new chapter to better understand the underlying mechanism and potential pathways on gut health and different axis in the field of nutrigenomics. Future studies are needed to

better understand the effects of processing methods on the dietary protein composition, nutritional value and their consequences. Furthermore, meta-proteomic, metabolomic, and meta-transcriptomic studies are needed to identify the changes in the gut microbiota as a result of dietary challenge.

Conflict of Interest

The authors declare no potential conflict of interest.

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Author Contributions

Conceptualization: Li C, Ahmad MI. Data curation: Ijaz MU. Software: Ahmad MI, Li C. Validation: Li C. Investigation: Ahmad MI, Ijaz H. Writing-original draft: Ahmad MI, Li C. Writing-review & editing: Ahmad MI, Ijaz MU, Ijaz H, Li C.

Ethics Approval

This article does not require IRB/IACUC approval because there are no human and animal participants.

References

Aalhus J, Dugan M. 2014. Spoilage, factors affecting (b) oxidative and enzymatic. In Encyclopedia of meat sciences. 2nd ed. Dikeman M, Devine C (ed). Academic Press, London, UK. pp 394-400.

Aesif SW, Kuipers I, Van der Velden J, Tully JE, Guala AS, Anathy V, Sheely JI, Reynaert NL, Wouters EF, van der Vliet A, Janssen-Heininger YM. 2011. Activation of the glutaredoxin-1 gene by nuclear factor κB enhances signaling. Free Radic Biol Med 51:1249-1257.

Ahmad MI, Zou X, Ijaz, UM, Hussain M. Liu C, Xu X, Zhou G, Li C. 2019. Processed meat protein promoted inflammation and hepatic lipogenesis by upregulating Nrf2/Keap1 signaling pathway in Glrx-deficient mice. J Agric Food Chem 67:8794-8809.

Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. 2004. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA 101:15718-15723.

Bax ML, Aubry L, Ferreira C, Daudin JD, Gatellier P, Remond D, Sante-Lhoutellier V. 2012. Cooking temperature is a key determinant of *in vitro* meat protein digestion rate: Investigation of underlying mechanisms. J Agric Food Chem 60:2569-2576.

Berardo A, De Maere H, Stavropoulou DA, Rysman T, Leroy F, De Smet S. 2016. Effect of sodium ascorbate and sodium nitrite on protein and lipid oxidation in dry fermented sausages. Meat Sci 121:359-364.

Berardo A, Devreese B, De Maere H, Stavropoulou DA, Van Royen G, Leroy F, De Smet S. 2017. Actin proteolysis during ripening of dry fermented sausages at different pH values. Food Chem 221:1322-1332.

Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, Norat T. 2011. Red and processed meat and colorectal cancer incidence: Meta-analysis of prospective studies. PLOS ONE 6:e20456.

Dean RT, Fu S, Stocker R, Davies MJ. 1997. Biochemistry and pathology of radical-mediated protein oxidation. Biochem J 15:1-18.

Du Y, Zhang H, Montano S, Hegestam J, Ekberg NR, Holmgren A, Brismar K, Ungerstedt JS. 2013. Plasma glutaredoxin activity in healthy subjects and patients with abnormal glucose levels or overt type 2 diabetes. Acta Diabetol 51:225-232.

Engelman HM, Alekel DL, Hanson LN, Kanthasamy AG, Reddy MB. 2005. Blood lipid and oxidative stress responses to soy protein with isoflavones and phytic acid in postmenopausal women. Am J Clin Nutr 81:590-596.

Estevez M. 2011. Protein carbonyls in meat systems: A review. Meat Sci 89:259-279.

Estevez M. 2015. Oxidative damage to poultry: From farm to fork. Poult Sci 94:1368-1378.

Estradaetal PD, Berton-Carabin CC, Schlangen M, Haagsma A, Pierucci APTR, van der Goot AJ. 2018. Protein oxidation in plant protein-based fibrous products: Effect of encapsulated iron and process conditions. J Agric Food Chem 66:11105-11112.

Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani PD. 2013. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci USA 110:9066-9071.

Fu J, Bonder MJ, Cenit MC, Tigchelaar EF, Maatman A, Dekens, JA, Brandsma E, Marczynska J, Imhann F, Weersma RK, Franke L, Poon TW, Xavier RJ, Gevers D, Hofker MH, Wijmenga C, Zhernakova A. 2015. The gut microbiome contributes to a substantial proportion of the variation in blood lipids. Circ Res 117:817-824.

Gatellier P, Kondjoyan A, Portanguen S, Sante-Lhoutellier V. 2010. Effect of cooking on protein oxidation in n-3 polyunsaturated fatty acids enriched beef. Implication on nutritional quality. Meat Sci 85:645-650.

Gurbuz G, Heinonen M. 2015. LC-MS investigations on interactions between isolated β-lactoglobulin peptides and lipid oxidation product malondialdehyde. Food Chem 175:300-305.

He J, Zhou G, Bai Y, Wang C, Zhu S, Xu X, Li C. 2018. The effect of meat processing methods on changes in disulfide bonding and alteration of protein structures: Impact on protein digestion products. RSC Adv 8:17595-17605.

Hernandez EA, Kahl S, Seelig A, Begovatz P, Irmler M, Kupriyanova YM, Nowotny B, Nowotny P, Herder C, Barosa C, Carvalho F, Rozman J, Neschen S, Jones JG, Beckers J, de Angelis MH, Roden M. 2017. Acute dietary fat intake initiates alterations in energy metabolism and insulin resistance. J Clin Invest 127:695-708.

Hu L, Ren S, Shen Q, Chen J, Ye X, Ling J. 2017. Proteomic study of the effect of different cooking methods on protein oxidation in fish fillets. RSC Adv 7:27496-27505.

IARC. 2015. Carcinogenicity of consumption of red and processed meat. Lancet 16:1599-1600.

Ijaz MU, Ahmed MI, Zou X, Hussain M, Zhang M, Zhao F, Xu X, Zhou G, Li C. 2018. Beef, casein, and soy proteins differentially affect lipid metabolism, triglycerides accumulation and gut microbiota of high-fat diet-fed C57BL/6J mice. Front Microbiol 9:2200.

Jakobsen LM, Yde CC, Van Hecke T, Jessen R, Young JF, De Smet S, Bertram HC. 2017. Impact of red meat consumption on the metabolome of rats. Mol Nutr Food Res 61:1600387-1600393.

Jongberg S, Skov SH, Torngren MA, Skibsted LH, Lund MN. 2011. Effect of white grape extract and modified atmosphere packaging on lipid and protein oxidation in chill stored beef patties. Food Chem 128:276-283.

Jiang J, Xiong YL. 2016. Natural antioxidants as food and feed additives to promote health benefits and quality of meat

products: A review. Meat Sci 120:107-117.

Kaur L, Maudens E, Haisman DR, Boland MJ, Singh H. 2014. Microstructure and protein digestibility of beef: The effect of cooking conditions as used in stews and curries. LWT-Food Sci Technol 55:612-620.

Kirpich IA, Marsano LS, McClain CJ. 2015. Gut-liver axis, nutrition, and non-alcoholic fatty liver disease. Clin Biochem 48:923-930.

Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, DiDonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WHW, Bushman FD, Lusis AJ, Hazen SL. 2013. Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 19:576-585.

Le Roy T, Llopis M, Lepage P, Bruneau A, Rabot S, Bevilacqua C, Martin P, Philippe C, Walker F, Bado A, Perlemuter G, Cassard-Doulcier AM, Gerard P. 2013. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. Gut 62:1787-1794.

Ley RE, Turnbaugh PJ, Klein S, Gordon JI. 2006. Microbial ecology: Human gut microbes associated with obesity. Nature 444:1022-1023.

Li L, Liu Y, Zou X, He J, Xu X, Zhou G, Li C. 2017. *In vitro* protein digestibility of pork products is affected by the method of processing. Food Res Int 92:88-94.

Liu Z, Xiong YL, Chen J. 2011. Morphological examinations of oxidatively stressed pork muscle and myofibrils upon salt marination and cooking to elucidate the water-binding potential. J Agric Food Chem 59:13026-13034.

Liu X, Xavier C, Jann J, Wu H. 2016. Salvianolic acid B (Sal B) protects retinal pigment epithelial cells from oxidative stress-induced cell death by activating glutaredoxin 1 (Grx1). Int J Mol Sci 17:1835-1840.

Lund MN, Heinonen M, Baron CP, Estevez M. 2011. Protein oxidation in muscle foods: A review. Mol Nutr Food Res 55:83-95.

Mann JP, Raponi M, Nobili V. 2017. Clinical implications of understanding the association between oxidative stress and pediatric NAFLD. Expert Rev Gastroenterol Hepatol 11:371-382.

Martinaud A, Mercier Y, Marinova P, Tassy C, Gatellier P, Renerre M. 1997. Comparison of oxidative processes on myofibrillar proteins from beef during maturation and by different model oxidation systems. J Agric Food Chem 45:2481-2487.

Miele L, Dall'armi V, Cefalo C, Nedovic B, Arzani D, Amore R, Rapaccini G, Gasbarrini A, Ricciardi W, Grieco A, Boccia S. 2014. A case-control study on the effect of metabolic gene polymorphisms, nutrition, and their interaction on the risk of non-alcoholic fatty liver disease. Genes Nutr 9:383-391.

Milkovska-Stamenova S, Mnatsakanyan R, Hoffmann R. 2017. Protein carbonylation sites in bovine raw milk and processed milk products. Food Chem 229:417-424.

Mitra B, Lametsch R, Akcan T, Ruiz-Carrascal J. 2018. Pork proteins oxidative modifications under the influence of varied time-temperature thermal treatments: A chemical and redox proteomics assessment. Meat Sci 140:134-144.

Moschen AR, Kaser S, Tilg H. 2013. Non-alcoholic steatohepatitis: A microbiota-driven disease. Trends Endocrinol Metab 24:537-545.

Oddy WH, Herbison CE, Jacoby P, Ambrosini GL, O'Sullivan TA, Ayonrinde OT, Olynyk JK, Black LJ, Beilin LJ, Mori TA, Hands BP, Adams LA. 2013. The Western dietary pattern is prospectively associated with nonalcoholic fatty liver disease in adolescence. Am J Gastroenterol 108:778-785.

Oliveira CP, de Costa LC, Tatai C, Della Bina BI, Janiszewski M, Lima ES, Abdalla DS, Lopasso FP, Laurindo FR,

Laudanna AA. 2002. Oxidative stress in the pathogenesis of nonalcoholic fatty liver disease, in rats fed with a choline-deficient diet. J Cell Mol Med 6:399-406.

Org E, Parks, BW, Joo JW, Emert B, Schwartzman W, Kang EY, Mehrabian M, Pan C, Knight R, Gunsalus R, Drake TA, Eskin E, Lusis AJ. 2015. Genetic and environmental control of host-gut microbiota interactions. Genome Res 25:1558-1569.

Philo JS, Arakawa T. 2009. Mechanisms of protein aggregation. Curr Pharm Biotechnol 10:348-351.

Roskams T, Yang SQ, Koteish A, Durnez A, DeVos R, Huang X, Achten R, Verslype C, Diehl AM. 2003. Oxidative stress and oval cell accumulation in mice and humans with alcoholic and nonalcoholic fatty liver disease. Am J Pathol163:1301-1311.

Rysman T, Utrera M, Morcuende D, Van Royen G, Van Weyenberg S, De Smet S, Estevez M. 2016. Apple phenolics as inhibitors of the carbonylation pathway during *in vitro* metal-catalyzed oxidation of myofibrillar proteins. Food Chem 211:784-790.

Sante-Lhoutellier V, Astruc T, Marinova P, Greve E, Gatellier P. 2008. Effect of meat cooking on physicochemical state and *in vitro* digestibility of myofibrillar proteins. J Agric Food Chem 56:1488-1494.

Sante-Lhoutellier V, Aubry L, Gatellier P. 2007. Effect of oxidation on *in vitro* digestibility of skeletal muscle myofibrillar proteins. J Agric Food Chem 55:5343-5348.

Sayd T, Chambon C, Sante-Lhoutellier V. 2016. Quantification of peptides released during *in vitro* digestion of cooked meat. Food Chem 197:1311-1323.

Shacter E. 2000. Quantification and significance of protein oxidation in biological samples. Drug Metab Rev 32:307-326.

Shelton MD, Kern TS, Mieyal JJ. 2007. Glutaredoxin regulates nuclear factor kappa-B and intercellular adhesion molecule in Muller cells: Model of diabetic retinopathy. J Biol Chem 282:12467-12474.

Skibsted LH. 2011. Nitric oxide and quality and safety of muscle based foods. Nitric Oxide 24:176-183.

Smith F, Clark JE, Overman BL, Tozel CC, Huang JH, Rivier JE, Blikslager AT, Moeser AJ. 2009. Early weaning stress impairs development of mucosal barrier function in the porcine intestine. Am J Physiol Gastrointest Liver Physiol 298:G352-G363.

Soladoye OP, Juarez ML, Aalhus JL, Shand P, Estevez M. 2015. Protein oxidation in processed meat: Mechanisms and potential implications on human health. Compr Rev Food Sci Food Saf 14:106-122.

Soladoye OP, Shand P, Dugan MER, Gariepy C, Aalhus JL, Estevez M, Juarez M. 2017. Influence of cooking methods and storage time on lipid and protein oxidation and heterocyclic aromatic amines production in bacon. Food Res Int 99:660-669.

Song S, Hooiveld GJ, Li M, Zhao F, Zhang W, Xu X, Muller M, Li C, Zhou G. 2016. Dietary soy and meat proteins induce distinct physiological and gene expression changes in rats. Sci Rep 6:20036.

Song S, Hua C, Zhao F, Li M, Fu Q, Hooiveld GJEJ, Muller M, Li C, Zhou G. 2018. Purified dietary red and white meat proteins show beneficial effects on growth and metabolism of young rats compared to casein and soy protein. J Agric Food Chem 66:9942-9951.

Stadtman ER. 2006. Protein oxidation and aging. Free Radic Res 40:1250-1258.

Sun W, Zhao M, Yang B, Zhao H, Cui C. 2011. Oxidation of sarcoplasmic proteins during processing of Cantonese sausage in relation to their aggregation behaviour and *in vitro* digestibility. Meat Sci 88:462-467.

Suman SP, Hunt MC, Nair MN, Rentfrow G. 2014. Improving beef color stability: Practical strategies and underlying

mechanisms. Meat Sci 98:490-504.

Tremaroli V, Backhed F. 2012. Functional interactions between the gut microbiota and host metabolism. Nature 489:242-249.

Turner KM, Keogh JB, Meikle PJ, Clifton PM. 2017. Changes in lipids and inflammatory markers after consuming diets high in red meat or dairy for four weeks. Nutrients 9:886-891.

Utrera M, Morcuende D, Ganhao R, Estevez M. 2015. Role of phenolics extracting from *Rosa canina* L. on meat protein oxidation during frozen storage and beef patties processing. Food Bioproc Technol 8:854-864.

Wen S, Zhou G, Li L, Xu X, Yu X, Bai Y, Li C. 2015. Effect of cooking on *in vitro* digestion of pork proteins: A peptidomic perspective. J Agric Food Chem 63:250-261.

Wruck W, Adjaye J. 2017. Meta-analysis reveals up-regulation of cholesterol processes in non-alcoholic and down-regulation in alcoholic fatty liver disease. World J Hepatol 9:443-454.

Xiong Y. 2000. Protein oxidation and implications for muscle foods quality. In Antioxidants in muscle foods. Decker EA, Faustman C, Lopez-Bote CJ (ed). Wiley, New York, NY. pp 85-111.

Xiong YL, Park D, Ooizumi T. 2009. Variation in the cross-linking pattern of porcine myofibrillar protein exposed to three oxidative environments. J Agric Food Chem 57:153-159.

Yang F, Yi M, Liu Y, Wang Q, Hu Y, Deng H. 2018. Glutaredoxin-1 silencing induces cell senescence via p53/p21/p16 signaling axis. J Proteome Res 17:1091-1100.

Youngman LD, Park JY, Ames BN. 1992. Protein oxidation associated with aging is reduced by dietary restriction of protein or calories. Proc Natl Acad Sci 89:9112-9116.

Zelber-Sagi S, Ivancovsky-Wajcman D, Fliss Isakov N, Webb M, Orenstein D, Shibolet O, Kariv R. 2018. High red and processed meat consumption is associated with non-alcoholic fatty liver disease and insulin resistance. J Hepatol 68:1239-1246.

Zhang X, Lu P, Xue W, Wu D, Wen C, Zhou Y. 2017. An evaluation of heat on protein oxidation of soy protein isolate or soy protein isolate mixed with soybean oil *in vitro* and its consequences on redox status of broilers at early age. Asian-Australas J Anim Sci 30:1135-1142.

Zhou F, Sun W, Zhao M. 2015. Controlled formation of emulsion gels stabilized by salted myofibrillar protein under malondialdehyde (MDA)-induced oxidative stress. J Agric Food Chem 63:3766-3777.

Zhu Y, Shi X, Lin X, Ye K, Xu X, Li C, Zhou G. 2017. Beef, chicken, and soy proteins in diets induce different gut microbiota and metabolites in rats. Front Microbiol 8:1395.