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Review

Biological effect of protein modifications by lipid peroxidation products

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ABSTRACT

The products of lipid peroxidation, resulting from cell metabolism as well as the action of external physical factors and xenobiotics, have a significant impact on cell functions. One of the mechanisms by which lipid peroxidation products influence cells is the formation of adducts with proteins, including enzymes and signaling molecules. This review describes the biological consequences of protein adduct formation with oxidative lipid fragmentation products such as 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), and acrolein, as well as cyclization products including isoprostanes, isoketals, and isolevuglandins. The generation of protein adducts with lipid peroxidation products can stimulate the antioxidant system, which may also possess proinflammatory or proapoptotic effects. However, the role of adducts between lipid peroxidation products and proteins depends on the condition of the cells and can range from the function of cytoprotective activity stimulation, to induction of toxicity involved in the development of degenerative diseases.

1. Introduction

Cellular physiological metabolism that occurs in every organism continuously generates molecules that are mediators of both intracellular and systemic signals. This ensures an efficient flow of signals in living organisms, which contributes to the maintenance of homeostasis. However, when homeostasis is disturbed by environmental factors and modifications of cellular metabolism, it alters signaling molecules generation (Domingues et al., 2013). Therefore, under pathological conditions, the organism's cells generate, receive, and react to signaling molecules whose formation is associated with the stimulus. A similar situation is also observed in the case of metabolic changes arising from or leading to pathological conditions and disease development. Such situations are inextricably linked to the generation of highly reactive molecules, such as reactive oxygen species (ROS), which act as short-term signaling molecules and stimulate the production of additional mediators such as lipid peroxidation products.

2. Lipid peroxidation

Lipid peroxidation occurs enzymatically and non-enzymatically, but in both cases the lipid molecule is oxidized upon lipid radical formation. The initiators of non-enzymatic lipid peroxidation are mainly hydroxyl and hydroperoxyl radicals that initiate oxidative chain reactions. The most sensitive molecules that undergo peroxidation are membrane phospholipids containing polyunsaturated fatty acids (PUFAs), including arachidonic, linoleic, linolenic, eicosapentaenoic, and docosahexaenoic acids. Therefore, due to ROS reacting with PUFAs, deprotonation occurs at the double bond, followed by oxygen introduction, promoting lipid peroxide radical formation, which undergoes oxidation forming lipid hydroperoxide (LOOH) (Halliwell and Chirico, 1993). Enzymatic lipid peroxidation is primarily catalyzed by cyclooxygenases (COX) (Liu et al., 2015) and lipoxygenases (LOX) (Brash, 2015), although reports have shown that other enzymes can also be involved in lipid metabolism, such as phospholipase A (PLA) (Adibhatla and Hatcher, 2006). PLA produces two classes of compounds: fatty acids as substrates for oxidative fragmentation and bioactive metabolites with the phosphoglyceride backbone, such as lysophosphatidylcholines or platelet-activating factors, as well as oxygenated derivatives of free fatty acids liberated from the sn-2 position, such as oxidative cyclization products and eicosanoids (e.g. prostanoids and leukotrienes) (Caslake et al., 2000). PLA releases products of

Abbreviations: 4-HNE, 4-hydroxynonenal; APC, antigen presenting cells; ARE, antioxidant response element; COX, cyclooxygenase; Cys, cysteine; ERK, extracellular signal–regulated kinase; Fas (Apo-1), tumor necrosis factor; His, histidine; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; IsoKs, isoketals; IsoLGs, isolevuglandins; IsoPs, isoprostanes; IκB, inhibitor of kappa B; JNK, c-Jun N-terminal kinase; Keap1, kelch-like ECH-associated protein 1; LOOH, lipid hydroperoxide; LOX, lipoxygenase; Lys, lysine; MDA, malondialdehyde; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOX, NADPH oxidase; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PKC, protein kinase C; PLA, phospholipase A; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SIR, sirtuin; TLR, toll-like receptors; TNFα, tumor necrosis factor α; VCAM, vascular cell adhesion molecule

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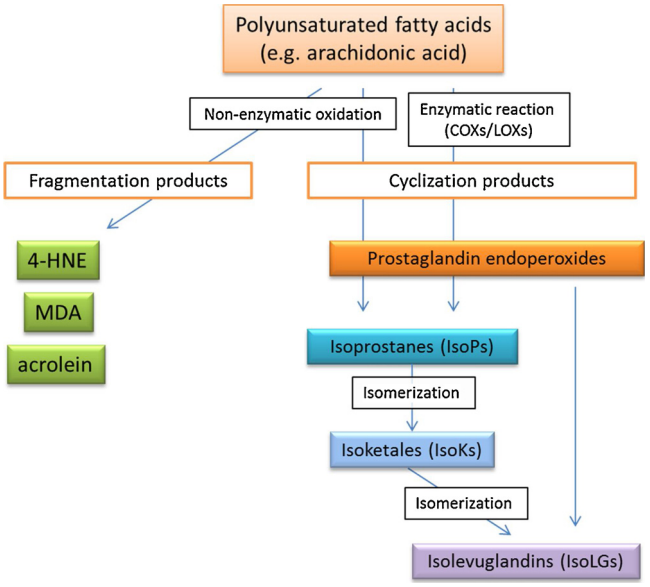

Fig. 1. ROS-dependent and enzymatic-dependent mechanisms of the main lipid peroxidation products formation. Abbreviations: 4-HNE, 4-hydroxynonenal; COXs, cyclooxygenases; IsoKs, isoketals; IsoLGs, isolevuglandins; IsoPs, isoprostanes; LOXs, lipoxygenases; MDA, malondialdehyde.

oxidative cyclization formed as a part of phospholipid (Hasanally et al., 2014).

Generated as a result of oxidative fragmentation lipid hydroperoxides undergo further oxidative fragmentation reactions forming unsaturated α,β−aldehydes, including 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), or acrolein (Fig. 1). In addition, the propagation of PUFAs oxidation chain reaction may lead to oxidative cyclization via unstable prostaglandin H2-like bicyclic endoperoxide intermediates, which are reduced to F2-isoprostanes (F2-IsoPs) or undergo rearrangement to form E2/D2-isoprostanes (E2/D2-IsoPs). E2/D2-IsoPs dehydration leads to A2/J2-isoprostanes (A2/J2-IsoPs) generation, also known as cyclopentenone IsoPs, because they contain an α,β-unsaturated cyclopentenone ring structure (Morrow and Roberts, 1996). Moreover, oxidative stress through the activation of cyclooxygenases also promotes isomerization of H2-isoprostanes (H2-IsoPs) and formation of isoketals (IsoKs) (Stavrovskaya et al., 2010), as well as IsoKs isomers - isolevuglandins (IsoLGs), mainly IsoLG D2 and E2 (Xiao et al., 2018). IsoLGs are also formed in the non-enzymatic rearrangement of prostaglandin H2 as by-products of the cyclooxygenase pathway or as products of the rearrangement of prostaglandin endoperoxides (Xiao et al., 2018) (Fig. 1). Whereas the cyclooxygenase-dependent pathway yields only two γ-ketoaldehydes, the prostaglandin pathway yields 64 different IsoLGs isomers.

The formation of lipid peroxidation products directly affects the physical properties and functioning of cell membranes within which they are formed, by interrupting their lipid asymmetry, which reduces the hydrophobicity of the lipid membrane interior causing depolarization (Sen et al., 2006). This may result in loss of membrane integrity (Wong-Ekkabut et al., 2007). Regardless of the above, lipid peroxidation products, due to their structure (the presence of a carbonyl groups and carbon-carbon double bonds) and electrophilic characteristics, are chemically reactive molecules that can easily form adducts with the majority of the cell's nucleophilic components, including DNA, lipids, peptides and proteins, leading to disturbances in cell metabolism. These reactions reduce the level of reactive lipid peroxidation products, while increasing the formation of adducts with proteins that promote cell signaling disorders, hence stimulating metabolic modifications which leads to cellular dysfunction and apoptosis (Sayre et al., 2006).

3. Protein adducts with products of PUFAs fragmentation

3.1. HNE – protein adducts

4-HNE as a α,β-unsaturated hydroxyalkenal is one of the most reactive electrophilic aldehydes and probably because of that is the most frequently studied product of lipid peroxidation, which forms adducts with proteins (Anavi et al., 2015; Łuczaj et al., 2017; Riahi et al., 2010). Due to the presence of carbonyl group at the C1 carbon, double bond between the C2 and C3 carbons, and hydroxyl group on the C4 carbon, 4-HNE is highly reactive and can generate both Schiff bases and Michael adducts with proteins. The amino acid residues that are capable of forming adducts with 4-HNE are cysteine, histidine, and lysine (Barrera et al., 2015). The generation of these adducts allows for 4-HNE to transfer information regarding oxidative stress from the cell membrane to the cytoplasm, thus causing cell signaling. Due to the different locations and biological significance of the amino acids, as well as the proteins in which they occur, 4-HNE-protein adducts can affect cell

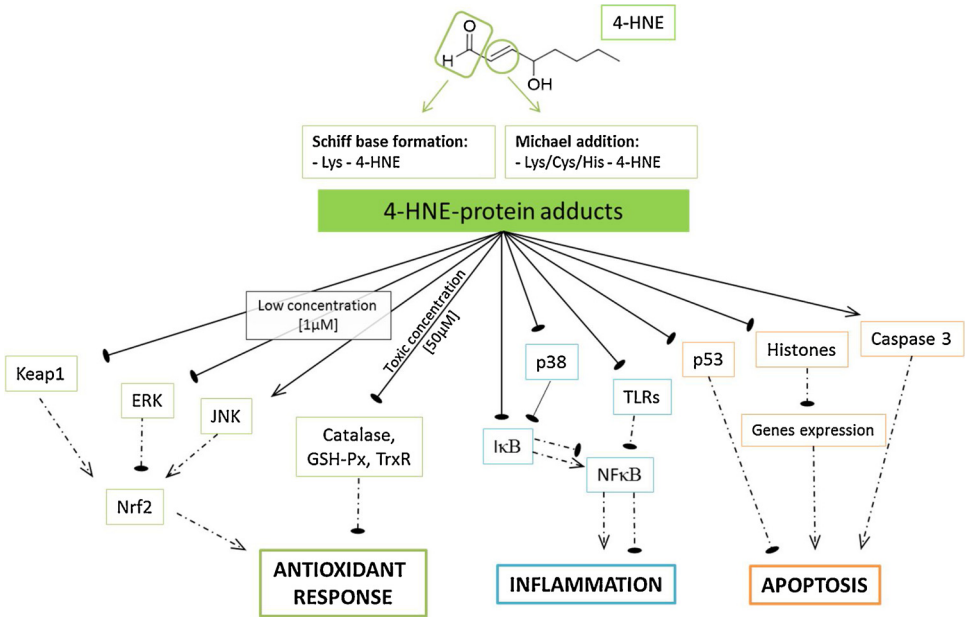

Fig. 2. 4-HNE-protein adducts formation and their effects on cellular metabolic pathways including antioxidant response, inflammation, and apoptosis (Barrera et al., 2015). Abbreviations: 4-HNE, 4-hydroxynonenal; Cys, cysteine; ERK, extracellular signal–regulated kinase; GSH-Px, glutathione peroxidase; His, histidine; IκB, inhibitor of kappa B; JNK, c-Jun N-terminal kinase; Keap1, kelch-like ECH-associated protein 1; Lys, lysine; NFκB, nuclear factor kappa B; Nrf2, nuclear factor (erythroid-derived 2)-like 2; p38, protein 38; p53, protein 53; TLRs, toll-like receptors; TrxR, thioredoxin reductase.

metabolism in various ways by activating or inhibiting metabolic pathways (Fig. 2). The formation of 4-HNE adducts are associated with antioxidant enzymes, such as catalase, glutathione peroxidase, and thioredoxin reductase, in which it is bound to the cysteine residue at the enzyme's active site and inhibits antioxidant action (Bauer and Zarkovic, 2015; Fang and Holmgren, 2006). The mechanism in which 4-HNE interacts with proteins was described for toxic concentrations of this aldehyde (10–50 μM) (Singh et al., 2005), however, it was discovered that at low concentrations (0.1–1 μM) 4-HNE may provoke a stimulating effect on the antioxidant system, especially at the level of antioxidant enzyme biosynthesis (Valko et al., 2007). Bound 4-HNE to cysteine residues of the cytoplasmic Keap1 protein (Gęgotek et al., 2018), which is the main inhibitor of the transcription factor Nrf2, promoting changes in Keap1 conformation and prevents its interaction with Nrf2. Consequently, free Nrf2 can move to the nucleus and, as a result of ARE DNA site interaction, initiate the biosynthesis of cytoprotective proteins (Itoh et al., 2003). The activity of the transcription factor Nrf2 is also influenced by its phosphorylation. Because the 4-HNE, at low concentration (0.1 μM), is capable to interacting with c-Jun N-terminal kinase (JNK), leading to activation and translocation into the cell nucleus (Gęgotek and Skrzydlewska, 2015; Parola et al., 1998), it's assumed that this interaction further promotes Nrf2 activation and an antioxidant response within the cell. However, high 4-HNE concentration (25–100 μM) causes adduct formation with extracellular signal–regulated kinases (ERK) on Cys-63 and His-230 residues (Sampey et al., 2007). Activation of the cytoplasmic ERK occurs through its phosphorylation and dimerization, which also stimulates it translocation to the nucleus, and favors phosphorylation of the nuclear transcription factors present there. 4-HNE-ERK adducts, produced by the prevention of ERK dimerization and activation, results in a decrease in Nrf2 activity, as well as loss of signal transduction, leading to disorders in homeostasis, cell proliferation, and cell viability (Lin et al., 2014).

At higher concentrations 4-HNE creates also adducts with histones, thus modifying proteins expression at DNA level. It is known that 4-HNE (50 μM) blocks histone H2A acetylation affecting its interaction with DNA and gene expression (Grune and Davies, 2003; Alzolibani et al., 2013), as well as contributing to the vulnerability of DNA to oxidation and apoptosis (Drake et al., 2004). Additionally, even at low concentrations (1 nM) 4-HNE can influence protein biosynthesis by inhibiting the activity of elongation factor-2 (eEF-2), which catalyzes the ribosomal translocation reaction, resulting in the movement of ribosomes along mRNA (Andersen et al., 2003). Therefore, 4-HNE-eEF-2 adduct formation additionally affect protein synthesis during translation (Argüelles et al., 2009).

The formation of 4-HNE adducts with proteins has a direct, as well as indirect, influence on pro-inflammatory signaling, including changes in the activity of the NFκB transcription factor. 4-HNE in high concentration (40 μM) binds to IκB, a cytoplasmic inhibitor of NFκB, thereby increasing the transcriptional activity of NFκB (Ji et al., 2001). The phosphorylation of IκB reduces its affinity to NFκB, therefore modifications of kinase activity by 4-HNE adduct formation give similar effects as for the Nfr2 factor. On the other hand, 4-HNE (concentration range 1–20 μM) interaction with Toll-like receptor (TLR) prevents this type I transmembrane protein activation. It has been reported that 4-HNE forms adducts with cysteine residues in the extracellular domain of TLR4, which suppresses dimerization and TLR4-mediated immune functions (Kim et al., 2009). TLR4 detects Gram-negative bacteria via the recognition of the lipid A moiety of lipopolysaccharide that causes TLR4 dimerization - the initial steps in the NFκB activation during microbial infection. This interaction allows the NFκB-dependent proinflammatory pathway to remain inactive even when increased 4-HNE generation occurs during microbial infection (Kim et al., 2009). Furthermore, non-toxic concentrations (0.1–5 μM) of 4-HNE may exhibit anti-inflammatory activities in human monocytes due to the inhibition of p38 kinase activity. P38 catalyzes the phosphorylation of IκB and, as a result, promotes NFκB activation, which leads to the expression of the TNFα protein. Therefore, p38 kinase activity inhibition through the formation of 4-HNE protein adducts is associated with a decrease in TNFα levels and suppression of the inflammatory response (Marantos et al., 2008). 4-HNE-protein adducts have been also proposed as a tryptophan 2,3-dioxygenase activator, which catalyzes the oxidation of L-tryptophan to N-formyl-1-kynurenine and regulates the circulation of tryptophan in the organism, which reduces humoral immunity (Gęgotek et al., 2018).

The formation of 4-HNE-protein adducts also affects the process of apoptosis, by reacting with caspase-3, causing its activation, which directly leads to the induction of apoptosis in cells that display heightened 4-HNE generation due to external factors (Mali and Palaniyandi, 2014). Moreover, a high level of 4-HNE in cells promotes the formation of Michael adducts with the p53 protein (Buizza et al., 2013). Such modifications result in conformational changes of the p53 molecule, which triggers exposure of the tyrosine residues that are particularly susceptible to nitration (Cenini et al., 2008). As a consequence, the p53 protein loses pro-apoptotic activity, which initiates the accumulation of damaged and mutated cells in the organism (Kruiswijk et al., 2015). Therefore, uncontrolled increased 4-HNE generation may interfere with proapoptotic signaling and lead to the development of pathological conditions (Łuczaj et al., 2017).

3.2. MDA – protein adducts

Malondialdehyde (MDA) is another reactive end product of lipid peroxidation. MDA shows high affinity for the formation of adducts with DNA, but its elevated level in the cytoplasm also results in MDA adduct formation with proteins through the generation of Nε- (2-propenal) lysine or 1-amino-3-iminopropene-type and pyridyl-dihydropyridine-type lysine-lysine cross-links (Del Rio et al., 2005). A common products of MDA-protein interactions are MDA-acetaldehyde-protein adducts (McCaskill et al., 2011), which are more stable than the MDA-protein adducts (Ayala et al., 2014). The formation of these adducts is characteristic of cellular stress caused by exposure to cigarette smoke or alcohol (Del Rio et al., 2005).

The formation of MDA-protein and MDA-acetaldehyde-protein adducts is indispensably associated with a pro-inflammatory reaction throughout the entire organism (Fig. 3). It was shown that an increase in MDA-protein adduct level leads to the activation of Th17 lymphocytes and triggers autoimmune reactions (Wang et al., 2012). The mechanism of MDA-acetaldehyde-protein action is based on the activation of protein kinases such as protein kinase C (PKC) (Ayala et al., 2014), which leads to the activation of factor NFκB. However, increased MDA-acetaldehyde levels in plasma, by albumin modification, influences the activation of intercellular adhesion molecule 1 (ICAM-1) and vascular adhesion molecule (VCAM) factors, directly leading to an increase in TNFα expression (Busch and Binder, 2017). In addition, increased levels of MDA-acetaldehyde-protein adducts in the plasma and blood vessels of atherosclerotic animals (Duryee et al., 2010) activate Th2 lymphocytes in atherosclerosis (Gonen et al., 2014), which in turn stimulates the secretion of pro-inflammatory cytokines such as interleukins IL6, IL8, and IL25 (Raghavan et al., 2012).

In the case of MDA, similar to 4-HNE, upon the formation of protein adducts it also affects protein biosynthesis. Through the generation of adducts with eEF-2, MDA directly blocks eEF-2 – ribosome interactions, resulting in the movement of ribosomes along mRNA stoppage and translation processes inhibition (Argüelles et al., 2009).

Collagen is a molecule susceptibly vulnerable to MDA modifications where MDA forms adducts with cysteine residues and favors glycation reactions (Slatter et al., 2000). Hence, MDA-protein adducts can affect the regeneration and reorganization of tissues. Therefore, MDA leads to collagen cross-linking and further covalent modifications, instigating a loss of elasticity and disturbance in tissue remodeling, which contributes to the development of pathology within the organism, with

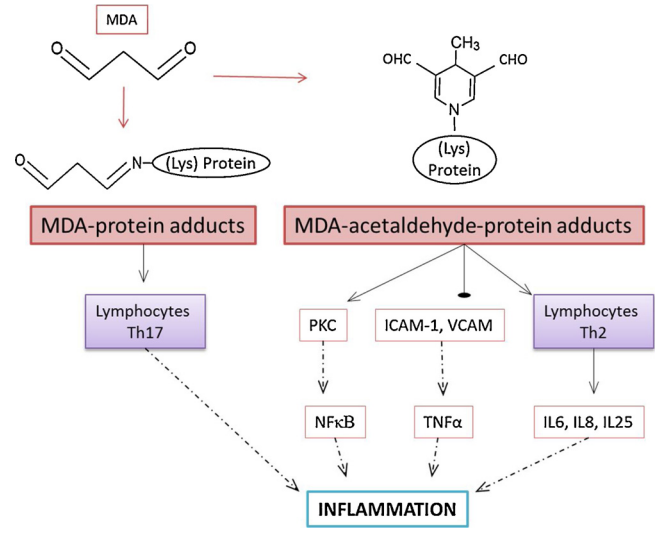

Fig. 3. The formation of MDA-protein and MDA-acetaldehyde-protein adducts and their pro-inflammatory action pathways leading to the lymphocytes Th17 and Th2 stimulation, as well as NFκB and TNFα activation (Del Rio et al., 2005; McCaskill et al., 2011). Abbreviations: ICAM-1, intercellular adhesion molecule 1; IL, interleukin; Lys, lysine; MDA, malondialdehyde; NFκB, nuclear factor kappa B; PKC, protein kinase C; TNFα, tumor necrosis factor α; VCAM, vascular adhesion molecule.

particular emphasis on the blood vessel system (Avery and Bailey, 2006; Yamada et al., 2009).

In *in vitro* cell cultures, it was shown that modifications caused by MDA also stimulate the antioxidant system of cells. Furthermore, the addition of MDA-acetaldehyde adducts activate the Nrf2 pathway, however the mechanism of action has not yet been described (Zimmerman et al., 2017).

3.3. Acrolein – protein adducts

Acrolein is a highly reactive unsaturated aldehyde with a simple chemical structure. *in vivo* acrolein is formed by intracellular metabolism, for example during threonine degradation by myeloperoxidase, amine catabolism by amine oxidase, or drug metabolism, as well as peroxidation of lipids containing polyunsaturated fatty acids (Stevens and Maier, 2008). Cytotoxicity of acrolein is associated with the formation of Michael adducts with thiol groups of cysteines, which affects the activity of selected proteins (Fig. 4) (LoPachin and Gavin, 2015). The acrolein binding reaction may occur spontaneously or be catalyzed by glutathione S-transferase (Awasthi et al., 2005).

To date, an increase in acrolein-protein adduct level is found in many pathological conditions, including spinal cord injury, photo-damaged skin, or alcoholic liver damage (Luo et al., 2005; Tanaka et al., 2001; Chen et al., 2015), and is accompanied by an increase in ROS and lipid peroxidation products generation. Reports have shown that acrolein creates specific adducts with PKC in the mitochondria that cause a significant decrease in kinase activity and inhibits intra-mitochondrial signaling (Wang et al., 2008), thereby altering the function of organelle, cellular respiration, and contributing to the generation of ROS. However, after affecting the protein maturation in the endoplasmic reticulum, as well as impairing the action of the antioxidant system (mainly by inhibiting the activity of glutathione S-transferase), acrolein significantly contributes to the generation of oxidative stress (Henning et al., 2017). In addition, acrolein significantly impairs the efficiency of the antioxidant system in pathological states by binding to the cysteine residue in glutathione or thioredoxin (Moghe et al., 2015). Under oxidative stress, acrolein adducts also change cell's metabolism via modification of the expression of cytoprotective proteins, since acrolein forms adducts with histones hindering acetylation, which limits gene expression (Esmaeili et al., 2017). In addition, *in vitro* studies have shown acrolein adduct formation with histones occurs without disturbing the redox balance in the cell (Fang et al., 2016). Higher concentration of acrolein also promotes the production of histone-histone cross-links (Chen et al., 2013).

The acrolein-protein adducts modify the expression of proteins at biosynthesis level but can also affect their degradation. It was shown that acrolein-protein adducts cause p53, p21 and p38 protein activation, directly leading to ligases activation, suggesting the role of acrolein in protein degradation (Rom et al., 2013). Acrolein also forms adducts with proteases, however, the nature of these interactions has not yet been described (Maeshima et al., 2012). The generation of acrolein adducts with enzymes, such as aldose reductase, blocks enzymatic activity and prevents the reconstruction of damaged tissues, which is particularly dangerous in the case of disturbed myocardium regeneration (Keith et al., 2009).

Acrolein-protein adducts are the most common cell signals for apoptosis. Acrolein has been shown to attach and activate ERK or JNK kinases, thus indirectly initiating the apoptosis process (Tanel and Averill-Bates, 2007; Chen et al., 2016). Simultaneously, acrolein

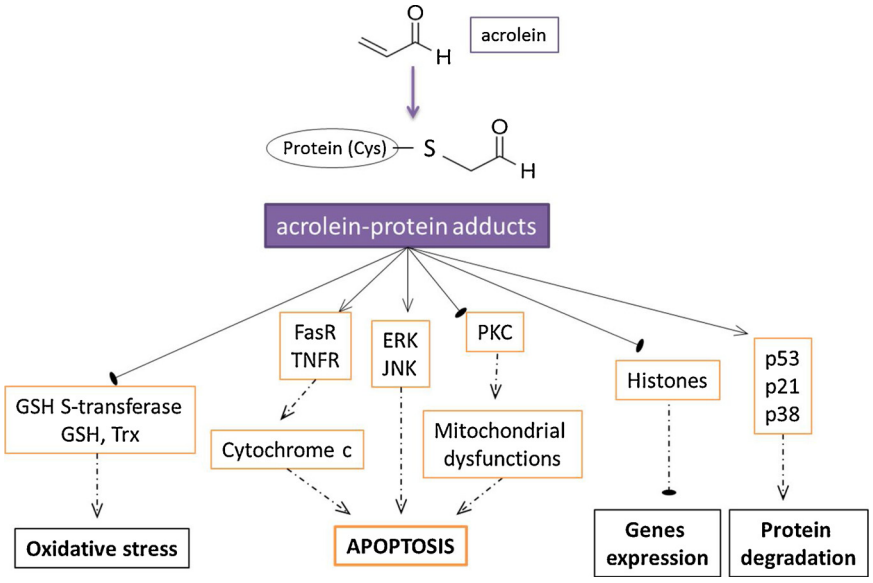

Fig. 4. The formation of the acrolein-protein adducts and their prooxidative and proapoptotic effect on cell functioning (LoPachin and Gavin, 2015). Abbreviations: Cys, cysteine; ERK, extracellular signal–regulated kinase; FasR (APO-1), apoptosis antigen 1; GSH, glutathione; JNK, c-Jun N-terminal kinase; p21, protein 21; p38, protein 38; p53, protein 53; PKC, protein kinase C; TNFR, tumor necrosis factor receptor.

interacts with Fas (Apo-1) death receptors and tumor necrosis factor receptor, resulting in the release of cytochrome C from the mitochondria and activation of caspases, thus directing the cell towards the apoptotic pathway (Yang and Seto, 2008).

Furthermore, acrolein reduces proteins level such as zonula occludens-1, occludin, and claudin-1, which limit the permeability of epithelial cell membranes, thereby disturbing the functioning of the membrane as a natural protective barrier not only for cells but the entire organism (Chen et al., 2017).

4. Protein adducts with products of PUFAs cyclization

Isoprostanes (IsoPs), stereoisomers of prostaglandins, are commonly found in biological fluids, such as blood, urine, or cerebrovascular fluid. *in vivo*, they are formed as a result of ROS-dependent peroxidation of arachidonic acid (AA). This process is independent of cyclooxygenase enzymatic activity, an enzyme that catalyzes the transformation of AA into prostaglandins (Korotkova and Lundberg, 2014). IsoPs are formed when PUFAs are associated with a glycerol backbone of phospholipid, and the hydrolytic activity of PLA2 within the membranes and acetylhydrolase of platelet activation factor in blood is essential in order to release them from esters (Bochkov et al., 2010).

Nowadays, it is considered that the main role of IsoPs is the function in modulation of inflammatory signaling (Roberts and Morrow, 2002). F2-IsoPs are potent vasoconstrictor in most vascular beds and can modulate platelet activity, inhibit angiogenesis, and promote atherosclerosis by stimulating adhesion of monocytes and neutrophils to endothelial cells. Their activity is primarily mediated through interaction with thromboxane as well as prostaglandin receptors (Wu et al., 2015). However, A2/J2-IsoPs undergoes Michael addiction reactions with thiol generating protein adducts (Fig. 5) (Milne et al., 2004). Hence, for example, they inhibit NFκB, induce heat shock protein transcription and modulation of cellular proliferation (Musiek et al., 2005). Upon adduct formation with proteins they can be directly metabolized by glutathione S-transferase to water soluble conjugates that are easily removed from the cell (Milne et al., 2005). It was proposed that the formation of lipid peroxidation product adducts with cysteine residues of enzymatic proteins invokes conformational changes, blocks the catalytic center or co-factor binding site, thereby affecting protein activity (Domingues et al., 2013). However, as yet, no specific proteins have been identified that can form adducts with IsoPs, so it is not clearly explained how IsoPs adducts with protein cysteines affect cell metabolism.

Isoprostanoids metabolism products - IsoKs can also play a role in the modification of protein structure, IsoKs are highly reactive molecules that produce toxic adducts with phosphatidylethanolamine (Sullivan et al., 2010). IsoKs molecules contain aldehyde and ketone groups adjacent to each other, whereby IsoKs can react with the ε-amino group of the protein lysine residue, creating the Schiff base (Roberts and Fessel, 2004). The molecules which are most vulnerable to modification by IsoKs are membrane proteins that can be covalently modified by IsoKs to bind with phospholipids, forming a heterotrimeric complex consisting of a phospholipid-IsoK-protein (Brame et al., 2004). In this way, IsoKs can modify the structure of proteins, creating transmembrane ion channels, mainly potassium channels, thus, causing membrane depolarization (Nakajima et al., 2010). Another protein interacting with IsoKs is sirtuin (SIR-2.1), a lysine deacetylase located in membrane-bound subcellular and membrane-rich compartments (e.g., mitochondria). According to SIR-2.1 localization, it is very close to the membrane lipids that are precursors of IsoKs. The formation of IsoK to SIR-2.1 adducts reduces the enzymatic activity of this protein (Nguyen et al., 2016), which increases acetylated protein levels. Acetylation not only neutralizes the positive charge of the lysine side chain, but also impairs its ability to create hydrogen bonds. Therefore, acetylated proteins in the cytoplasm significantly affect the protein-protein interactions, as well as intracellular signal transduction (Chen et al., 2016).

The elevated level of free IsoKs in the cells cytoplasm increases the amount of IsoKs adducts with cytoplasmic proteins, which significantly reduces 20S proteasomal degradation of such proteins (Davies et al., 2002). IsoKs modified proteins are labeled for degradation, however, the modification of their structure by IsoKs results in blocking proteasome activity, thus leading to an accumulation of IsoK-protein-protease

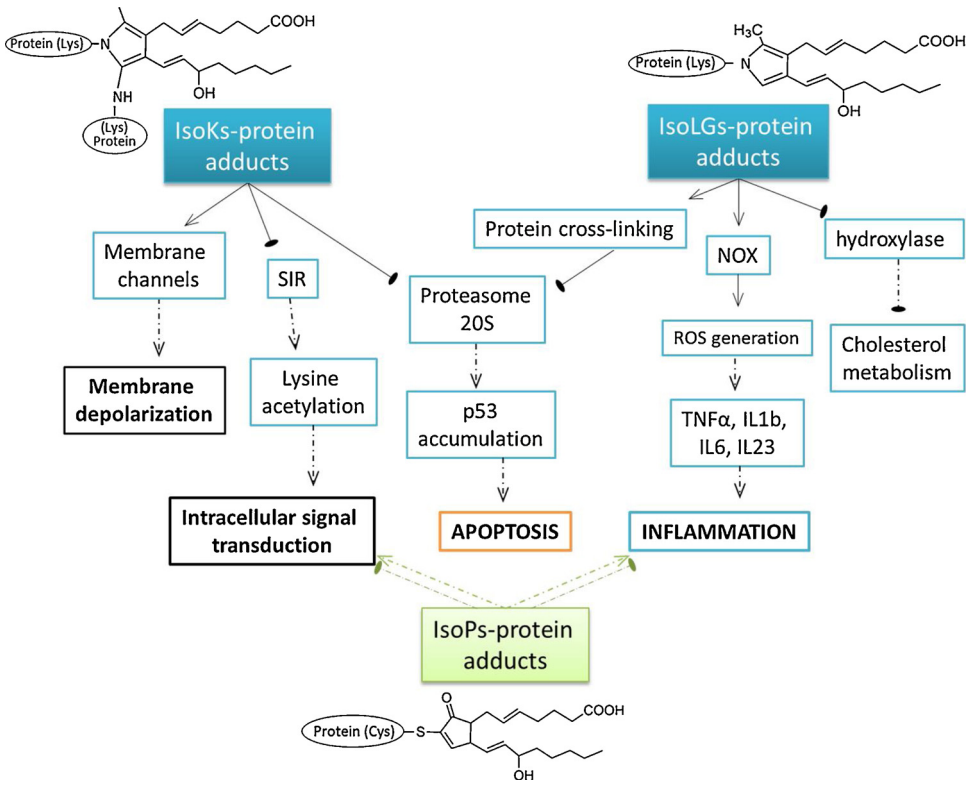

Fig. 5. The effect of protein adducts with products of PUFAs cyclisation on inflammation, apoptosis and intracellular signal transduction (Milne et al., 2004; Roberts and Fessel, 2004; Salomon and Bi, 2015). Abbreviations: Cys, cysteine; IL, interleukin; IsoKs, isoketals; IsoLGs, isolevuglandins; IsoPs, isoprostanes; Lys, lysine; NOX, NADPH oxidase; p53, protein 53; ROS, reactive oxygen species; SIR, sirtuin; TNFα, tumor necrosis factor α.

complexes (Davies et al., 2002). Inhibition of proteasomal degradation often allows for the accumulation of continuously synthesized proapoptotic proteins, such as p53, which leads to neurodegeneration through the activation of programmed cell death pathways (Balser et al., 2014). There are numerous studies that show an increase in the level of IsoKs-protein adducts for many diseases, such as atherosclerosis, myocardial infarction, hypertension, and Alzheimer's disease (Salomon and Bi, 2015; Fukuda et al., 2005; Davies and May-Zhang, 2018; Wu et al., 2016; Zagol-Ikapitte et al., 2005).

Another PUFAs cyclization product is IsoLGs, which, similar to IsoKs, modifies proteins by forming Schiff bases with the ε-amino group of the protein lysine residue. For example, the mitochondrial C27-hydroxylase (CYP27A1), which acts as an enzyme that degrades cholesterol, is susceptible to such modifications. The attachment of IsoLG to the lysine residues at position Lys134, Lys358, or Lys476 significantly reduces the activity of the enzyme in *in vitro* experiments (Salomon and Bi, 2015). Moreover, IsoLGs, similar to IsoKs, block the proteolytic process by binding to proteins, thereby activating the NFκB transcription factor and leading to the proinflammatory reaction (Davies et al., 2002, 2007). Regardless, IsoLGs, through covalent modifications of proteins, create cross-linked molecules, additionally preventing their proteolysis (Salomon and Bi, 2015).

IsoLG-protein adducts are also involved in the signal transmission between blood cells. The appearing stimuli activate NADPH oxidase in antigen presenting cells (APC), thus increasing the level of ROS and consequently promoting oxidation of arachidonic acid as well as the generation of a large amount of lipid peroxidation products, including IsoLGs. IsoLG reactions with cytoplasmic proteins producing immunogenic adducts. Modified proteins stimulate APCs to generate proinflammatory cytokines, including interleukins IL1b, IL6, and IL23. These interleukins stimulate T lymphocytes to proliferate and produce signaling molecules, including IL-17A, TNF-α, and IFN-γ, which can lead to the development of various diseases, such as hypertension (Kirabo et al., 2014).

5. Conclusion

The products of lipid peroxidation, which are an indispensable outcome of cell metabolism as well as external physical factors/xenobiotics action, have a significant impact on cell functioning by affecting the structure and activity of proteins. However, their role depends on the condition of the cells and can range from the activation of specific signaling molecules that stimulate cytoprotective activity to the production of highly toxic molecules, which induces apoptosis.

Conflicts of interests

The authors declare no conflicts of interests.

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