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Pathophysiology And the Biochemical and Clinical Significance of Malondialdehyde

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ABSTRACT: Malondialdehyde is a highly reactive three-carbon dialdehyde that is produced via lipid peroxidation. Lipid peroxidation is an oxidative degradation process of lipids that leads to the generation of reactive species of oxygen and free radicals. These highly reactive molecules can act upon DNA, proteins, and lipids, resulting in several pathological effects. Since MDA is capable of reacting with several cellular macromolecules like proteins, DNA, and phospholipids, it has been suggested as a possible causal factor in the pathogenesis of numerous human diseases. Therefore, the knowledge of formation and metabolism of malondialdehyde is essential for the comprehension of its biochemistry and clinical significance.

1. INTRODUCTION TO MALONDIALDEHYDE

Malondialdehyde, along with other aldehydes and compounds like 4-hydroxy-alkenal, is one of the major products resulting from the oxidative damage of phospholipids, notably arachidonic acid. MDA is extremely reactive and can readily react with amino acids of proteins for producing MDA-protein adducts. Such adducts modify both the structure and action of proteins, further enhancing oxidative stress.

The decomposition products of lipid peroxides into MDA occur due to their low molecular weight, and this property makes them highly inflammatory. MDA is a very active signaling molecule in the initiation and perpetuation of the response to an inflammatory stimulus. MDA levels are increased in neurodegenerative diseases: Alzheimer's, Huntington's, and Parkinson's; as well as other pathological states: atherosclerosis, hyperlipidemia, chronic obstructive pulmonary disease (COPD), cystic fibrosis, chronic bronchitis, hepatotoxicity, rheumatoid arthritis, and lung cancer, ischemia-reperfusion injury (Ayala et al., 2014).

The MDA-hs adducts have now emerged as a vital biomarker of oxidative stress and have been determined in a variety of human diseases. Durable compounds of MDA were identified in lipid extracts obtained at different states of IO rat liver. The data suggested that an MDA-albumin adduct could be formed during the oxidative peroxidative effect of iron overload. The concentration ratios of MDA and its class of LE fractions depend on the degree of LPO and the effectiveness of their decomposition by antioxidants. Compounds with MDA components were suggested to form the basis for covalent adduction of MDA and albumin protein during tissue injury (Wang et al., 2014).

Understanding the formation and metabolism of malondialdehyde is therefore paramount for its biochemistry and clinical significance.

1.1. Chemical Structure

Malondialdehyde (MDA) is a simple aldehyde composed of a six-carbon chain with aldehyde groups at both ends. It has two forms, L- and D-, although naturally only the L-form occurs. Because it is unsaturated, MDA is an aldehyde of very high reactivity and can polymerize spontaneously with certain proteins, thereby possibly inhibiting their biological functions. MDA is largely produced as a byproduct of lipid peroxidation; lipid peroxidation is the reaction of unsaturated fatty acids, in membrane lipids, with reactive oxygen species like superoxide ions, hydroxyl radicals, or peroxyl radicals. Lipid peroxidation subsequently yields a variety of aldehydes: 2-propenal, butenal, crotonaldehyde, hexanal, 4-hydroxyalkenal, and MDA. MDA is easily formed because it is the end product of radical oxidation of polyunsaturated fatty acids during the peroxidation of membrane phospholipids.

The MDA molecule contains one carbonyl group and one reactive double bond within a β-carbonyl structure, which is responsible for the enhanced reactivity of MDA toward a variety of biologically relevant low-molecular-mass nucleophilic compounds such as glutathione and proteins. These reactions yield different adducts and cross-linked products that are able to covalently modify protein

amino acid side chains. MDA has been reported to readily react with arginine, lysine, cysteine, and histidine residues (Onyango & Baba, 2010)

1.2. Formation and Metabolism

Malondialdehyde (MDA) is a three-carbon aldehyde compound produced during the process of lipid peroxidation of unsaturated fatty acid and is one of the major toxic products of membrane lipid peroxidation. This MDA becomes highly reactive to the other tissues and biological fluid components after membrane lipid peroxidation. Since MDA can react with a wide variety of cellular macromolecules (protein, DNA, phospholipids), it has been considered a possible causing factor in the development of different human pathologies. (Traverso et al., 2002004).

Reactive products of lipid peroxidation that are derived from cellular membranes may, after oxidative injury, accumulate in biological tissues and biological fluids. One of the most indicative and one of the earliest arising products in lipid peroxidation is malondialdehyde (MDA) formed from phospholipids of the membrane. MDA can react with amino acids to form carbonyl derivatives, which are characterized as advanced lipid peroxidation end products. The production of MDA-protein adducts and carbonylated cysteine or histidine mediators is proposed as potentially initiating events for oxidative cell signaling, including calcium mobilization. (Pineda-Alemán et al., 2023).

MDA has been detected and measured in various mammalian tissues or organs including kidney, lung, brain, and liver. Enzyme activities involved in the removal of MDA adducts were found in a variety of tissues including liver, kidney, brain, and heart. MDA was produced at a higher relative quantity in the aqueous phase at acidic pH than in an aerobic environment, 1-3. At pH 5.5, the half-life of the diformyl compound 66 is frozen out and is no longer able to form MDA. Although in vivo MDA-protein interactions were suggested to involve free protein amino groups, both in vitro and in vivo MDA can react with the carbon side chains and 6-amino groups of lysine, and MDA can readily unite with sulfhydryl groups to produce thiol-S-methylation derivatives of cysteine. The formation of MDA in vivo is inhibited by ethoxyformic acid, a lipoxygenase inhibitor. The isomerization of DEA and HEAA with time yields 1-hexenoic acid, suggesting that the vinyl conjugate isomer ease DAS and DEAA employed a radical mechanism characterized by carbon skeleton rearrangement followed by fragmentation (Tuma, 2002).

2. BIOCHEMICAL PROPERTIES OF MALONDIALDEHYDE

Malondialdehyde is a simple aldehyde that is an important intermediate in the metabolism of polyunsaturated fatty acids. It reacts with both intracellular and extracellular biomolecules to form adducts that are known as MDA-modified biomolecules. These adducts are important biomarkers of polyunsaturated fatty acid lipid peroxidation. MDA clearly has multiple effects on cellular and molecular processes that are distinct from lipid peroxidation. It has the potential to exert pro-oxidant effects by enhancing lipid peroxidation within cells. However, MDA also has the potential to exert antioxidant properties by reduction in 1O2 production and membrane peroxidation besides modulating cellular responses to oxidative stress. In addition to this, MDA itself is a potent cytotoxic mediator because of its reactivity with cellular proteins and other biomolecules. Finally, MDA modifies proteins by adduct formation on ways further reactions that lead to protein aggregation, loss of function, proteolytic resistance, altered proteolytic processing, and other events that eventually end in dysfunction and cell death. In other words, MDA has unique biochemical properties that may be capable of simultaneously exerting distinct pro- or antioxidant; cytotoxic; and cellular signaling effects. As a simple lipid peroxidation product, it may act as a more complex signal than previously thought.

As such, lipid peroxidation is somewhat of a misnomer because this process actually involves the oxidative degradation of lipids to give a complex mixture of species of oxidized lipids. It seems well accepted that one of the prime events linked to the cellular and tissue damage induced by oxidative stress is the peroxidation of polyunsaturated fatty acids and phospholipids, leading to the formation of lipid hydroperoxides. The primary and secondary products associated with this hydroperoxide forming chain reaction make up a large and varied family of compounds, resulting from the oxidation of all classes of lipids. Among them are a large number of hydrocarbons, carbonyls, alcohols, ketones, esters, oxoacids, heterocyclics, furans, and oxirenes. Of particular interest among these advanced glycation end products (AGEs) are the reactive carbonyl compounds (RCCs) generated in secondary processes of lipid peroxidation due to their ample reactivity toward biological nucleophiles like proteins, nucleic acids, aminated lipids, or thiols, leading to deleterious effects (Sapkota et al., 2017).

2.1. Role in Oxidative Stress

Both Extracellular and intracellular sources in biological systems contribute to a complex network of generation of free radicals and other reactive oxygen species as by-products of oxidative biochemical processes. It has been proposed that the ability of free radicals to induce cellular injury is mediated by a deficiency in antioxidant defenses. More than 200 classes of compounds are known to act as antioxidants to help maintain physiological redox state in vivo. The action of these antioxidants includes radical scavenging of hydrogen atoms or electrons, metal ion chelation, formation of unreactive adducts, and nutrient precursor actions. All are believed to prevent the initiation and propagation of free radical chain reactions. Pro-oxidant actions occur with these compounds at concentrations exceeding a presumed threshold level. Some can act as promoters of cell proliferation and malignancy. The mechanism of radical generation and toxicity by these compounds is unclear (Slimen et al., 2014).

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Polyunsaturated fatty acids (PUFAs) are the targets of free radicals leading to lipid peroxidation, a free radical chain reaction. The peroxidation products of PUFAs greatly affect cellular functions. They include cyclic endoperoxides which have been proposed to act as agonists to excitatory neurotransmitter receptors, hydroperoxides, and aldehydes. These aldehyde end-products are very reactive toward nucleophiles in proteins, lipids, and nucleic acids. Non-enzymatic reactions of aldehydes with biomolecules form amphiphilic and lipophilic adducts, leading to the formation of cross-linked polymers. MDA is currently assessed as an index of lipid peroxidation by various methods, including the measurement of adduct formation with thiobarbituric acid and HPLC techniques employing fluorescence detection. Norepinephrine and dopamine. It is believed to be a sensitive biomarker of oxidative damage. However, it has low specificity as free aldehydes can form similar adducts (Ng et al., 2022).

The pathophysiological consequences of MDA-induced macromolecular changes remain largely unknown. The cross-linking of proteins consisting of MDA-lysyl and MDA-cysteinyl adducts may affect catalytical efficiency, solubility, bioavailability, and degradation of proteins. MDA-deoxynucleosides binding to N-7 guanine and N-1 adenine may lead to cytotoxicity and mutagenicity, depending on the intra- and extracellular milieu. MDA-induced 1,N2-propanodeoxyguanosine lesions in DNA may affect replication fidelity, leading to the substitution of guanine and adenine bases. Such oxidative lesions have been detected in human atherosclerosis, lung cancer, and other diseases. It is presently unclear whether the formation of MDA-36R-1 and MDA-N2-aminofluorescein-modified nucleoside adducts occur in vivo. Recent studies indicate a significant increase of MDA-MA adducts in the protein fraction of aorta, liver, kidney, and brain from diabetic rats and in the serum proteins of alcohol-fed rats. However, direct evidence for other types of adducts in pathophysiological conditions is lacking (Cajanding, 2019).

3. PHYSIOLOGICAL FUNCTIONS OF MALONDIALDEHYDE

With the overall knowledge of malondialdehyde (MDA), a brief exploration of the physiological functions of MDA is given. MDA is a rather multifactorial nature important signaling molecule, functioning in processes in both plant and animal physiology. It acts as a second messenger in response to stress tolerance, growth, and development and also regulates enzyme activities and gene expression to mediate diverse cellular responses. There is increasing evidence supporting MDA as implicated in cellular homeostasis. On the one hand, it is involved in the general regulation of macromolecules since the compound itself has a wide range of controlling properties, for example, the stabilization of nucleic acids and translational inhibition. On the other hand, it regulates multiple protective pathways through ROS scavenging and enhancing anthocyanin biosynthesis and peroxidase activity in MDA-signaled cells (Xu & Rothstein, 2018).

Malondialdehyde (MDA) is the major carbonyl product of lipid peroxidation resulting from polyunsaturated fatty acids and is a dialdehyde of three carbons. The confusion in nomenclature has been because MDA does not arise only from lipid oxidation but also from the nonoxidative decomposition of amino acids and carbohydrates. MDA is involved in a plethora of physiological functions while initially being considered a harmful second messenger with various detrimental effects, such as protein modification, lipotoxicity, and DNA mutation, at higher concentrations. The discovery of its important roles in multiple physiological processes in both plants and animals has recently emerged, marking the "paradoxical" nature of MDA. In general, the regulatory pathways regulated by MDA are distinct from those regulated by hydrogen peroxide (H2O2) or nitric oxide (NO) and are dependent on concentrations, physiological contexts, and agents that promote MDA formation and accumulation (Afzal et al., 2023).

3.1. Signaling Molecule

Emerging evidence indicates that MDA is an important signaling molecule. It is proposed as an integral part of Ca2+ signal networks, mediating cytosolic Ca2+ concentration and oscillation patterns and activating diverse downstream Ca2+-dependent processes in the establishment of salt tolerance, growth, and development. It can regulate enzyme activity by copper ion coordination and hydroxymethylation on its histidine residues at a low concentration. MDA is also involved in gene expression modulation, including enhancements in the transcription of antioxidant genes, LRR-RLK, ethylene biosynthesis-related genes, and PERK1 and IRE1. It inhibits the transcription of cyclic nucleotide phosphodiesterase, phospholipase C, and lipoxygenase genes at high concentrations (Lankin et al., 2022).

3.2. Cellular Homeostasis

Malondialdehyde (MDA), the simplest dialdehyde formed from lipid peroxidation, is involved in several physiological processes. MDA levels in the body can be used as a biomarker for the oxidative stress associated with various diseases such as cancer, obesity, cardiovascular disease, and diabetes. 4-hydroxynonenal and malondialdehyde, low-molecular-weight and highly reactive intermediates in lipid peroxidation, are formed non-enzymatically by the oxidative degradation of polyunsaturated fatty acids (PUFAs). Numerous studies have demonstrated that excessive exposure to MDA negatively affects cellular physiology and viability by altering cellular redox homeostasis. Though those experimental efforts have increased the understanding of MDA-induced toxicity, the molecular mechanism of such changes remains to be fully understood (Esterbauer et al., 1991).

Current studies indicated that MDA causes cellular injury and studies how vascular endothelial cells respond to MDA. The injury was characterized by changes in cell morphology, inhibition of endothelial cell migration, increased cellular permeability, and disruption of adherens junctions. In addition to these early events, the aberrant expression of JNK-2 and ATF-2 was found as late

consequences of BME and MDA-induced cellular injury. It was found that MDA inhibits basal migration of human umbilical vein endothelial cells (HUVECs) in a concentration-dependent manner. While HUVECs would migrate into a fibrinogen-coated space in the absence of MDA, they appeared immobile on the same surface in the presence of MDA. Most adherent cells became rounded up after 10 min of exposure to 5 and 10 µM MDA, while cells gathered into colonies that translocated to the fibrinogen-coated space in response to serum within the same time period.

MDA-induced cellular injury and the initial interaction of MDA with endothelium have upstream vascular biological significance. The initiation of atherosclerosis is intimately related to the deposition of lipoproteins in large arteries. The oxidized LDLs (oxLDL) are cytotoxic to vascular endothelial cells and smooth muscle cells and are implicated in the progression of atherosclerosis. The oxLDL includes lipids as well as proteinaceous components. Though the degree of atherogenicity is heterogeneous, several oxLDL's protein components have been identified and characterized as immunogenic, cytotoxic, and of altered activity. MDA and 4-hydroxy-nonenal are major low molecular weight products of lipid peroxidation formed during the oxidation of polyunsaturated fatty acids containing lipids, such as those found in membranes and lipoproteins, and have been implicated in cellular injury. They are hydroxyl-terminated reactive carbonyls that can covalently modify proteins through nucleophilic attack by lysine amine groups, cysteine thiol groups, and imidazole groups that result in the irreversible formation of fluorescent crosslinked protein aggregates (Lankin et al., 2023).

4. PATHOLOGICAL IMPLICATIONS OF MALONDIALDEHYDE

In recent times, research has yielded strong support for the role of oxidative stress in the pathogenesis of various diseases. As an important by-product of oxidative stress, malondialdehyde (MDA) is thought to play a significant role in disease processes. It is now being viewed as a biomarker in the evaluation of the content and enzyme activity of the lipid peroxidation system. MDA is rapidly assuming vital impetus as a worthy target for pharmaceutical initiatives. The spectrum of changes brought about by lipid peroxidation on membrane phospholipid composition consequently alters membrane structure and function. Thus, there are no barriers to looking for drugs that selectively block or regulate the effect of peroxides, peroxyl radicals, processes of MDA formation, and conjugated diene fatty acids production. (Lankin et al., 2023).

4.1. Cardiovascular Diseases

Malondialdehyde is the principal end-product of polyunsaturated fatty acid peroxidation reaction under oxidative stress through which MDA is formed. Polyunsaturated fatty acid-derived cytotoxic products of the HNE type composed of 4-hydroxy-2,3-alkenal active components are generated under oxidative stress conditions by both lipoxygenases and cyclooxygenases enzymes. MDA has been applied as a lipid peroxidation marker in clinical diagnostics of a wide array of pathologies. The role of oxidative stress as the principal factor in the pathogenesis of cardiovascular diseases and atherosclerosis is being currently actively discussed. An important aspect for the development of this hypothesis was data obtained from model experiments on a dog, rabbit, rat, pig when undergoing tests for tissue and plasma nitro fatty acids with human coronary disease. Consequently, disease prevalence in these mammals with tissue and plasma nitro fatty acids higher than that biomarker observed for humans is clearly indicative that MDA may also participate in diseases of cardiovascular origin promoting infarction and apoptosis. (Lankin et al., 2022).

Lipid peroxidation is one kind of chain reaction that can damage various structures in mammalian cells such as cellular lipoproteins, phospholipids, and polyunsaturated fatty acids. These lipid peroxidation products also include various aldehydes. MDA, one of the toxic products resulting from lipid peroxidation, is a 3-carbon dialdehyde. High levels of MDA can result in toxicity including growth inhibition, cytolysis, and DNA damage in various cells. MDA can induce several important hallmarks of cancer and disease in normal and immortalized cell lines. MDA can trigger apoptotic cell death via ROS upregulation in renal mesangial cells. MDA exposure can trigger cell senescence in human umbilical vein endothelial cells (Ayala et al., 2014).

4.2. Neurodegenerative Disorders

The role of oxidative stress in neurodegenerative diseases and the research on oxidative stress byproducts as diagnostic markers have demonstrated that malondialdehyde is an important biomarker for oxidative brain damage. The balance between reactive oxygen species (ROS) production and antioxidant defense plays a crucial role in neurodegenerative conditions. Excessive ROS production can promote cell death through apoptosis, necrosis, and autophagy. Mitochondria are the primary generators of ROS and the primary targets for oxidative damage in neurons. All neurodegenerative conditions are associated with oxidative stress within the brain, and many studies have determined the existence of elevated levels of lipid peroxidation byproducts, especially malondialdehyde and related substances (Haro Girón et al., 2023).

5. ROLE OF MALONDIALDEHYDE IN CANCER DEVELOPMENT

Malondialdehyde (MDA) is a highly reactive biogenic aldehyde that is considered one of the important byproducts of lipid peroxidation. Upon the generation of lipid hydroperoxides, MDA may be formed through a series of degradation steps involving alkoxyl radicals, 1,4-dicarbonyls, and singlet oxygen. The formation of MDA is acutely associated with an imbalance between pro-oxidants and anti-oxidants as loss of membrane phospholipids, cytotoxicity, and direct aberrations of proteins and deoxyribonucleic

acids. MDA-like, aldehydic products are believed to mediate important toxic effects of endogenously produced free radicals. A wealth of data suggests that free radicals, lipid peroxidation, altered levels of certain fatty acids, and anti-oxidant enzyme systems play a vital role in initiation, promotion, and progression stages of carcinogenesis. Indeed, a close correlation between free radicals and cancer has been drawn; however, the precise molecular mechanism underlying the multi-stage development of cancer is unclear (Zhang et al., 2002).

Lipid peroxidation has been proposed to play an important role in tumor initiation. It has been shown that several mutagens are able to induce lipid peroxidation, whereas tumor inhibitors do not. Accumulation of the lipid peroxidation products can also lead to a direct modification of cellular macromolecules such as proteins and nucleic acids. Various types of modified proteins can be generated following detection of 4-hydroxy-2-alkenal. More stable products such as pyrroles may further be formed. The results suggest that through an oxidative process, MDA-type aldehydes may modify enzymes or other proteins with important effects on cellular function. Cancer cells may differ from normal cells by their resistance to lipid peroxidation. Studies of metabolic byproducts and/or mRNA of enzymes involved in the synthesis and degradation of arachidonic acid metabolism have provided evidence in favor of involvement of lipid peroxidation in the carcinogenic process (Ray & Husain, 2002).

6. MALONDIALDEHYDE AS A BIOMARKER OF DISEASE

Malondialdehyde (MDA) is known as a marker for various toxicological studies and used as a reliable biomarker of the oxidative stress status. The biochemical mechanistic information regarding MDA was initially provided by a well-known biochemist. MDA is associated with several diseases like neurological disorders, cardiovascular diseases, liver dysfunction, diabetes mellitus, and cancer. MDA and acetaldehyde stimulate the permeability of cerebral microvessels. Increased vascular permeability can amplify the effects of excitatory amino acids and involve an early change in the course of developing focal brain damage. The MDA scission site of DNA is counter-selected by DNA damage recognition systems, which suggests that MDA formation represents a significant pathway of endogenous DNA damage. Administration of MDA leads to systemic arterial hypertension and accompanying vascular changes. Increased MDA levels indicate an increase in lipid peroxidation and imply the role of oxidative stress in the pathogenesis of the disease. Diabetic patients have significantly higher serum MDA content than healthy individuals. These significant levels of elevated MDA indicated an increase in lipid peroxidation (Haro Girón et al., 2023).

7. CONCLUSION AND FUTURE DIRECTIONS

Malondialdehyde (MDA) is an unsaturated aliphatic aldehyde molecule with a low molecular weight. This molecule belongs to the family of reactive aliphatic aldehyde compounds with electrophilic properties. It is a three-carbon compound and one of the primary polyunsaturated aldehyde reaction products of lipid peroxidation. MDA is usually measured with high-performance chromatography (HPLC) and then various spectrophotometric techniques. It can be determined directly or indirectly. The indirect methods use one of the MDA molecules' reactions, usually with thiobarbituric acid (TBA) and carbonyl compounds, to form a chromogen pigment in acidic solutions. The colorimetric method was developed by Yagi in 1976 and has then undergone several modifications. Although this method has been widely used, it has been shown that the reaction between MDA and TBA is not selective. Other aldehyde molecules with a similar structure can also react with TBA to yield chromogenic pigments, leading to misinterpretation of the results. MDA is of great importance to human health because it greatly contributes to the development of important diseases. Many studies have summarized the link between MDA levels in biological fluids (e.g., blood, liver, kidney, etc.) and the pathogenesis of specific diseases (stroke, cancer, myocardial infarction, diabetes, chronic gastritis, etc.). Moreover, the role of MDA in cell signaling transduction pathways needs to be continuously explored. As the involvement of MDA in human health becomes gradually understood, its interactions with proteins or SNARE proteins will also be a hot topic in the future.

8. REFERENCES

1) Afzal, S., Abdul Manap, A. S., Attiq, A., Albokhadaim, I., Kandeel, M., & Alhojaily, S. M. (2023). From imbalance to impairment: the central role of reactive oxygen species in oxidative stress-induced disorders and therapeutic exploration. Frontiers in pharmacology, 14, 1269581. https://doi.org/10.3389/fphar.2023.1269581
2) Ahmad, R., Tripathi, A. K., Tripathi, P., Singh, S., Singh, R., & Singh, R. K. (2008). Malondialdehyde and protein carbonyl as biomarkers for oxidative stress and disease progression in patients with chronic myeloid leukemia. In vivo (Athens, Greece), 22(4), 525–528.
3) Ayala, A., Muñoz, M. F., & Argüelles, S. (2014). Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxidative medicine and cellular longevity, 2014, 360438. https://doi.org/10.1155/2014/360438
4) Bartoli, M. L., Novelli, F., Costa, F., Malagrinò, L., Melosini, L., Bacci, E., Cianchetti, S., Dente, F. L., Di Franco, A., Vagaggini, B., & Paggiaro, P. L. (2011). Malondialdehyde in exhaled breath condensate as a marker of oxidative stress in different pulmonary diseases. Mediators of inflammation, 2011, 891752. https://doi.org/10.1155/2011/891752

5) Cajanding R. J. M. (2019). MDMA-Associated Liver Toxicity: Pathophysiology, Management, and Current State of Knowledge. AACN advanced critical care, 30(3), 232–248. https://doi.org/10.4037/aacnacc2019852
6) Esterbauer, H., Schaur, R. J., & Zollner, H. (1991). Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free radical biology & medicine, 11(1), 81–128. https://doi.org/10.1016/0891-5849(91)90192-6
7) Haro Girón, S., Monserrat Sanz, J., Ortega, M. A., Garcia-Montero, C., Fraile-Martínez, O., Gómez-Lahoz, A. M., Boaru, D. L., de Leon-Oliva, D., Guijarro, L. G., Atienza-Perez, M., Diaz, D., Lopez-Dolado, E., & Álvarez-Mon, M. (2023). Prognostic Value of Malondialdehyde (MDA) in the Temporal Progression of Chronic Spinal Cord Injury. Journal of personalized medicine, 13(4), 626. https://doi.org/10.3390/jpm13040626
8) Lankin, V. Z., Tikhaze, A. K., & Melkumyants, A. M. (2022). Malondialdehyde as an Important Key Factor of Molecular Mechanisms of Vascular Wall Damage under Heart Diseases Development. International journal of molecular sciences, 24(1), 128. https://doi.org/10.3390/ijms24010128
9) Ng, S. C. W., Furman, R., Axelsen, P. H., & Shchepinov, M. S. (2022). Free Radical Chain Reactions and Polyunsaturated Fatty Acids in Brain Lipids. ACS omega, 7(29), 25337–25345. https://doi.org/10.1021/acsomega.2c02285
10) Onyango, A. N., & Baba, N. (2010). New hypotheses on the pathways of formation of malondialdehyde and isofurans. Free radical biology & medicine, 49(10), 1594–1600. https://doi.org/10.1016/j.freeradbiomed.2010.08.012
11) Pineda-Alemán, R., Alviz-Amador, A., Galindo-Murillo, R., Pérez-González, H., Rodríguez-Cavallo, E., & Méndez-Cuadro, D. (2023). Cysteine carbonylation with reactive carbonyl species from lipid peroxidation induce local structural changes on thioredoxin active site. Journal of molecular graphics & modelling, 124, 108533. https://doi.org/10.1016/j.jmgm.2023.108533
12) Ray, G., & Husain, S. A. (2002). Oxidants, antioxidants and carcinogenesis. Indian journal of experimental biology, 40(11), 1213–1232.
13) Sapkota, M., Burnham, E. L., DeVasure, J. M., Sweeter, J. M., Hunter, C. D., Duryee, M. J., Klassen, L. W., Kharbanda, K. K., Sisson, J. H., Thiele, G. M., & Wyatt, T. A. (2017). Malondialdehyde-Acetaldehyde (MAA) Protein Adducts Are Found Exclusively in the Lungs of Smokers with Alcohol Use Disorders and Are Associated with Systemic Anti-MAA Antibodies. Alcoholism, clinical and experimental research, 41(12), 2093–2099. https://doi.org/10.1111/acer.13509
14) Slimen, I. B., Najar, T., Ghram, A., Dabbebi, H., Ben Mrad, M., & Abdrabbah, M. (2014). Reactive oxygen species, heat stress and oxidative-induced mitochondrial damage. A review. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group, 30(7), 513–523. https://doi.org/10.3109/02656736.2014.971446
15) Traverso, N., Menini, S., Maineri, E. P., Patriarca, S., Odetti, P., Cottalasso, D., Marinari, U. M., & Pronzato, M. A. (2004). Malondialdehyde, a lipoperoxidation-derived aldehyde, can bring about secondary oxidative damage to proteins. The journals of gerontology. Series A, Biological sciences and medical sciences, 59(9), B890–B895. https://doi.org/10.1093/gerona/59.9.b890
16) Tuma D. J. (2002). Role of malondialdehyde-acetaldehyde adducts in liver injury. Free radical biology & medicine, 32(4), 303–308. https://doi.org/10.1016/s0891-5849(01)00742-0
17) Wang, X., Lei, X. G., & Wang, J. (2014). Malondialdehyde regulates glucose-stimulated insulin secretion in murine islets via TCF7L2-dependent Wnt signaling pathway. Molecular and cellular endocrinology, 382(1), 8–16. https://doi.org/10.1016/j.mce.2013.09.003
18) Xu, Z., & Rothstein, S. J. (2018). ROS-Induced anthocyanin production provides feedback protection by scavenging ROS and maintaining photosynthetic capacity in Arabidopsis. Plant signaling & behavior, 13(3), e1451708. https://doi.org/10.1080/15592324.2018.1451708
19) Zhang, Y., Chen, S. Y., Hsu, T., & Santella, R. M. (2002). Immunohistochemical detection of malondialdehyde-DNA adducts in human oral mucosa cells. Carcinogenesis, 23(1), 207–211. https://doi.org/10.1093/carcin/23.1.207