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Review article

# Lipoxidation and cancer immunity

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ABSTRACT

Lipoxidation is a well-known reaction between electrophilic carbonyl species, formed during oxidation of lipids, and specific proteins that, in most cases, causes an alteration in proteins function. This can occur under physiological conditions but, in many cases, it has been associated to pathological process, including cancer. Lipoxidation may have an effect in cancer development through their effects in tumour cells, as well as through the alteration of immune components and the consequent modulation of the immune response. The formation of protein adducts affects different proteins in cancer, triggering different mechanism, such as proliferation, cell differentiation and apoptosis, among others, altering cancer progression. The divergent results obtained documented that the formation of lipoxidation adducts can have either anti-carcinogenic or pro-carcinogenic effects, depending on the cell type affected and the specific adduct formed. Moreover, lipoxidation adducts may alter the immune response, consequently causing either positive or negative alterations in cancer progression. Therefore, in this review, we summarize the effects of lipoxidation adducts in cancer cells and immune components and their consequences in the evolution of different types of cancer.

## 1. Introduction

Oxidative stress is usually associated with an increase of reactive oxygen species (ROS), or a decrease on the antioxidant defences which, in turn, can favour the peroxidation of the polyunsaturated fatty acids (PUFAs) in membrane lipid bilayers, leading eventually to the formation of highly reactive aldehydes [1]. These electrophilic reactive aldehydes can spread from the site of origin and react with major biomolecules, like proteins, even at distant sites [2], causing a lipoxidation process. Lipoxidation is a well-known reaction between electrophilic carbonyl lipids species formed during oxidation of lipids and specific proteins [3].

Lipid oxidation products may accumulate and covalently modify proteins, driving not only to physiological but also to pathological process through altering protein structure and function or changing signalling pathways. This has an effect in different pathologies such as cancer, in which lipid oxidation products may influence cancer progression either directly, through the modulation of cancer cells behaviour, or through the modulation of the immune response (Fig. 1) [4].

The biological effects of reactive lipid carbonyl species generated by lipid peroxidation process are modulated by their local concentration and availability, which depends on the initial lipid targeted by peroxidation, as well as on the presence of cellular detoxifying and conjugating systems, and the cell ability to degrade modified proteins [5].

*Abbreviations:* ACR, acrolein; ADCC, antibody-dependent cellular cytotoxicity; AKR, aldo-keto reductases; AP-1, activator protein-1; ARE, antioxidant response element; ASK1, apoptosis signal regulating kinase; COX-2, cyclooxygenase-2; CTLs, cytotoxic T lymphocytes; cyPG, cyclopentenone prostaglandins; 15d-$PGJ_2$, 15-deoxy$\Delta^{12-14}$ $PGJ_2$; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; PDGFR, platelet-derived growth factor receptor; GCL, glutamate cysteine ligase; GSH, glutathione; GST, glutathione S-transferasaes; 4-HHE, 4-hydroxy-hexenal; HNE, 4-hydroxy-2-nonenal; hPGD2s, hematopoietic prostaglandin $D_2$ synthase; IκB, inhibitor of kappaB; IKK, IκB kinase; iNOS, inducible nitric oxide synthase; JNKs, c-Jun N-terminal kinase; Keap1, Kelch-like ECH associating protein 1; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MSA, mouse serum albumin; NFκB, nuclear factor-κB; NK, natural killer; PGA1, prostaglandin A1; PGA2, prostaglandin A2; $PGD_2$, prostaglandin $D_2$; Pin1, peptidylprolyl cis/trans-isomerase A1; PKB, protein kinase B; PPARs, peroxisome proliferator activated receptors; PUFAs, polyunsaturated fatty acids; RAGE, receptor for advanced glycation end products; RNS, reactive nitrogen species; ROS, reactive oxygen species; Th, T helper; TKRs, tyrosine kinase receptors; Tregs, $Foxp3^+$ regulatory T cells; XIAP, X-linked inhibitor of apoptosis protein

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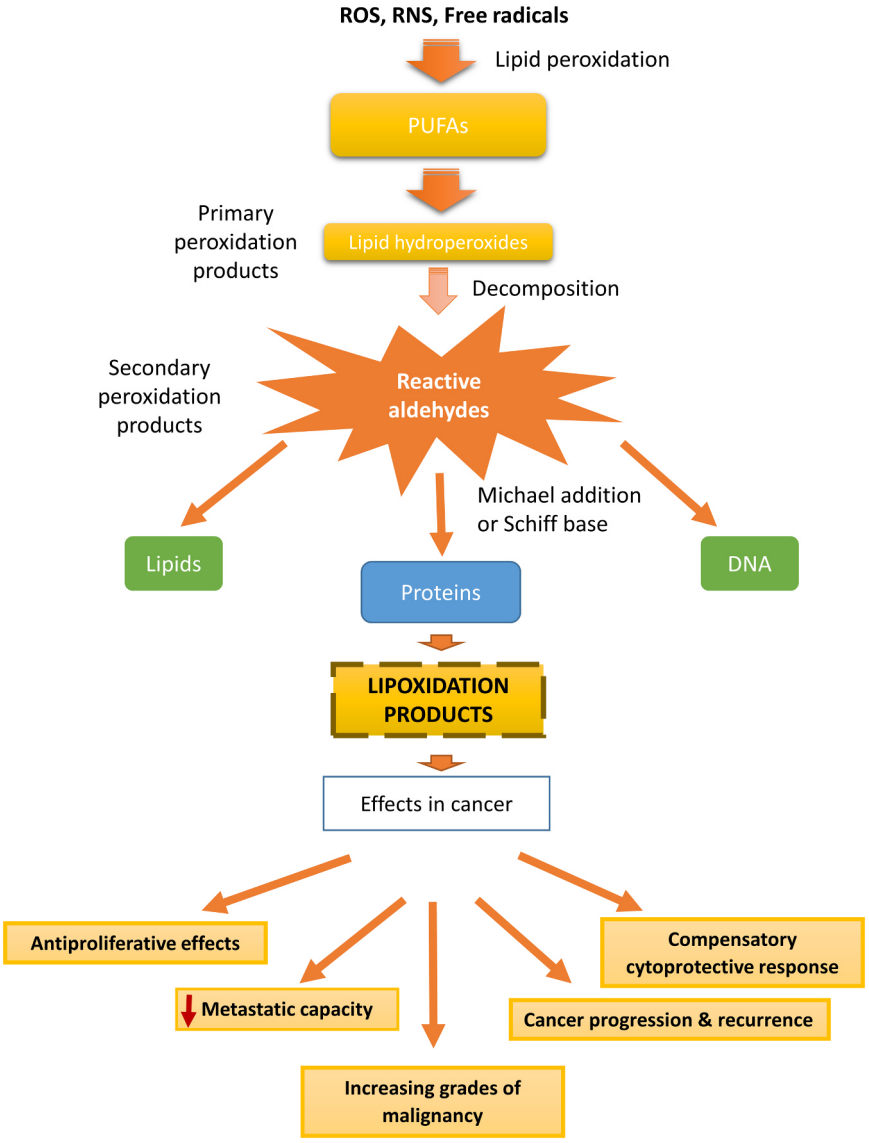


**Fig. 1.** Diagram illustrating the formation of lipoxidation adducts and their possible effects on the progression of cancer.

Also, quite important as well, depending on the type of protein modified, different effects can occur in the physiologic or the pathophysiologic signalling [6].

Oxidative modified molecules, including lipoxidation adducts, are also reported to have a significant role in the modulation of inflammation and immune response. They can induce adaptive immunity and have been implicated in the pathogenesis of various diseases [7]. In fact, it has been reported that the covalent reaction of electrophilic aldehydic products with proteins might lead to the formation of immunogenic biomolecules [8], and these lipoxidation products may alter the cellular signalling in the immune response in several pathologies, including cancer [9]. Moreover, it is well established that the immune system plays a very important role in cancer progression. In this regard, several studies in the past few years have demonstrated a dual role of leukocytes themselves contributing to either "pro-tumour" microenvironment or to "anti-tumour" microenvironment [10].

In this review, we will discuss and summarize the most recent advances in lipoxidation formation and its influence on the pathophysiology of cancer. We will also highlight the effect of lipoxidation in tumour and immune cells during cancer progression.

## 2. Chemistry of lipoxidation adducts and its relevance in disease pathophysiology

The unsaturated fatty acid are main targets of oxygen radicals leading to the formation of primary peroxidation products. These oxidized lipids can be decomposed to form secondary peroxidation products (carbonyl-based derivatives), and can react by addition reactions of the carbonyl groups (electrophiles) with amino and thiol groups (nucleophiles), leading to the formation of lipid-protein adducts or lipoxidation products [11] (Fig. 1). The aldehydes and other electrophilic carbonyl species generated will depend on the initial PUFA targeted by peroxidation. In this sense, the peroxidation of n-3 PUFAs (α-linolenic acid and docosahexaenoic acid) generates mainly 4-hydroxy-hexenal (4-HHE), while the peroxidation of n-6 PUFAs, such as linoleic acid and arachidonic acid, generates mostly 4-hydroxy-2-nonenal (HNE), which is the most intensively studied electrophilic reactive aldehyde [12–14]. The type of adducts that can be generated depends on the reactivity of the oxidized lipid species. In addition, the reaction of these compounds with a protein can take place by two principal reactions: (i) the addition of the aldehydic group to an amino group of the protein (e.g. lysine) forming a Schiff´s base adduct by loss of water and (ii) by a Michael addition to a nucleophile by the active C=C double bond [3,9]. While

Schiff base formation is reversible, Michael adducts are quite stable, thus the formation of the latter seems to be preferred *in vivo*. It is also important to consider that lipoxidation depends on the balance of the rate of formation of the lipid oxidation product, its reactivity, and the rate of detoxification by enzymes such as glutathione peroxidases [15], glutathione S-transferasaes (GST) [16], or aldo-keto reductases (AKR) [17].

Lipoxidation can occur in healthy individuals [18,19], since protein modification by reactive electrophilic species not only may inhibit protein function, but also, in a small number of cases, may cause a gain of function, even leading to beneficial effects [20–22].

Nevertheless, the importance of lipoxidation and its pathophysiological relevance have been broadly discussed in several works [14,23–26]. In fact, the measurement of global protein adducts, such as HNE-protein adducts, is commonly used as a biomarker of inflammation/oxidative stress/lipid peroxidation under various pathological conditions [27]. The accumulation of lipid peroxidation products, and therefore of lipoxidation adducts, has been involved in ageing and in well-defined diseases of liver, kidney, neurological and cardiovascular systems, endocrine and metabolic disorders, diabetes and its complications, and other oxidative stress related pathologies [28].

Furthermore, lipoxidation is highly associated with chronic degenerative diseases such as cancer. These topics will be discussed in the following section.

## 3. Lipoxidation in cancer: Effect on tumour and immune cells

Carcinogenesis and cancer therapies are strongly influenced by oxidative stress and by lipid peroxidation [28] and, consequently, by lipoxidation adducts. The most reported reactive carbonyl products formed during lipid peroxidation are malondialdehyde (MDA), acrolein (ACR), 4-hydroxy-hexenal (4-HHE) and 4-hydroxy-2-nonenal (HNE) [29], and several studies reported the formation of protein adducts with several proteins in different types of cancer [30–33]. In fact, the greater reactivity of HNE, one of the major products of lipid peroxidation, with proteins, gave rise to the assumption that HNE has a cytotoxic and carcinogenic effect through the modulation of proteins involved in DNA repair [34]. Moreover, other works demonstrated that oxidative stress and electrophilic lipid peroxidation products, such as HNE, also play important roles in the induction of cell cycle arrest, differentiation process, and apoptosis in cancer cells [35]. However, some studies show controversial results regarding the influence of HNE, or HNE-adducts in different types of human cancers [36–39], and the pattern of HNE histological appearance has been shown to be dependent on the histological origin of cancer [40].

Likewise, cancer cells are sensitive to lipid oxidation products since these products act as second toxic messengers of free radicals, as well as signalling molecules and growth regulating factors that influence important processes for cancer progression such as proliferation, differentiation and apoptosis [28]. But there are discrepancies in the appearance of lipoxidation adducts in distinct cancer types. For example, in hepatoma cells, it was shown that the majority of HNE was converted to the HNE-GSH conjugate, which was rapidly and efficiently exported from the cell [41]. However, in astrocytic and ependymal glial tumours, HNE-protein adducts were detected in mitotic, necrotic and apoptotic cells, and were associated with increasing grades of malignancy [42].

The disparity observed in the formation of lipoxidation adducts in various tumours may be explained by: a) the different membrane composition of lipids in different cancer cell types, as well as different cholesterol/PUFAs ratios, which determine different tendencies to form lipid peroxidation products and, therefore, different electrophilic lipids and, thus, different lipoxidation adducts [43]; b) the higher expression of detoxification enzymes and antioxidant proteins observed in some tumour cells, what results in a more efficient and rapid metabolism of lipid peroxidation products [44]; c) the different effects, either physiological or pathological, triggered by some lipid peroxidation products, that act through the antioxidant response element (ARE) to induce the expression of key metabolizing enzymes, such as GST [45], influencing on Keap1–Nrf2–ARE pathway [46,47]; d) the local of formation and e) the targeted protein or enzyme that are adducted to the electrophilic lipid.

### 3.1. Effect of lipoxidation in tumour cells

As it was mentioned above, the level of oxidative stress and, consequently, the level of lipoxidation products vary among cancer types in relation with cell type. In liver cancer, it was found lower levels of lipid peroxidation products in hepatoma cells when compared to normal liver cells [48,49], probably leading to lower levels of lipoxidation products, what can be explained, in part, by the observed increase in the activity of enzymes metabolizing toxic aldehydes during rat liver carcinogenesis [50], thus rendering the cancer cells more protected against the cytotoxic effect of lipoxidation products.

Several enzymes involved in tumour resistance due to their ability to metabolize electrophilic lipids are, at the same time, targets for lipoxidation themselves. This is the case of AKR that catalyse the reduction of ketones and aldehydes [51] or GST enzymes that are involved in drug detoxification [3]. AKR1B10, a member of AKR family, is overexpressed in several types of tumours, and it may contribute to tumorigenesis through various mechanisms, in addition to be involved in chemoresistance [52,53]. This protein is a selective target for lipoxidation and inhibition by A-class cyclopentenone prostaglandins (cyPG) and it has been demonstrated that low concentrations of prostaglandin A1 (PGA1) potentiate the intracellular accumulation and G2/M cell cycle arresting effect of the topoisomerase inhibitor doxorubicin in A549 lung cancer cells [54,55]. Due to their electrophilic nature, cyPG may form Michael adducts with GSH both enzymatically, through the action of GSTs, and non-enzymatically [56,57]. Likewise, it has been found HNE adducts with GST detected by immunoprecipitation of GST followed by Western blot analysis using anti-HNE antibody [58]. On the top of that, GSTP1-1, a very important enzyme in tumour chemoresistance, can be covalently bound by various electrophilic lipids, including PGA1 and PGA2, causing its inactivation [22,59,60]. Hence, lipoxidation of GSTP1-1 could help to overcome the resistance of certain tumour cells to chemotherapy or radiation [55,61].

On the other hand, lipoxidation adducts were found in renal [62], and colon cancer cells [63], as well as in astrocytic and ependymal glial tumours, in which the incidence of HNE-positive tumour cells increased with increasing grades of malignancy [42]. Although the amount of lipoxidation products in cancer cells, like HNE-protein adducts, has been often assayed as a means of assessing the level of oxidative stress, only in some cases the identification and the consequences of HNE-protein adduct formation on cancer cell growth or behaviour have been reported [14].

We have summarized the effect of HNE-protein adducts in distinct cancer cell lines, such as human epidermoid carcinoma, leukemic cells, adenocarcinoma human alveolar basal epithelial, breast cancer cells, or colon cancer cells, reported by different studies [64–71], in Fig. 2. Both endogenous and exogenous HNE lead to lipoxidation adducts with many diverse proteins such as epidermal growth factor receptor (EGFR), α-enolase, peptidylprolyl cis/trans-isomerase A1 (Pin1), liver kinase B1 (LKB1), IκB kinase (IKK), or glutamate cysteine ligase (GCL), triggering different effects very important in avoiding cancer progression, such as suppression of cell growth, reduction of metastatic capacity or anti-proliferative effects, but also in other cases triggering effects that favour cancer progression, as the modulation of tumour microenvironment to become more pro-tumorigenic or the cytoprotective response in cancer cells (Fig. 2).

Moreover, other studies have shown that the formation of HNE protein adducts in renal and colon cancer tissues has been related to the growth and progression of kidney and colon cancer [30], although the progression of colon cancer results in loss of lipoxidation adducts in the

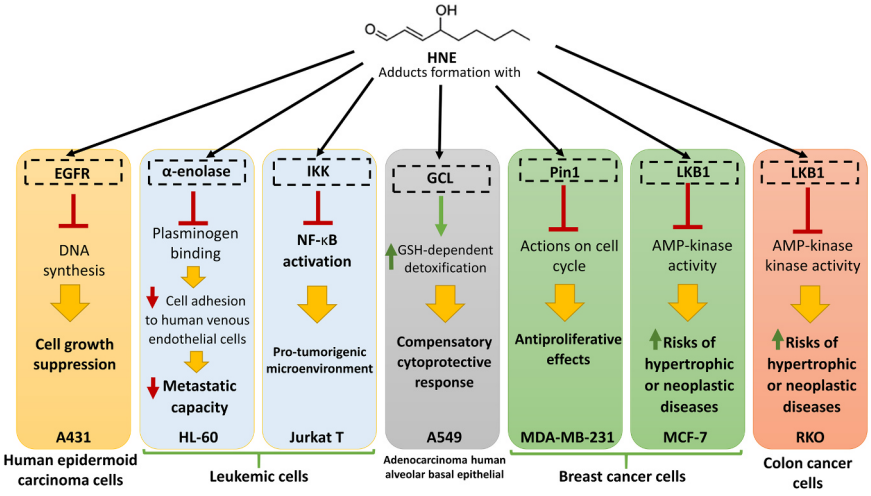


**Fig. 2.** Summary of the possible effects of HNE-protein adducts on different proteins and different cancer cell lines.

malignant tissue and increase of reactive aldehydes in the surrounding area [31]. In accordance with these results, a different study in prostate cancer showed that ACR protein adducts could be associated with tumour progression and recurrence [32]. Moreover, tumour tissues in lung cancer showed lower antioxidant capacity than healthy tissues, which was accompanied by lower levels of fatty acids and higher levels of reactive aldehydes detected in the necrotic and stromal cells in these tumours, thus favouring the formation of lipoxidation products like the HNE-His protein adducts observed in necrotic lung cancer tissues [33].

Protein adducts are also involved in the inactivation of the proteasome [72], which is responsible for the intracellular degradation of proteins, whether they are damaged or no longer required for cellular processes [73]. Proteasome is then essential for many cellular pathways, including cell cycle, regulation of gene expression and resistance to oxidative stress. Therefore, protein lipoxidation adducts could alter carcinogenesis through their effect in the inactivation of the proteasome since cross-linked proteins are able to inhibit the proteasome, and further impair cellular protein turnover [74]. In fact, there are some studies showing that proteasome inhibitors induce apoptosis in leukemic cell lines, turning the proteasome into one of the possible targets with potential for therapeutic agents against cancer [75–77].

It is important to remark that, in several cases, the progression of malignancy is accompanied by reductions of oxidative stress, due to the upregulation of antioxidant capacity [78], and the induction of the Nfr2/Keap1 pathway, which negatively regulates the HNE intracellular concentration [79]. This also matches with the results showing that the adaptation to intrinsic oxidative stress in cancer cells can confer drug resistance. Thus, anticancer drugs and radiotherapy can induce oxidative stress and trigger cancer cells to undergo apoptosis, however some cancer cells escape from this process through the adaptation to intrinsic oxidative stress [34]. On the other hand, despite the reduction of intrinsic oxidative stress, the level of lipoxidation products in cancer cells may increase, due to the inflammatory response present in the tissues surrounding cancer lesions [14].

Transcription factors of the peroxisome proliferator activated receptors (PPARs) family play a key role both in tumour biology and in immune function [80]. The mechanisms reported so far suggest that each PPAR isotype is associated with pathways that relate to carcinogenesis due to direct effect in the cancer cells themselves, since they are involved in the control of cell proliferation, cell differentiation and apoptosis [81,82]. But in addition to these functions, PPARs may act on the tumour environment by regulating inflammatory processes [83–85]. This family of nuclear receptors is also a target of lipoxidation processes. It has been demonstrated that 15-deoxy$\Delta^{12-14}$ $PGJ_2$ (15d-$PGJ_2$) binds covalently to a cysteine residue located in the PPARγ ligand binding pocket [86–88]. Further on, it was shown that 15d-$PGJ_2$ activates PPARδ's transcriptional activity through formation of a covalent adduct between its endocyclic enone at $C_9$ and Cys249 in the receptor's ligand-binding domain [89]. In addition, HNE has been reported as an endogenous ligand for PPARβ/δ that causes its activation [90].

The divergent results obtained documented that the formation of lipoxidation adducts can have either anti-carcinogenic or pro-carcinogenic effects, depending on the cell type affected and the specific adduct formed [14]. The abundance of a protein, as well as the high reactivity and accessibility of some nucleophilic sites, may determine if a protein becomes, or not, a lipoxidation target [91,92]. Moreover, depending on the nature/structure of the lipid oxidation product, which could have different structural features and, as well, different reactivity, it may lead to the formation of different types of lipoxidation adducts and thus to different functional consequences in the targeted protein [22,93,94]. In fact, it has been shown that biotinylated cyPG mimic many of the effects of cyPG in cellular models, including inhibition of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and induction of HO-1 and Hsp70 expression, but they are unable to elicit PPAR activation *in vitro* or in intact cells [95,96]. Hence, by adding a bulky moiety to the carboxyl group of cyPG, it may be possible to dissociate some biological actions [97]. More studies are needed to disclose these effects depending on the type of cancer, their stage, the implicated targeted protein, or the reactive species involved.

### 3.2. *Effect of lipoxidation on immune cells and their correlation with cancer*

Chronic inflammatory processes induce oxidative/nitrosative stress and, as consequence, lipid peroxidation products and lipoxidation processes. In addition, it has been described that different chronic inflammatory conditions pre-dispose susceptible cells to malignant transformation and cancer progression [28], so that it has been estimated that chronic infection and associated inflammation contribute to about one in four of all cancer cases worldwide [98].

ROS, reactive nitrogen species (RNS) and lipid peroxidation products can modulate signalling molecules [99] and alter functions of proteins involved in inflammation and carcinogenesis [100], such as the nuclear transcription factor NFκB or stress response enzymes, namely iNOS and COX-2 [101,102]. Furthermore, it has been reported that non-enzymatic oxidative modification of proteins, including lipoxidation, renders proteins immunogenic and leads to the generation of antibodies against oxidatively modified proteins [8,103].

In fact, aldehydes exert a dual effect on inflammatory signalling, mainly depending on the concentration levels. On the one hand, at low concentrations, HNE activates PKCβ-signalling, inducing the

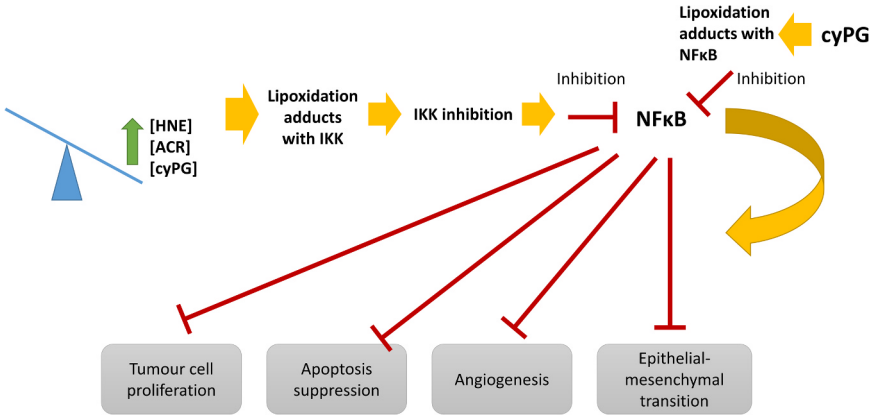


**Fig. 3.** Effects of NFκB inhibition mediated by lipoxidation adducts. High concentration of aldehydes, such as HNE or acrolein, or high concentration of cyclopentenone prostaglandins (cyPG) inhibits IKK activity through the formation of lipoxidation products. IKK inhibition results in the suppression of NFκB activity, hindering the effects triggered by NFkB, such as tumour cells proliferation, suppression of apoptosis, angiogenesis and epithelial-mesenchymal transition, which facilitates distant metastasis. Moreover, cyPG can directly modify NFκB subunits leading to NFκB inhibition, and therefore, the suppression of NFkB effects.

production and secretion of CCL2 (MCP-1) by macrophages [104]. On the other hand, high concentrations of reactive aldehydes, such as HNE or ACR, inhibit the activation of NFκB, either via a direct inhibitory effect on proteasome, or via inhibition of the phosphorylation of inhibitor of kappaB (IκB) and its subsequent proteolysis [105], or a modification of IκB kinase (IKK) β -sub-unit by aldehydes [106] that has also been found to be a target of cyPG (Fig. 3) [107]. Moreover, 4-HHE activates the IKK, via the IKK/NFκB inducing kinase (NIK) pathway, through the increase in the activity of p38 MAPK and ERK1/2 kinase, resulting in NFκB activation [108]. In contrast, it has been described that cyPG can directly modify NFκB subunits p65 and p50, leading to NFκB inhibition by blocking its ability to bind DNA, studied by immunohistochemistry and Western blot analysis (Fig. 3) [109,110]. Moreover, it has been proposed a role for 15d-$PGJ_2$ in the control of lymphocyte proliferation and activation through mechanisms relying on NFκB inhibition, studied in knockout mice for hematopoietic prostaglandin $D_2$ synthase (hPGD2s), which metabolizes cyclooxygenase (COX)-derived $PGH_2$ to $PGD_2$ and 15d-$PGJ_2$ [111]. Furthermore, it was shown that 15d-$PGJ_2$ controlled the balance of pro- vs. anti-inflammatory cytokines regulating leukocyte influx and macrophage efflux through draining lymphatics [112]. This is very important for cancer progression since NF-κB activation promotes the accumulation of pro-inflammatory cytokines at the tumour site, contributing to the pro-tumorigenic microenvironment. The activation of this transcription factor has been associated with tumour cells proliferation, suppression of apoptosis, angiogenesis and epithelial-mesenchymal transition, which facilitates distant metastasis [113].

Additionally, it has been demonstrated that PPAR-α ligands and PPAR-γ ligands (15d-$PGJ_2$) inhibit cell growth and induce monocytic differentiation in human promyelocytic leukemia cells (HL-60 cells), and HNE, which alone induces granulocytic-like differentiation of HL-60 cells, potentiates the monocytic differentiation induced by 15d-$PGJ_2$. Moreover, HNE treatment significantly inhibits U937 (human histiocytic lymphoma) cell growth and potentiates the inhibition of cell growth in PPAR-γ ligand-treated cells [68]. And, in addition, it has been reported that HNE can form adducts with cysteine residues in the extracellular domain of TLR4 peptides, demonstrated by LC–MS/MS analysis, inhibiting its activation [114]. Hence, the formation of lipoxidation adducts with HNE can differentially regulate the activation of TLR4 and subsequently provoking an effect in the immune response.

It has been shown that both MDA-adducted mouse serum albumin (MSA) and HNE–MSA were able to significantly promote $CD4^+$ T cell proliferation, leading to the hypothesis that lipoxidation adducts, could serve as an immunological trigger in the activation of $CD4^+$ T cells. Moreover, it has been suggested that lipid peroxidation derived aldehydes preferentially promote Th1 differentiation, analysed by flow cytometry and ELISA in splenic lymphocytes from trichloroethene-treated mice [115]. In that sense, we could consider lipoxidation adducts a positive factor since Th1 cells have been associated with the promotion of anti-tumour responses: Th1 cells enhance the cytotoxic functions of NK and $CD8^+$ cells, upregulate MHC Class I expression in tumour cells, and support $CD8^+$ cell proliferation through the secretion of IL-2 [116].

Regarding monocytes function, it has been suggested that synthetic MDA-Lys, used as a prototype of advanced lipoxidation end products, can promote monocyte activation and vascular complications via the induction of inflammatory pathways and networks. In a candidate gene profiling approach, MDA-Lys increased the expression of key NFκB-dependent genes, such as MCP-1, iNOS, RAGE, IP-10, CCR-2, IL-6, IL-8, and COX-2 that are associated with monocyte activation. Antibody array profiling revealed that MDA-Lys can upregulate the chemokines CCL11 (eotaxin), TNFSF14, and CCL18. In addition, key factors that were noted to be induced by MDA-Lys, such as MCP-1, eotaxin, IL-6, IL-8, β1- and β2-integrins, and COX-2, are associated with monocyte activation, adhesion, and migration [117].

Neutrophils mediate key components of the cellular immune response which involves cellular adhesion, migration, phagocytosis and degradation and turnover of phagocytic metabolites [118]. It has been demonstrated, by mass spectrometry analyses, the existence of lipoxidation adducts of HNE with proteins involved in key pathways of neutrophil oxidative burst, phagocytosis, redox homeostasis and glucose metabolism. The same study also confirmed the formation of neutrophil protein-HNE adducts using candidate proteins found to be modified, by mass spectrometry. Taken together, these data suggest that HNE induces a pleiotropic mechanism to inhibit neutrophil function [119].

In addition, it has been reported that HNE seems to be an important cell growth regulating factor, acting as a signalling molecule interacting with the growth regulating effects of various cytokines [120–123]. HNE, as a second messenger of ROS, activates activator protein 1 (AP-1) that promotes TGFβ synthesis and fibrogenesis. Hence, HNE could, at the same time, support fibrogenesis and inhibit the cancer growth.

The regulation of the immune system is very important in determining cancer progression [10]. Therefore, lipoxidation products may have an effect in cancer development by affecting immune components and modulating the immune response.

### *3.3. Overview of tumour immunology at tumour microenvironment and its relation with reactive aldehydes and lipoxidation*

There are few studies on the role of lipoxidation adducts with respect to tumour immunology, but considering what is known about lipid peroxidation products, their influence in immunology, as described above, and the influence of immune microenvironment in tumour progression [10,124–126], altogether it suggests that lipoxidation is a very important process in this field. Moreover, recent studies have revealed that immune cells possess distinct metabolic characteristics that influence their immunological functions [127]. For example,

macrophage polarization is related to distinct metabolic characteristics pertaining to lipid metabolism, among others [128]. In this sense, it has been found that genes involved in glycolysis and phospholipid metabolism, differentially expressed between M1 and M2 macrophages, are major distinguishing features of inflammatory (M1) macrophages [128].

Clinically manifest neoplasms can develop when tumour cells are able to escape immunosurveillance [129,130]. In addition, the efficacy of most chemotherapeutic and radiotherapeutic agents commonly employed in the clinic, critically depends on the activation or reactivation of tumour-targeting immune responses [131–133].

Tumour-infiltrating leukocyte subsets can play strikingly antagonistic functions. One of the key features of inflammation is the functional phenotype of macrophages that depend on the activating stimuli in their microenvironment. Macrophages are prototypical $O_2^{\cdot-}$, $H_2O_2$, and NO producing cells, and oxidants represent one of the most potent weapons of activated macrophages in the fight against cancer cells [134,135]. In addition, it is known that the increase of oxidant is associated with higher formation of lipid peroxidation products and, therefore, this could lead to a higher presence of lipoxidation adducts [136]. Moreover, it has been reported that macrophages, when stimulated, can produce HNE through COX-2 [124]. The inhibition of COX-2 in murine macrophages was associated with a decrease in HNE production following *E. faecalis* infection ($P < 0.001$). In the same study, using IL-10-knockout mice colonized by *E. faecalis,* it was observed increased levels of COX-2 expression in colonic macrophages in association with HNE-protein lipoxidation adducts [124].

Natural killer (NK) cells and $CD8^+$ cytotoxic T lymphocytes (CTLs) provide highly complementary anti-tumour strategies. Oxidants have a dual role in the regulation of CTLs and NK cell function. It has been observed that the most potent caspase inhibitor, X-linked inhibitor of apoptosis protein (XIAP), confers resistance to antibody-dependent cellular cytotoxicity (ADCC). Thus, XIAP is a critical modulator of ADCC responsiveness [137]. In this sense, strategies have been proposed to reduce the oxidative stress to enhance the ability of CTLs to kill tumour cells. However, activated CTLs may partly adapt to the oxidative stress in the tumour microenvironment by upregulating antioxidant proteins as demonstrated with IL-2-activated NK cells [138] and as was described above.

On the other hand, Th17 cells have been associated with poor prognosis in some type of cancers and its pro-tumour functions have been tightly linked to angiogenesis and promotion of tumour vascularization. Nevertheless, the role of Th17 cells is much more controversial due to its association with better overall survival in ovarian cancer and in esophageal squamous cell carcinoma [10]. In this sense, lipid peroxidation products may also have an influence since it has been reported that aldehydes, such as MDA, transcriptionally upregulate the expression of IL-17E in lymphocytes and alter lymphocyte differentiation towards the pathogenic Th17 subset [68]. Finally, $Foxp3^+$ regulatory T (Treg) cells accumulation in the tumour microenvironment is considered a bad prognosis factor [10]. This population can also be influenced by lipoxidation effects, as it was observed in atherosclerotic lesions of a mice model, in which there was an inhibition in the generation of Treg cells induced by MDA-laminin adduct [126].

In sum, the modulation of immune components in the tumour microenvironment has a very relevant effect over the development of tumours as well as over the type of patient's response to a specific treatment, and lipoxidation products may have a very important role in this modulation. In this regard, the combination of conventional therapeutics with ROS modulators may increase specific tumour cytotoxicity.

### 3.4. Molecular targets and signalling properties of lipoxidation

Lipoxidation adducts may alter progressively the structure and function of circulating and tissular proteins, with consequences on the inflammatory status, cell proliferation and viability, thus influencing cancer development [5]. Studies of proteins modified by reactive aldehydes indicated hundreds of molecular targets [8,139,140], therefore, we will highlight in this section targeted protein involved in cell proliferation, apoptosis, and some protein kinases.

#### 3.4.1. Modification of tyrosine kinase receptors

It has been previously reported that HNE present in oxLDLs or exogenously added induces both modification and dysfunction of tyrosine kinase receptors (TKRs), such as epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR), involving lipoxidation adducts, which triggers TKR autophosphorylation and the activation of the downstream signalling pathways, extracellular signal-regulated kinase (ERK)1/2 phosphorylation and cell cycle progression [141,142]. However, high concentrations of HNE inhibit cell proliferation mediated by EGFR and PDGFR involving the formation of HNE and ACR adducts with PDGFRβ [64,143]. Thus, it has been suggested that HNE and others electrophilic lipids may potentially disturb PDGFR-mediated responses such as proliferation and cell migration [144].

#### 3.4.2. Apoptosis signalling and other protein kinases

In human myeloid HL-60 cells, HNE adducts were shown to be correlated with the induction of apoptosis, the activation of c-Jun N-terminal kinase (JNK) and caspase 3, and they have been associated with the activation of caspases 3, 8, and 9 in embryonic fibroblasts isolated from mice [145,146]. Moreover, HNE induce the expression of antioxidant genes such as heme-oxygenase and thioredoxine-1 via the activation of the mitogen-activated protein kinase (MAPK) pathway and the transcription factor Nrf2 [147,148]. Thioredoxin and thioredoxin reductase are involved in the maintenance of various proteins in a reduced state required for their normal function, and they are also targets of lipoxidation by 15d-$PGJ_2$, what results in their inactivation [149]. Modified thioredoxin reductase may mediate the conformational disruption of p53 and PG-induced apoptosis via activation of caspase 3 [150]. Moreover, in Jurkat cells, it was reported that both Fas and Daxx proteins are targets of lipoxidation by HNE. Fas adducts promote proapoptotic signalling via ASK1, JNK, and caspase 3. While Daxx lipoxidation promotes its export from the nucleus to the cytosol, where it interacts with Fas to self-limit the extent of apoptosis by inhibiting the downstream proapoptotic signalling [151]. In addition, the proapoptotic protein BAX is a direct target of lipoxidation by PGA2, triggering a conformational change that leads to BAX activation and induction of apoptosis [152]. Different studies reported the direct modification and inactivation of the phosphoinositide-3-phosphatase and tumour suppressor PTEN by several reactive aldehydes and ketones, such as ACR, HNE and α,β-enones such as PGA2, Δ12-PGJ2 and 15d-$PGJ_2$, with ensuing activation of PKB/Akt kinase, phosphorylation of Akt substrates, increased cell proliferation, and increased nuclear β-catenin signalling [153–155]. This combined and sustained inactivation of tumour suppressors could contribute significantly to inflammation-associated tumorigenesis [153]. Additionally, it has been observed that cyPG and cyclopentenone isoprostanes target the oncogenic H-Ras proteins. Whereas 15d-$PGJ_2$ and Δ12-$PGJ_2$ preferentially target the C-terminal region, PGA1 and 8-iso-PGA1 bind mainly to cysteine 118, located in the GTP-binding motif what has been correlated with H-Ras activation [156]. In human hepatic stellate cells, the p46 and p54 isoforms of JNKs were identified as HNE targets and were activated by this aldehyde. This leads to JNK nuclear translocation as well as to c-jun and AP-1 induction [157]. Furthermore, it has been shown that 15d-$PGJ_2$ can covalently modify c-Jun at cysteine 269, which is located in the c-Jun DNA binding domain, and directly inhibit the DNA binding activity of AP-1, both *in vitro* and in intact cells [59,158].

## 4. Concluding remarks and future perspectives

Many of the previously described studies provide emerging molecular evidence of the importance of lipoxidation in carcinogenesis, where inflammation represents one of the fundamental links. There is a great complexity in the possible roles of lipoxidation products in cancer pathology. It has been reported contradictory results in which lipoxidation products seem to be toxic for tumour cells [159] but also, other studies report an association with the increase of the level of malignancy in tumours [31]. Therefore, lipoxidation products can have a crucial role not only in carcinogenesis but also in the host defence against cancer, through their effects in tumour cells and through their interactions with immune components.

Future studies will be necessary to distinguish physiologic and pathologic roles of lipoxidation processes occurring during carcinogenesis, with particular attention to the pro-oxidant anticancer agents and the drug-resistant mechanisms, which could be modulated to obtain a better response to cancer therapy [34].

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## Conflicts of interest

The authors have no competing financial interests to declare.

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