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Cyclooxygenases and Lipoxygenases in Cancer Drug Resistance

Kanserde İlaç Dirençliliğinde Siklooksijenaz ve Lipooksijenazlar

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ABSTRACT

Cancer drug resistance is a critical factor restricting the success rate of chemotherapeutics. Alterations in both cellular and systemic mechanisms could induce drug resistance in cancer. At the cellular level, numerous pathways have been associated with cancer drug resistance depending on the tumor origin and anti-cancer agent. Amongst other pathways including overexpression of multidrug resistance proteins, lipid modifier enzymes have also been linked to drug resistance in cancer via regulation of multidrug resistance protein levels, cell death mechanisms, and reactive lipid and oxygen species. Here the involvement of cyclooxygenases (COXs) and lipoxygenases (LOXs) as members of lipid modifier enzymes in cancer drug resistance should be emphasized. In this review, we summarize the studies examining the vital role of COXs/LOXs in the development and modulation of cancer drug resistance and cancer treatment.

Keywords: Cyclooxygenases, lipoxygenases, cancer drug resistance

ÖZ

Kanserde ilaç dirençliliği kemoterapötiklerin başarı oranını kısıtlayan kritik faktörlerden bir tanesidir. Hücresel ve sistemik mekanizmaların bozulması, ilaç dirençliliğini tetikleyebilir. Hücresel düzeyde, tümör orijinine ve anti-kanser ajana bağlı olarak birçok farklı yolak kanserde ilaç dirençliliği ile ilişkilendirilmiştir. Çoklu ilaç dirençliliği proteinin aşırı ekspresyonu gibi mekanizmalara ek olarak lipid düzenleyici proteinler de çoklu ilaç dirençliliği protein seviyelerini, hücre ölüm mekanizmalarını ve reaktif lipid ve oksijen türlerini regüle ederek kanserde ilaç dirençliliği ile ilişkilendirilmiştir. Bu noktada, lipid düzenleyici enzimlerin birer üyesi olarak siklooksijenazların (COX) ve lipooksijenazların (LOX), ilaç dirençliliğindeki rolü önem arz etmektedir. Sunulan derleme çalışmada, COX ve LOX'ların kanserde ilaç dirençliliğinin gelişimindeki ve modülasyonundaki ve kanser tedavisindeki hayati rollerini inceleyen çalışmalar özetlenmiştir.

Anahtar Sözcükler: Siklooksijenaz, lipooksijenaz, kanserde ilaç dirençliliği

INTRODUCTION

Cancer drug resistance is a critical phenomenon that limits the efficacy of cancer treatment. It is defined as the reduction in effectiveness of the anticancer drugs, due to several cellular and/or systemic alterations. Numerous studies elucidated the molecular mechanisms of cancer drug resistance and how a wide range of fundamental molecular pathways, such as cell death, cellular metabolism, and inflammation, have been affected by cancer drug resistance (1-3).

One of the major drug resistance mechanisms is the utilization or shaping of prostanoid and leukotriene (LT) biosynthetic pathways (4). The significance of these metabolites is immense in adjusting the tumor microenvironment by controlling angiogenesis, inflammation, and immunosuppression. Inflammation is a crucial response in organisms against a wide variety of threats. The process ensures the defense against pathogens, tissue repair, regeneration, and homeostasis (5). The inflammatory response governs the disease progression in cancer, including the stages of initiation, promotion,

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malignant conversion, invasion, and metastasis (6). Although the relation between inflammation and cancer has been on the table since 1863 with Virchow's hypothesis, the mechanism is yet to be elucidated (7). Eicosanoids, including prostaglandins (PGs) and LTs, are active lipid-based substances that regulate inflammatory processes (4). PGs and LTs are synthesized from AA, an omega-6 polyunsaturated fatty acid (PUFA), by cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, respectively (8), implying that these enzymes could be decisive for the development of cancer drug resistance.

In the present review article, we summarize the studies focusing on the involvement of COXs and LOXs in cancer drug resistance. We regard that concentrating on these enzymes may provide a better understanding of cancer drug resistance in terms of lipid modification and inflammatory regulations.

Cyclooxygenases

The COX family, also known as PG G/H synthases (PGHS), is one of the well-studied enzymes due to its involvement in a wide variety of mechanisms including regulating inflammatory response, adjusting tumor microenvironment, and altering the response to anticancer agents. COX-1 (PGHS-1) isoform is continuously expressed in the majority of tissues to sustain homeostasis by regulating PGs (9). However, COX-2 (PGHS-2) is an inducible gene and is upregulated in inflammatory sites and cancer cells (10,11). Therefore, targeting COX-2 is a promising approach for better prognosis and treatment of cancer (12). The last isoform of COXs is COX-3, a splice variant of COX-1 producing a longer protein (633 amino acids long) (13,14).

COX-1 activity has been shown to be at a basal level in general and to increase when the free arachidonic acid (AA) increases. Contrary to COX-2, our knowledge of the role of COX-1 in cancer has been limited. In cooperation with COX-2, COX-1 has been reported to be deregulated in diverse cancers including renal cell carcinoma, skin, head and neck, esophageal, colorectal, breast, cervical, endometrial, and ovarian cancer and hematological tumors. Accordingly, selective inhibition of COX-1 has been proposed for cancer treatment (15). Selective COX-1 inhibitor SC-560 reduced tumor growth in the ovarian cancer grafts through inhibition of prostacyclin (PGI2), which is the major PG produced by COX-1 (16).

COX-2 was discovered in 1991 (17,18). The cDNA sequence of COX-2 was reported to be highly similar to that of COX-1, and its expression was shown in mouse fibroblasts, cultured rat mesangial cells, in RAW 264.7, and in rat alveolar macrophages as well as the ovary (19). Functional analyses showed that although there were remarkable sequence similarities between COX-1 and COX-2, they demonstrate diverse chromosomal organizations and tissue expression profiles. More importantly, the COX-2 promoter was found to have critical elements that were switched on by glucocorticoids and off by cellular stress, while COX-1 was regarded as a housekeeping gene (19,20).

COX-2 converts AA to PGs, specifically PGE2, and regulates diverse physiological mechanisms such as platelet disaggregation, inflammation, vasodilation and bone resorption. However, any disruptions in COX-2 activity could result in pathophysiological conditions, including cancer (21,22).

The role of COX-2 in carcinogenesis is well-documented. COX-2 is generally overexpressed in cancer cells and the contribution of COX-2 to the carcinogenesis is associated with the function of its main product, PGE_2 (23,24). The relationship between COX-2 and colorectal (24,25), breast (26-28), skin (29), pancreatic (30), cervical (31), lung (32), gastric (33), intestinal (34), and prostate (35) cancers has been reported. Overexpression of COX-2 caused increased genomic instability in the non-tumorigenic breast epithelial cell line MCF10A (27) and the breast adenocarcinoma cell line MCF7 (28).

COX-1 and Cancer Drug Resistance

The association of COX-1 with cancer drug resistance has not been studied in detail. It was shown that COX-1 inhibition by indomethacin elevated vincristine and doxorubicin cytotoxicity in T98G malignant glioma and doxorubicin-resistant K562 myeloid leukemia cells through downregulation of multidrug resistance protein 1 (MRP1) (36,37). On the other hand, Radilova et al. (38) showed that COX-1 downregulation in human cervical cells caused an upregulation in (MRP4; ABCC4), which was explained by the role of MRP4 in the transport of the prostanoids (38). In another study, cisplatin conditioning was shown to trigger resistance to different platinum analogs, including cisplatin, oxaliplatin and carboplatin in mesenchymal stem cells by preventing apoptosis. The researchers identified the resistance mechanism was the production of PUFAs 12-oxo-5,8,10-heptadecatrienoic acid and hexadeca-4,7,10,13-tetraenoic acid [16:4(n-3)] by cisplatin preconditioning, which was reversed by the inhibition of COX-1 and thromboxane synthase (TXAS) (39). Bottone et al. (40) also reported that selective COX-1 inhibitor SC-560 elevated the expressions of NAG-1, NAG-3, ATF3 and C/EBPB while downregulating the expressions of INSIG-1, MSX1, MAD2 and NRG-1, implying a chemopreventive effect in HCT-116 human colorectal carcinoma cells (40). On the other hand, COX-1 was shown not to be expressed in either sensitive or taxane-resistant ovarian cancer cells (41). However, the limited number of studies cannot allow us to draw comprehensive conclusions about the function of COX-1 in cancer drug resistance.

COX-2 and Cancer Drug Resistance

The effects of the alterations in COX-2 expression and activity have frequently been observed in drug resistance, in addition to its role in carcinogenesis (42). Several studies reported that COX-2 expression is enhanced in drug resistance to various chemotherapeutics. Lu et al. (43) showed that COX-2 expression was significantly elevated in cetuximab-resistant DiFi colorectal cancer cells compared to cetuximab-sensitive parental cell lines (43). Stable COX-2 transfection in LNCaP prostate cancer cells caused 3-fold resistance to carboplatin by repressing apoptotic response through upregulation of survivin, Bcl-2, and AKT (44). Krysan et al. (45) revealed that constitutive COX-2 expression stabilized survivin and caused the development of resistance to apoptosis in non-small cell lung cancer cell lines, A549 and H157 (45). Tang et al. (46) reported that COX-2 transfection conferred resistance to TRAIL-induced apoptosis in HCT-15 colon cancer cells via the transcriptional suppression of DR-5, upregulation of Bcl-2, and inhibition of the activation of caspase 3, 8, and 9 (46). The COX-2-TXA2 signaling pathway was shown to inhibit apoptosis in gefitinib-resistant non-small cell lung cancer cells (47). Recently, COX-2 upregulation through the activity of yes-associated protein 1 (YAP) has been shown to confer resistance by co-expression of myeloid cell leukemia-1 (MCL-1), multidrug resistance

(MDR), and survivin. The use of a YAP and COX-2 inhibitor reversed the resistance to taxol in colorectal cancer cells (48). In another study, COX-2 expression has been positively correlated with increased levels of P-gp and phosphorylated c-Jun, and COX-2 downregulation promoted resensitization of HCT8/V colorectal cancer cells against vincristine (49). In a similar manner, overexpression of COX-2 led to the development of acquired cross-resistance to cisplatin and doxorubicin in TRAIL-resistant H460 and H1568 lung cancer cells (50). Janakiraman et al. (51) showed that overexpression of COX-2 blocked the cleavage of caspase 3 and HuR, thereby inhibiting apoptotic pathways in paclitaxel-resistant oral squamous cell carcinoma. COX-2-deficient HT-29 colon cancer cells were reported to exhibit resistance to apoptosis when COX-2 was overexpressed. At the same time, 3-hydroxy-30,4,40,50-tetra-methoxy-chalcone (3-HTMC, an open chain flavonoid chalcone) was proven to be more potent in terms of apoptosis induction in COX-2-deficient HCT-116 cells than COX-2-sufficient HT-29 cells (52). The main product of COX-2, PGE2, acts as a cytoprotective agent (24). The stimulation of PGE2 release from stromal cells due to overexpression of COX-2 rendered prostate cancer cells resistant to the tetracycline derivative COL-3, and docetaxel (53). Similarly, Sun et al. (54) showed that overexpression of COX-2 and subsequent PGE_2 production alleviated the induction of apoptosis by 5-fluorouracil in colon cancer cells by increasing Bcl-2 at mRNA and protein levels, attenuating caspase 3/9 activation and inhibiting cytochrome c release (54).

COX-2 expression also showed positive correlation with tumorigenesis, as well as poor prognosis and increased drug resistance in cancer patients. Singh et al. (28) showed that MCF-7/COX-2 mammospheres displayed enhanced colony-forming ability. COX-2 positivity was higher in primary advanced ovarian cancer patients who were non-responding to the platinum-based chemotherapy (55). In a similar manner, patients with advanced head and neck squamous cancer displayed higher tumor recurrence due to cisplatin resistance caused by increased COX-2 expression (56). COX-2 expression was reported to be markedly increased in breast cancer-associated macrophages and correlated with poor prognosis in breast cancer (57). Similarly, a strong correlation between the expression levels of COX-2 and BCRP was reported in non-treated non-Hodgkin's lymphoma patients who displayed poor response to chemotherapy, and shorter progression-free survival time (58).

COX-2 and Cellular Drug Transporters

A correlation between high COX-2 expression and MDR1/P-gp expression was reported. Several studies have shown that MCF7 cells expressing COX-2 exhibited increased MDR1/P-gp expression and resistance to doxorubicin coupled with increased Bcl-2 expression (28,59). Li et al. (57) demonstrated that ectopic expression of COX-2 triggered cellular proliferation and survival of breast cancer cells by stimulating P-gp expression. Similarly, cisplatin-resistant SGC-7901 gastric cancer cells were found to display increased COX-2 and P-gp expression (60). Lee et al. (41) reported that COX-2 was significantly expressed in taxane-resistant SKOV3.ip1 ovarian carcinoma cells that exhibited upregulated P-gp expression (41). Likewise, TT medullary thyroid carcinoma (an extremely chemoresistant malignant neoplasia) cell line was reported to express elevated levels of COX-2 and P-gp (59). Imatinib-resistant K562 chronic myeloid leukemia (CML) cells were shown to exhibit increased histone deacetylase expression and activity, which, in turn, elevated CREB activation, COX-2 expression, and consequently, MDR1 expression and decreased intracellular doxorubicin accumulation. In the same cell line, the overexpression of COX-2 increased ABC transporter (MRP1-5, ABCG2, ABCA2) expression at both mRNA and protein levels, which was downregulated upon celecoxib treatment due to inhibition of WNT and ERK signaling pathways (60). Liu et al. (61) stated that after the interaction with Shc3, triggers, where it stimulates COX-2 expression by binding to the COX-2 promoter, which, in turn, mediated P-gp expression, resulting in decreased sensitivity to chemotherapy. It was also reported that COX-2 expression was correlated with higher MDR1/P-gp expression in primary invasive breast (62), ovarian (54,62) and non-small cell lung cancer cases (62), which were coupled with shorter progression-free survival time and decreased treatment response. Not only does COX-2 expression affect MDR1/P-gp-mediated drug resistance. MRP1 expression and subsequent chemoresistance to cisplatin were reported after COX-2 overexpression in HCT-15 colon cancer cells, which were normally lacking COX-2 (63). Kochel et al. (64) reported that in triple-negative breast cancers, high COX-2 activity was associated with increased MRP4 and decreased PG transporter (PGT) activities, which contributed to poor prognosis. Similarly, the upregulation of COX-2, stimulated MRP4 expression in the A549 non-small cell lung cancer (65). Kalalina et al. (66) showed that TPA-induced COX-2 expression in mitoxanthrone-resistant MCF7 (MCF7-MX) cells resulted in higher ABCG2/BCRP activity. COX-2 catalyzes the production of PGE2, which is imported by PGT and exported by MRP4 (67). Chung et al. (68) showed that TGFβ1 promoted COX-2 expression via the activation of the p38-MAPK-ERK pathway through galectin-1 interaction with Ras. The knockdown of galectin-1 resensitized A549 lung cancer cells to cisplatin and repressed cellular migration and invasion by suppressing COX-2 activity.

Inhibition of COX-2 in Resistant Cancer Cells

Inhibition of COX-2 is a frequently used strategy due to the involvement of COX-2 in cancer initiation and progression. Moreover, the efficacy of COX-2 inhibitors in halting multidrug resistance by downregulating efflux pumps has been confirmed (69). Selective inhibition of COX-2 gains more attention because of advantages in avoiding the undesired side effects of non-selective therapies, such as non-steroidal anti-inflammatory drug (NSAID) conjugates (70). COX-2 inhibitor NS-398 was shown to be effective at resensitizing MCF7 cells by impairing P-gp expression and function (59). Treatment with another specific COX-2 inhibitor, celecoxib, reversed the effects of high ABCG2 (BCRP) activity in MCF7-MX cells (66). Similarly, celecoxib was shown to increase apoptosis by downregulation of survivin and upregulation of glutathione S-transferase pi (GSTpi) in carboplatin-resistant prostate cancer cells (44). Additionally, celecoxib decreased stroma-induced resistance to COL-3 and docetaxel, and triggered in situ prostate cancer cell death by increasing the levels of active caspases 3 and 9 (53). Fantappie et al. (71) demonstrated that celecoxib alleviated drug resistance by decreasing the expression levels of P-gp, Bcl-xL and Bcl-2, enhancing the translocation of Bax to the mitochondria and promoting the release of cytochrome c into the cytoplasm in multidrug-resistant hepatocellular carcinoma cells. It was also reported that celecoxib treatment decreased P-gp expression in doxorubicin-resistant HT-29 colorectal

cancer cell lines (71). In the same cell line, the use of celecoxib along with imatinib resulted in decreased cell viability through diminished COX-2 and increased caspase 3 levels (72). Lee et al. (41) showed that COX-2 inhibition resulted in decreased MDR1/P-gp expression and enhanced paclitaxel cytotoxicity in taxane-resistant ovarian carcinoma. COX-2 was found to be downregulated in C-Phycocyanin-treated (a biliprotein obtained from Spirulina platensis)-treated HepG2 hepatocellular carcinoma cells. The downregulation of COX-2, in turn, decreased the expression of MDR1 and enhanced the intracellular accumulation of doxorubicin and subsequently the chemosensitivity of the cells (73). In a similar fashion, indomethacin (NSAID) and SC236 (selective COX-2 inhibitor) caused elevated doxorubicin cytotoxicity due to higher drug accumulation and retention through partial decrease in P-gp and MRP1 expressions in HepG2 cells (74). Specific COX-2 inhibitors, NS-398, rofecoxib, and celecoxib, reduced MDR1 expression, decreased drug efflux, triggered apoptosis, and increased the efficacy of doxorubicin and vinorelbine in medullary thyroid carcinoma (59,75). Celecoxib or NS398 treatment increased sensitivity to vinblastine or paclitaxel in multidrug resistant subline of KB oral squamous carcinoma cells (76). It was also reported that celecoxib sensitized renal cancer cells to sorafenib by stabilizing COX-2 mRNA in stress granules (77). Xu et al. (69) revealed that celecoxib inhibited PGE2 release, downregulated P-gp expression, and displayed synergism with cisplatin. It also promoted apoptosis through enhanced p53 expression, caspase 3 activation, and a low Bcl-2/Bax ratio in cisplatin-resistant gastric cancer cells (69). Similarly, another COX-2 inhibitor, meloxicam, was found to downregulate MDR1 expression in HL-60 acute myeloid leukemia cell lines (78). In a similar manner, JTE 522 (selective COX-2 inhibitor) was suggested as effective in resensitizing colon cancer cells to cisplatin (63). Zrieki et al. (79) pointed out that the non-specific COX inhibitor indomethacin heptyl ester could reverse the upregulation of P-gp expression and activity, which was induced due to COX-2 stimulation by 2,4,6 -trinitrobenzene sulfonic acid in colorectal cancer (79). Peng et al. (80) reported that COX-2 inhibitor NS-398 promoted the expression of cyclin dependent kinase inhibitors p21WAF1 and p27Kip1, and enhanced chemotherapy-induced apoptosis in hypopharyngeal cancer cells. In lung cancer, the inhibition of COX-2 activity repressed the resistance to apoptosis by enhancing the proteasomal degradation of survivin (45) and upregulating anti-apoptotic MCL-1 (50). The induction of apoptosis after treatment with COX-2 inhibitors was recorded in Caco-2 colorectal adenocarcinoma cell lines, which are known to be intrinsically resistant to cetuximab (43). Moreover, Neumann et al. (81) utilized cisplatin-COX-2 inhibitor conjugates to benefit from the tumor-inhibiting capacity of COX-2 inhibitors and to maximize the apoptosis-inducing effect of cisplatin in colon, ovarian, triple-negative breast and squamous cell cancers.

The use of NSAIDs was also effective against COX-2-mediated drug resistance. Tang et al. (46) showed that sulindac sulfide restored the expression of death receptor 5 (DR-5) and augmented the efficacy of TRAIL in colon cancer cells. Another NSAID, etodolac, was found to have additive effects with oxaliplatin, inhibiting the growth of RKO colon cancer cells and promoting cell death by diminishing survivin (82). Additionally, nimesulide was shown to downregulate P-gp expression and activity, providing chemoprevention and chemosensitization to CaCo-2 colorectal cancer cells (79).

In addition to small molecule inhibitors, COX-2 downregulation by genetic manipulations has also been studied in cancer drug resistance. COX-2 is a direct target of miR-101, which was significantly downregulated in cisplatin-resistant T24 human bladder cancer cells. The overexpression of miR-101 augmented the anti-proliferative effects of cisplatin and helped the induction of apoptosis (83). MiR-216a-3p was also reported to directly bind to the 3' UTR of COX-2 mRNA, and the ectopic expression of miR-216a-3p was efficient in the suppression of colorectal cancer cells (84). In BRAF and MEK inhibitor-resistant melanoma cells, increased miR-146-5p expression downregulated COX-2, resulting in elevated drug sensitivity, decreased cellular proliferation, and increased apoptosis by hampering NF-kB signaling (85). The depletion of COX-2 sensitized PARPi-resistant BRCA2-deficient pancreatic Capan-1 cells, increasing their sensitivity by 70% (86). Similarly, siRNA-mediated inhibition of COX-2 expression resulted in the induction of apoptosis in 3-HTMC-treated colon cancer cells (52). Stable knockdown of COX-2 led to partial sensitization of cetuximab-resistant DiFi cells to the agent (43). Likewise, in doxorubicin-resistant MCF7 breast cancer cells, inhibition of COX-2 by siRNA decreased the aggressiveness of the resistant cells (87).

COX-2 expression affects proliferation and resistance status not only monolayer cell lines, but also of 3D cultures and cancer patients. Ben-Batalla et al. (88) demonstrated that COX-2 inhibitors showed additive effects with anti-VEGFR-2 antibodies or the VEGFR inhibitor sunitinib in 4T1 tumors. The use of COX-2 inhibitors decreased the levels of pro-angiogenic HGF and FGF2, the migratory capacity of cancer-associated fibroblasts (CAFs) and the infiltration of CAFs into tumors (88). The specific COX-2 inhibitor, celecoxib, increased the sensitivity of the multicellular spheroids of HepG2 hepatocellular carcinoma cells to 5-fluorouracil, sorafenib, and gefitinib (89). Kim et al. (90) showed that NS-398 decreased both the expression and activity of P-gp and triggered apoptosis by downregulating Bcl-2 protein in monolayer cell cultures derived from COX-2-positive ependymoma patients (90). Additionally, Pi et al (91) reported that inhibition of COX-2 reversed resistance to anti-PD-1-mAB therapy in B16F10-R tumors in which knockout of the PTSG2 gene restored sensitivity.

Inhibition of COX-2 not only sensitizes the cancer cells to chemotherapy but also to radiation. Celecoxib was found to be effective in sensitizing HeLa cells to radiation by decreasing COX-2 mediated AKT phosphorylation (92). Moreover, Sun et al. (93) revealed that aspirin downregulated COX-2 by irreversibly disrupting the chromatin looping in COX-2 locus and increased the survival of A549 and H1299 lung cancer cells (93).

Lipoxygenases

LOXs are enzymes catalyzing the PUFAs, specifically AA and linoleic acid. The metabolic products of LOXs (5-LOX, 12-LOX, 15-LOX-1 and 15-LOX-2) are involved in several physiological and pathophysiological conditions, including inflammation and cancer (94). Due to having a wide range of roles, LOXs are studied exclusively by numerous therapeutic strategies, including screening new inhibitors and activators of LOXs, designing or repurposing drugs (95, 96). Particularly, development of LOX inhibitors is one of the promising approaches to regulate LOX enzymes' metabolites in cancer therapy as well as for the treatment of inflammation,

allergy, and cardiovascular disease (96). The importance of LOXs in cancer drug resistance should be addressed in detail because of not only their role in the production of bioactive lipids but also their ability in membrane modification and balancing redox states (97). Nevertheless, the limited number of studies in the literature have mostly been restricted to 15-LOX-1.

5-Lipoxygenase

5-Lipoxygenase (5-LOX) was shown to be involved in the modulation of angiogenesis, cellular viability and proliferation, higher metastasis and invasive capacity, lower survival rates in cancer patients, and disruption of chemopreventive efforts (98). The inhibition of 5-LOX was associated with reduced growth and increased apoptosis in gastric, esophageal, bladder, and hepatocellular cancers (99-101). Edderkaoui et al. (102) showed that 5-LOX controls reactive oxygen species production by NADPH oxidase by modulating fibronectin. The inhibition of 5-LOX resulted in decreased ROS accumulation, leading to caspase stimulation and eventual DNA fragmentation in pancreatic cancer (102). Ding et al. (103), stated that the 5-LOX pathway was overactivated in pancreatic cancer cells and the combined use of COX-2 inhibitor celecoxib and 5-LOX inhibitor MK886 significantly decreased the growth of SW1990 cells (103). Roos et al. (104) reported that selective 5-LOX inhibitor CJ13,160 inhibited WNT signaling and disrupted stem cell capacity in acute myeloid leukemia (104). Similarly, Wang et al. (105), showed that synthetic dl-nordihydroguaiaretic acid compound (dl-NOGA or Nordy) inhibited 5-LOX, resulting in a decrease in self-renewal, abrogation of clonogenicity, as well as induced differentiation in glioma stem-like cells that were resistant to radio- and chemotherapy. Additionally, 5-LOX inhibitor, auranofin, was reported to induce apoptosis in cisplatin-resistant ovarian cancer (106). On the other hand, Catalano et al. (107) showed that 5-LOX interfered with p53-induced apoptosis by decreasing the relocalization of p53 within promyelocytic leukemia protein (PML)-nuclear bodies, which induced transcription of pro-apoptotic genes.

12-Lipoxygenase

Yin et al. (108) showed that cancer stem cell-like populations isolated from DU-145 prostate cancer cell line exhibited upregulated 12-Lipoxygenase (12-LOX) and ABCG2. Similarly, Lövey et al. (109) reported that upregulation of 12-LOX resulted in resistance to radiation in pancreas cells, and 12-LOX inhibitors baicalein or BMD122 sensitized these cells to radiation. The combined use of 12-LOX inhibitors and radiation displayed a synergistic effect, leading to decreased colony formation capacity of LNCaP and PC3 cells as well as reduced tumor growth *in vivo* (109). In cisplatin-resistant SKOV3 ovarian cancer cells, targeting 12-LOX or SP1 (the mutual transcription factor for 12-LOX, COX-1, MRP1 and MRP4) inhibited EMT and metastasis and reversed cisplatin resistance (110).

15-Lipoxygenase-1 and Cancer Drug Resistance

The studies reporting the involvement of Arachidonate 15-Lipoxygenase (ALOX15)/ 15-Lipoxygenase-1 (15-LOX-1) expression and/or activity in carcinogenesis and cancer drug resistance are not only limited but are also controversial.

Kim et al. (111) showed that overexpression of 15-LOX-1 promoted growth arrest and decreased cellular viability in HCT-116 colorectal cancer cells through the upregulation of p21WAF1/CIP1 and MDM2, and the induction of p53 phosphorylation. In gastric cancer, COX-2 inhibitor SC-236 promoted apoptosis by upregulating 15-LOX-1 expression and the production of 13-S-HODE (112). Similarly, it was reported that 15-LOX-1 overexpression in the same cell line led to enhanced indomethacin-induced apoptosis, and the treatment of the cells with exogenous 13-S-HODE further strengthened this apoptosis (113). Wolff et al. (114) showed that three different 15-LOX-1 metabolites, 13-HpOTrE, 13-HpODE and 15-HpETE, reduced the viability of monolayer skin cancer cells and decreased the release of interleukin-6 to the level of tumor-free samples in 3D skin cell cultures. In K562 CML cells, the hydroperoxy metabolite of 15-LOX-1, 13-S-HpODE, inhibited cellular growth and induced apoptosis via the generation of reactive oxygen species and the activation of caspase 3 (115). However, in leukemia stem cells (LSCs), both the deletion of ALOX15 and the chemical inhibition of 15-LOX-1 impaired the function of LSCs, inhibited cell division, triggered apoptosis, and consequently attenuated CML. Additionally, combining the specific 15-LOX-1 inhibitor, PD146176, with imatinib was proven to be more effective in decreasing the number of LSCs (116). Similarly, Kelavkar et al. (117) demonstrated that the increased expression of 15-LOX-1 promoted the tumorigenesis of PC3 prostate cancer cells by increasing VEGF and Factor VIII levels as well as cellular proliferation. In our study, we found that *ALOX15* was transcriptionally downregulated in doxorubicin-resistant MCF7 breast cancer and HeLa cervical cancer cell lines. Although the ectopic expression of ALOX15 resensitized both resistant cell lines to doxorubicin, the mechanisms by which ALOX15 overexpression exerted its effects differed. The ALOX15 overexpression stimulated apoptosis via the activation of PPARγ and increased intracellular doxorubicin accumulation by altering membrane dynamics in doxorubicin-resistant MCF7 cells. In contrast, increased apoptosis was monitored in 13-S-HODE-treated doxorubicin-resistant HeLa cells (118). Downregulation of ALOX15 by miR-522 packed into exosomes and secreted by CAFs, upon de-ubiquitination of hnRNPA1 by ubiquitin-specific protease 7 (USP7), was shown to increase chemoresistance in gastric cancer cells. Zhang et al. (119) reported that downregulated ALOX15 decreased lipid-ROS accumulation in the cells, which led to the inhibition of ferroptosis, and consequently, decreased chemosensitivity.

Shureiqi et al. (120) found that NSAIDs induced 15-LOX-1 expression during apoptosis in esophageal cancers, which otherwise exhibited lower 15-LOX-1 expression. In contrast, Yoshinaga et al. (113) reported a significant decrease in 15-LOX-1 expression in colorectal surgical samples of NSAID users compared to NSAID non-users. However, in both cases, the increased expression or activity of 15-LOX-1 stimulated apoptosis, indicating its enhancing effect on NSAID-induced apoptosis.

CONCLUSION

In this review, we have summarized numerous studies that emphasized the importance of COXs and LOXs in cancer drug resistance. These studies suggest that COXs and LOXs directly and/or indirectly are involved in the development, progression, and modulation of cancer drug resistance and could be vital candidates in overcoming cancer drug resistance, and possibly, in more personalized cancer treatments. However, the involvement of these enzymes in the modulation of cancer drug resistance appears to be

in a cell/tumor origin-specific and drug-specific manner. Additionally, it is important to note that those enzymes participate in other vital functions including the regulation of inflammatory pathways, cellular redox balance, cell death mechanisms, and cell membrane modifications that affect the membrane dynamics. Unfortunately, we still have limited knowledge about the widespread effect of COX and LOX family enzymes on the regulation of these cellular processes in drug-resistant cancers. The lack of information reveals the need for further studies on the role of COXs and LOXs in the regulation of these cellular processes, as well as their effects on cancer drug resistance.

Footnotes

Authorship Contributions

Concept: H.H.K., Ç.U.M., Design: H.H.K., Ç.U.M., Analysis or Interpretation: Supervision: Ç.U.M., Literature Search: H.H.K., A.Ç.Ö., Ç.U.M., Writing: H.H.K., A.Ç.Ö., Ç.U.M., Critical Review: H.H.K., A.Ç.Ö., Ç.U.M.

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