Review Article

Potential COX2 mediated Therapeutic effect of Ciprofloxacin

Marwa A. Eisa, Moustafa Fathy and Maiiada H. Nazmy
Department of Biochemistry, Faculty of Pharmacy, Minia University, Minia, Egypt.

Abstract
Fluoroquinolones (FQs) are broad-spectrum, synthetic antibiotics that inhibit bacterial DNA synthesis. FQs directly block DNA synthesis in the bacterial cell via inhibition the activity of two tetrameric, ATP-dependent, homologous type II topoisomerase enzymes: topoisomerase II-called DNA gyrase and topoisomerase IV. FQs are also active against eukaryotic topoisomerase II. This property results in inhibition of this enzyme and pro apoptotic effects on mammalian tumor cell lines, including human cells, and creates the possibility of using FQs as potential anticancer drugs. In one study, it was found that ciprofloxacin induced the production of prostaglandin E_2 in monocytes in a concentration-dependent manner.

Introduction
The fluoroquinolones (FQs) are broad-spectrum, synthetic antibiotics that inhibit bacterial DNA synthesis (Majalekar & Shirote, 2020), (Beberok et al., 2018). These drugs are widely used in clinical practice for the treatment of urinary, respiratory, gastrointestinal tract infections, bone, skin or soft tissue infections as well as ocular diseases (Majalekar & Shirote, 2020), (Beberok et al., 2018),(Aminov, 2017).

FQs directly block DNA synthesis in the bacterial cell via inhibition the activity of two tetrameric, ATP-dependent, homologous type II topoisomerase enzymes: topoisomerase II-called DNA gyrase and topoisomerase IV (Beberok et al., 2018), (Aminov, 2017) . DNA gyrase introduces negative super coils in DNA helix and relieves tension torsion, caused by the accumulation of positive supercoils during replication. The enzyme cuts the double-stranded DNA, inserts one single strand through break and then the helix is relegated. Topoisomerase IV is responsible for decate-nation of the linked daughter chromosomes during cell division (Krogh et al., 2018), (Dorman, 2020).

FQs bind to enzyme and form stable, ternary complexes: topoisomerase-drug-DNA. This results in inhibition of replication progression and introduces the cell into apoptosis due to accumulation of fragmented genetic material and to disorders in replication, transcription, recombination and DNA repair processes (Dorman, 2020), (Majalekar & Shirote, 2020) .
FQs are also active against eukaryotic topoisomerase II. This property results in inhibition of this enzyme and pro apoptotic effects on mammalian tumor cell lines, including human cells, and creates the possibility of using FQs as potential anticancer drugs (Beberok et al., 2018),(Pommier, 2013).

Studies have shown that FQs inhibit neoplasms growth by inducing apoptosis and cell cycle arrest in various cancer cell lines ,e.g. levofloxacin, enoxacin, ofloxacin and fleroxacin were shown to inhibit the growth of bladder carcinoma cell lines and transitional cells(Beberok et al., 2018), while moxifloxacin and gatifloxacin suppressed the proliferation of pancreatic cancer cells by cell cycle arrest and apoptosis (Yadav et al., 2015),(Beberok et al., 2018).

Ciprofloxacin also has potential benefits in bladder cancer management. In vitro studies on tumor cells made from ransitional cell carcinoma of the bladder resulted in both a dose- as well as time-dependent inhibition of cell growth. These results were achieved by ciprofloxacin with concentrations that are easily attainable in the urine of patients.(Alaaeldin et al., 2020)

Ciprofloxacin as anticancer

Evidence Favoring Ciprofloxacin As An Anti-Cancer Drug.

In 1989 Somekh et al showed that Cipro exerted a dose dependent inhibition of colony formation of hematopoietic progenitor cells and of leukemic cell lines. (Somekh et al., 1989). The concentration required for this inhibition was between 25 and 50 micrograms/ml. In 1990 two possible mechanisms for this inhibition were described: (Masadeh et al., 2017)

1) Uncoupling of oxidative phosphorylation with reduction of intracellular energy (decrease of ATP) achieved with 200 microM (Tomas Koltai, 2017); this is preceded by selective loss of mitochondrial DNA content, that can be obtained with concentrations between 40 and 80 micrograms/ml(Pietruszyński et al., 2020). Mitochondrial DNA breaks were found, suggesting that the mitochondrial damage may be due to interference with a mitochondrial topoisomerase II like activity.

2) Inhibition of topoisomerase II (Eder et al., 1990), (Akhtar et al., 2019), (Kloskowski et al., 2012). This mechanism of action is probably the main effect in order of an anti-proliferative activity. Pessina et al., (Pessina et al., 2001) developed a leukemia cell line with specific resistance to Cipro. The resistance was characterized by a decreased capacity of Cipro to produce cleavage of DNA and they propose a decreased affinity of Cipro for the topoisomerase II-DNA complex in these cells.

Also, other possible mechanisms were added:

3) Inhibition of Mcm2-7 replicative helicase (Simon et al., 2013) (minichromosomal maintenance protein 2-7) preventing proliferation of human cells.

4) In lymphoblastoid cells a growth arrest pathway was described that does not include double strand DNA breaks which includes topoisomerase II mediated DNA changes without double strand break but with ATM activation that triggers the G2 M check point and G2 arrest (Smart et al., 2008) .

5) Lysosomal membrane permeabilization inducing apoptosis through the mitochondrial membrane permeabilization (Domagala et al., 2018) . Fluoroquinolones are lysosomotropic agents which means that they are lipophilic bases that accumulate inside the lysosome producing a detergent-like effect on lysosomal membranes. Ciprofloxacin is a lysosomotropic agent and can induce apoptosis by permeabilization of lysosomal membrane (TOMAS Koltai, 2020) , (Erdal et al., 2005) .

Another Cipro derivative, trovafloxacin showed growth inhibition of P388 murine leukemia cells and prolonged survival of experimental animals (Thadepalli et al., 2005). Kloskowski et al (Kloskowski et al., 2011) tested Cipro in vitro against five different cancer cell lines: human non-small cell lung cancer, human and mouse melanoma, hepatocellular carcinoma, and rat glioblastoma. Important reduction in cell viability was observed in human non-small cell lung cancer, while rat glioblastoma was insensitive to Cipro.

The other 3 lines showed partial sensitivity. They worked with concentrations between 10 and 1000 micrograms/ml. In a comparative study of apoptosis induction among four different fluoroquinolones used on a human non-small cell lung cancer cell line in culture, all of them caused growth inhibition. The most effective was enoxacin, followed by norfloxacin, Cipro and levofloxacin (TOMAS Koltai, 2020).

Cyclooxygenase-2

COX exists in two isoforms: COX-1 and COX-2 (Figure 1). COX-1 is present normally in tissues and has housekeeping functions, while COX-2 is expressed at low levels in normal cells in response to physical, biological, chemical, or UV light stimuli (Kim et al., 2014).

COX-2 catalyzes the conversion of free arachidonic acid to prostaglandins, and COX-1-derived products drive the initial phase of acute inflammation with COX-2 upregulation occurring within several hours (Smyth et al., 2009). COX-2 is an enzyme that is released at the site of tissue injury to produce a hormone-like substance called prostaglandin E2 (PGE2) that stimulates pain and inflammation.

COX-2 derived prostaglandin can promote tumor growth by binding its receptors and activating signaling pathways which control cell proliferation (Sheng et al., 2001) promote angiogenesis (Shang et al., 2018), (Tsuji et al., 1998), inhibit apoptosis and increase metastatic potential (Kakiuchi et al., 2002).

In breast cancer cells COX-2 expression alters extracellular matrix structure and function and numbers of cancer associated fibroblasts (Krishnamachary et al., 2017). The role of the

COX-2 pathway in creating an immunosuppressive microenvironment, and in initiation and progression of Wilms' tumor, was discussed recently (Maturu et al., 2017). Elevated COX-2 expression is exhibited in various cancers including gastric, hepatic, esophageal, pancreatic, head and neck, lung, breast, bladder, cervical, endometrial, skin, and colorectal cancers when compared with nonmalignant tissue (Kuesap et al., 2021).

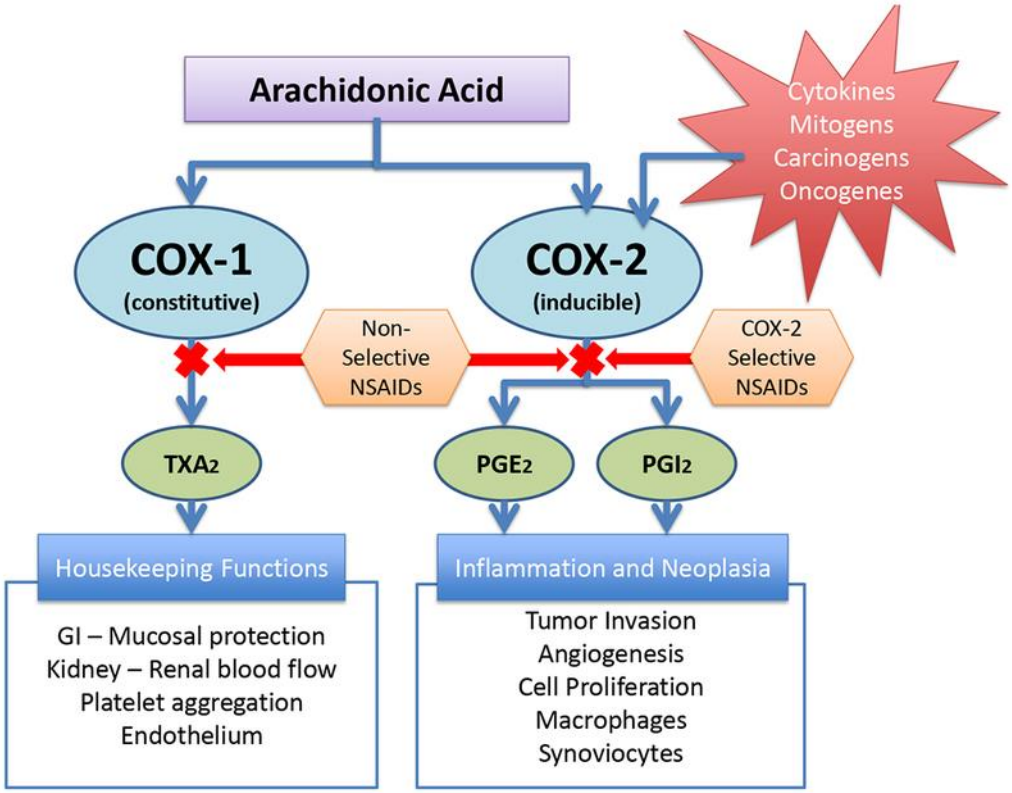

Figure 1: A model for COX biosynthesis and function. COX-1: cyclooxygenase-1; COX-2: cyclooxygenase 2; TXA2: thromboxane A2; PGE2: prostaglandin E2; PGI2: prostaglandin I2 (prostacyclin); GI: gastrointestinal.(Desai et al., 2018)

COX-2 is induced by inflammatory stimuli such as bacterial endotoxin and cytokines, and is the molecular target for analgesic and anti-inflammatory drugs. Mechanistically, increased COX-2 decreases the intracellular levels of free arachidonic acid, thereby preventing apoptosis and facilitating the growth of cancer cells (Nagendraprabhu & Sudhandiran, 2011).

COX-2 inhibitors are designed to block COX-2 enzyme activity and relieve pain. Phospholipids transform to arachidonic acid in response to tissue injury and are then further transformed to PGE2 through COX enzymes.

Cyclooxygenase donates two oxygen molecules to arachidonic acid to form PGG2 by peroxidation, which is then reduced to PGH2 in a committed step. Ultimately PGE2s and other prostaglandins are formed through activation of PGE synthase (Murakami & Ohigashi, 2007).

COX-2 is inducible and is elevated when there is tissue damage. Notably, COX-2 overexpression is correlated with high levels of intracellular telomerase - a vital reverse transcriptase enzyme associated with increased cell proliferation and lessened apoptosis (Harris et al., 2020).

The continuous overexpression of COX-2 could initiate and promote carcinogenesis by: Increasing production of reactive oxygen species that are carcinogenic (mutagenesis); (Horneber et al., 2012), increasing production of PGE2 and other factors that strongly promote cell proliferation (mitoge-nesis); (Bishop et al., 2010), stimulation of VEGF and PDGF by PGE2 resulting in the formation of

blood vessels (angiogenesis); (Perlman et al., 2013), increasing production of metalloproteinases, thus enhancing invasive potential (metastasis); (Rayburn et al., 2009), decreasing bioavailable arachidonic acid pools, thereby reducing cell differentiation and apoptosis (anti-apoptosis); (Bismark et al., 2014) and inhibiting proliferation of B and T lymphocytes, particularly natural killer T cells (Sing et al., 2011), thus limiting anti-neoplastic activity (immunosuppression) reviewed in (Harris et al., 2014).

Role of Inflammation in Cancer

Cancer and inflammation are related by epidemiology, histopathology, inflammatory profiles, and the efficacy of anti-inflammatory drugs in prophylaxis. Inflammation is a pathophysiological manifestation of numerous diseases. (Nahoum, 2006).

COXs are key enzymes for production of prostanoids implicated in inflammation, and can stimulate tumor cell proliferation, promote angiogenesis, and suppress apoptosis. The mechanisms by which prostaglandins promote cancer formation include suppression of the immune system, stimulation of cell growth and inhibition of apoptosis. COX-2 is induced by inflammatory stimuli such as bacterial endotoxin and cytokines, and is the molecular target for analgesic and anti-inflammatory drugs and natural products (Desai et al., 2018). (Figure 2).

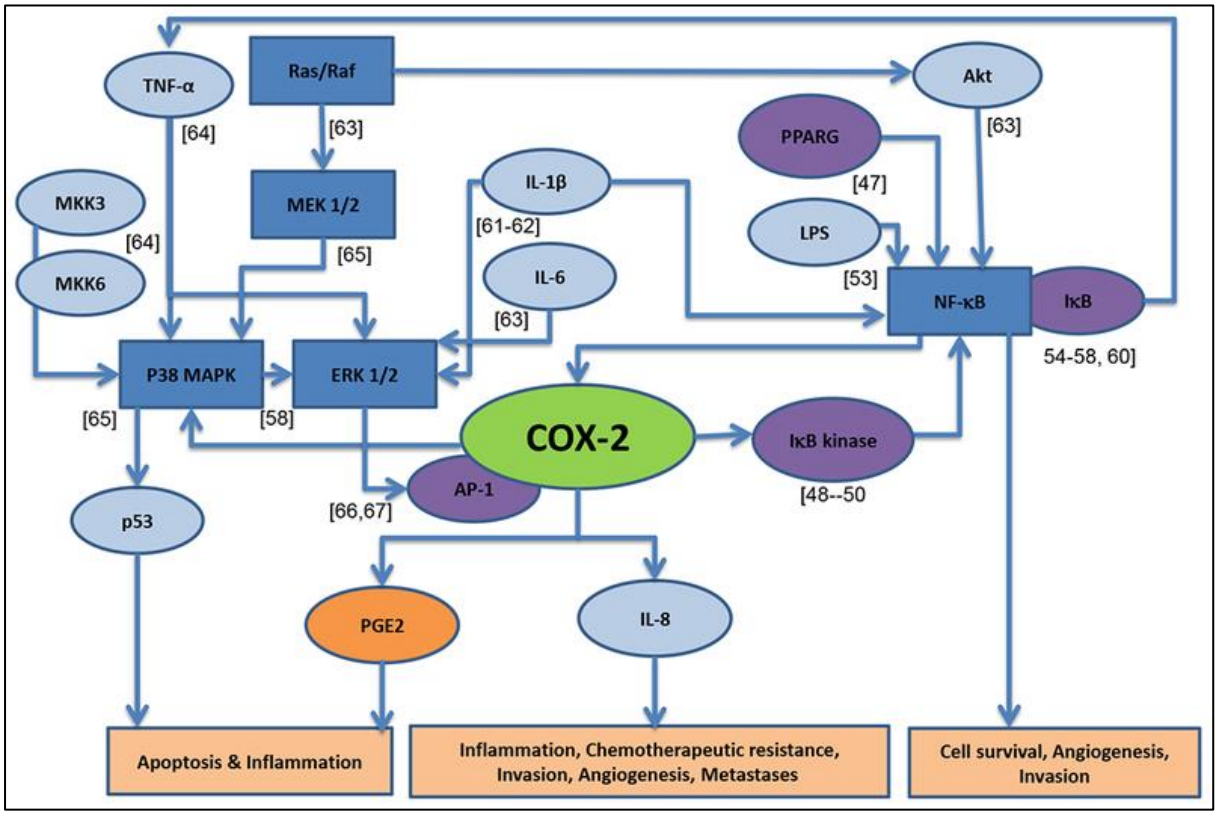

Figure (2): Model of COX-2: induction by proinflammatory cytokines, stimulation of cell proliferation, increase of metastatic potential, and effect on apoptosis and inflammation. (Desai et al., 2018)

There are many uses of anti-inflammatory agents. For example, synthetic drugs and natural herbs have been used to target and suppress dysregulated pathways that could lead to chronic inflammation and carcinogenesis. Anti-inflammatory phytochemicals or synthetic compounds for chemoprevention of almost any cancer including colon cancer (C.-Z. Wang et al., 2016), breast cancer (Yiannakopoulou, 2015), lung cancer (Conte et al., 2015), prostate cancer (X. Wang et al., 2014) were described.

Many molecules of natural origin, semi-synthesis and synthesis with anti-inflammatory and anticancer utilities were reviewed recently (M Lourenco et al., 2012), (Orlikova et al., 2014).

The active constituents of natural compounds are being studied more extensively due to their potential in the treatment and prevention of cancer (C. Wang et al., 2018) and compared to many drugs they have fewer side effects.

COX-2 REGULATORY PATHWAYS

Acute inflammation initiates a cascade of cytokines and chemokines that attract immune and non-immune cells to infiltrate disrupted and damaged tissue. The model of COX-2 regulation and induction by proinflammatory cytokines, stimulation of cell proliferation, increase of metastatic potential, and effect on apoptosis and inflammation (Fishbein et al., 2020) (Figure 5).

Pro-inflammatory signals include cytokines TNF-α and IL-1, UV radiation, carcinogens, tumor promoter (TPA), lipid mediators and other factors. These signals (Figure 5) stimulate COX-2 transcription via activation of mitogen-activated protein kinase (MEKK), mitogen-activated protein kinase (MAPKK), mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB), activator protein 1 (AP-1), p300 and IκB kinase (IKK)-κB/NF-κB-mediated signaling pathways regulating COX-2 transcription. Here we address two main arachidonic acid regulatory pathways, the NF-κB regulation of COX-2 transcription and the MAPK pathway. (Desai et al., 2018)

Ciprofloxacin effect on cox2

In one study, it was found that ciprofloxacin induced the production of prostaglandin E_2 in monocytes in a concentration-dependent manner regardless of the presence of interleukin-18 by enhancing the expression of cyclooxygenase-2 protein and that this in turn led to the elevation of intercellular cyclic AMP in monocytes via the stimulation of prostaglandin receptors. (Takahashi et al., 2005)

The prostaglandin E_2 and cyclic AMP production increased by ciprofloxacin was inhibited by indomethacin, a nonselective cyclooxygenase-2 inhibitor, and NS398, a selective cyclooxygenase-2 inhibitor. (Takahashi et al., 2005)

In addition, ciprofloxacin suppressed the interleukin-18-induced production of tumor necrosis factor alpha, gamma interferon, and interleukin-12 in peripheral blood mononuclear cells by inhibiting the expression of intercellular adhesion molecule 1, B7.1, B7.2, and CD40 on monocytes, and this effect could be reversed by the addition of indomethacin or NS398. (Chide & Orisakwe, 2007)

These results indicate that ciprofloxacin exerts immune modulatory activity via the production of prostaglandin E_2 and imply therapeutic potential of ciprofloxacin for the treatment of systemic inflammatory responses initiated by interleukin-18.(Katsuno et al., 2006)

Interleukin-18 (IL-18) requires cleavage at its aspartic acid residue by IL-1β-converting enzyme/caspase-1 to become an active and mature protein (Bianling Liu et al., 2000), and monocytes produce IL-18 while interacting with cognate T cells (Kupz et al., 2020).

Furthermore, IL-18 is located upstream of production of Th1 cytokines(Bianling Liu et al., 2000), (Yasuda et al., 2019), acts in synergy with IL-12 to induce gamma interferon (IFN-γ) production in $CD4^+$ cells via different signaling pathways (Rackov et al., 2021), and along with IL-12 is necessary for Th1 responses.

Cell-to-cell interactions brought about via the engagement between intercellular adhesion molecule 1 (ICAM-1), B7.1, B7.2, CD40, and CD40L on monocytes and their ligands on T/NK cells are also involved in the IL-18-induced production of cytokines, including IL-12, tumor necrosis factor alpha (TNF-α), IFN-γ, and IL-10 (Takahashi et al., 2005).

A major product of cyclooxygenase (COX)-initiated arachidonic acid metabolism, prostaglandin E_2 (PGE_2), which is released from antigen-presenting cells, primes naive human T cells and enhances their production of anti-inflammatory cytokines while inhibiting their synthesis of proinflammatory cytokines (Harizi et al., 2008).
Among the four PGE_2 receptor subtypes, E-prostanoid 1 (EP_1), EP_2, EP_3, and EP_4, activation of the EP_2 and EP_4 receptors leads to an increase in cyclic AMP (cAMP) levels and protein kinase A (PKA) activity (Sokolowska et al., 2015).

The stimulation of EP_2 receptors directly inhibits T-cell proliferation, while that of EP_2 and EP_4

receptors regulates antigen-presenting cell functions (Vojtech et al., 2019). In a previous study, It was found that PGE_2 prevented the IL-18-induced expression of ICAM-1, B7.2, and CD40 on monocytes and the production of IL-12, TNF-α, and IFN-γ in human peripheral blood mononuclear cells (PBMC) (Tamura et al., 2004).

The effects of fluoroquinolone antibacterial agents on immune modulation have been well documented (Breijyeh et al., 2020), and fluoroquinolones are known to exert their bactericidal activity by inhibiting bacterial type II topoisomerases (TOPO II), a major component of mitotic chromosomes.
Ciprofloxacin (CIP), a fluorinated 4-quinolone, may interact with TOPO II in human T cells, because the quinolone derivative CP-115,953, which displays high specificity against mammalian TOPO II, mimics the inducing effect of CIP on the production of IL-2 (Takahashi et al., 2005).

The synthesis of IL-1β and TNF-α by lipopolysaccharide-stimulated human monocytes is significantly inhibited by CIP (Baranek et al., 2007). However, little is known about the mechanism responsible for CIP activity, including the regulation of adhesion molecule expression. In that study, It was found that CIP induces the production of PGE_2 in monocytes through the induction of COX-2 protein.(Takahashi et al., 2005)

Relation between cox2 and p53

Cyclooxygenase (Cox), also termed prostaglandin H synthase, is the enzyme catalyzing the rate-limiting step that converts free arachidonic acid to prostaglandin (PG) H_2 on the arachidonic cascade(Kanso et al., 2021).
Presently, three isoforms, Cox-1, Cox-2, and Cox-3 have been identified. Cox-1 is present under normal conditions in most tissues and is responsible for housekeeping functions.
On the other hand, Cox-2 is not normally present under the basal conditions or is present in very low amounts. However, it is rapidly induced in response to a wide variety of cytokines (Rajagopal et al., 2021), growth factors(Abu Bakar et al., 2018), and ligands of G protein-coupled receptors(Tanaka et al., 2020).The induction of the Cox-2 gene is regulated at both transcriptional (promoter-based) and post-transcriptional levels(Abu Bakar et al., 2018), (Uchida, 2017),(C.-N. Zhang et al., 2019).

Intriguingly, Subbaramaiah et al., (Subbaramaiah et al., 1999) have suggested that Cox-2 gene expression is negatively regulated by p53, implying functional interactions of Cox-2 with p53. Cox-3 is a splice variant of Cox-1 that shares the catalytic features of Cox-1 and Cox-2 and has a sensitivity for acetaminophen (G. Dai et al., 2021).

The tumor suppressor protein p53 is a transcription factor that regulates the response to a variety of stimuli such as DNA damage, hypoxia, oxidative stress, and oncogene expression (Chillemi et al., 2017). Inactivation of the p53 gene, either by mutation or deletion, has frequently been found in a variety of human malignant tumors (Pavlakis & Stiewe, 2020), (Sanghvi, 2019).

Under normal conditions, p53 is a very labile protein. The rapid degradation of p53 is largely achieved through the ubiquitin–proteasome pathway. However, once cells are exposed to stimuli, the p53 protein increases promptly and regulates the various gene expressions.

The accumulation of p53 protein in response to various stimuli occurs mainly through post-translational modification rather than the transcriptional level. p53 has many phosphorylation sites, and the phosphorylation status of p53 is thought to be involved in stabilization and function of the protein(Mahendran et al., 2020).

P53 exerts its role through the transcriptional regulation of genes involved in cell cycle control, DNA repair, senescence, and apoptosis. p53 increases the gene expression involved in the cell cycle and apoptosis such as p21(Sun et al., 2019), MDM2(Hafner et al., 2019), Bcl-2 (Bingxian Liu et al., 2021) and Bax (Ruefli-Brasse & Reed, 2017).
On the other hand, p53 also represses the transcription of a number of genes, including topoisomerase IIα (Oscilowska et al., 2021), MRP (Ceballos et al., 2019), and human reduced folate carrier (Ding et al., 2001).

Lipid peroxidation proceeds by a free radical chain reaction mechanism and yields lipid

hydroperoxides as major initial reaction products. A key feature of the lipid peroxidation is the breakdown of these hydroperoxy fatty acids to yield a broad array of smaller fragments, 3–9 carbons in length, including reactive aldehydes, such as 2-alkenals and 4-hydroxy-2-alkenals (Halliwell & Gutteridge, 2015), (Gasparovic et al., 2017), (Guerby et al., 2019).

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