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Redox regulation of DUBs and its therapeutic implications in cancer

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ABSTRACT

Reactive oxygen species (ROS) act as a double-edged sword in cancer, where low levels of ROS are beneficial but excessive accumulation leads to cancer progression. Elevated levels of ROS in cancer are counteracted by the antioxidant defense system. An imbalance between ROS generation and the antioxidant system alters gene expression and cellular signaling, leading to cancer progression or death. Post-translational modifications, such as ubiquitination, phosphorylation, and SUMOylation, play a critical role in the maintenance of ROS homeostasis by controlling ROS production and clearance. Recent evidence suggests that deubiquitinating enzymes (DUBs)-mediated ubiquitin removal from substrates is regulated by ROS. ROS-mediated oxidation of the catalytic cysteine (Cys) of DUBs, leading to their reversible inactivation, has emerged as a key mechanism regulating DUB-controlled cellular events. A better understanding of the mechanism by which DUBs are susceptible to ROS and exploring the ways to utilize ROS to pharmacologically modulate DUB-mediated signaling pathways might provide new insight for anticancer therapeutics. This review assesses the recent findings regarding ROS-mediated signaling in cancers, emphasizes DUB regulation by oxidation, highlights the relevant recent findings, and proposes directions of future research based on the ROS-induced modifications of DUB activity.

1. Introduction

Organisms are adapted to the atmospheric environment containing approximately 80% nitrogen and 20% oxygen and have evolved to maintain a balance between oxidants and antioxidants [1]. Free radicals are chemical species that possess one or more unpaired electrons in their outer shell [2–5]. There are two major species of free radicals: reactive oxygen species (ROS) derived from oxygen and reactive nitrogen species (RNS) derived from nitrogen and oxygen [1]. Oncogenic transformation is commonly associated with a shift in redox balance to a higher oxidized state in many cancer types, including breast, liver, bladder, colon, and ovarian cancers [6–8]. The combination of environmental and internal factors has an additive effect on cellular ROS levels in oncogenic transformed cells. Higher levels of ROS disrupt the redox balance and homeostasis, resulting in severe damage to various cellular components such as DNA, lipids, and proteins, which have implications in many diseases including cancer [9,10].

Post translational modifications (PTMs) act as a molecular switch to activate or deactivate the molecular function of their target proteins. For instance, during cell signaling events, the reversible addition or deletion of phosphate groups modulates the activity of kinases [11], and ubiquitination marks cyclins for destruction at defined time points during the cell cycle [12,13]. There are several categories of PTMs, including phosphorylation, acetylation, and methylation, which have been implicated in many cellular processes, including the regulation of enzyme activity, protein stabilization, protein localization, and protein degradation [14,15]. The most widely studied PTM is the regulation of protein dynamics by the conjugation or removal of ubiquitin (Ub) from target proteins with the help of enzymes central to ubiquitination and deubiquitination processes [16–21].

The ubiquitin-proteasome system (UPS) regulates protein turnover of their substrates implicated in different cellular processes including the cell cycle, DNA repair, and cell apoptosis [22,23]. Importantly, the enzymes responsible for ROS production are also known to undergo 26S

Abbreviations: AP1, Activator protein 1; Chk2, Checkpoint kinase 2; DDR, DNA damage response; DUBs, Deubiquitinating enzymes; GLUT:, Glucose transporters; NOXs, NADPH oxidases; ROS, Reactive oxygen species; PHLPP1, PH Domain and Leucine Rich Repeat Protein Phosphatase 1; PPP1CA, Protein Phosphatase 1 Catalytic Subunit Alpha; TNFα, Tumor necrosis factor α; TGFβ1, Transforming growth factor β1; USP, Ubiquitin specific protease; UCHL1, Ubiquitin C-terminal hydrolase 1; UAF1, USP1-associated factor 1.

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proteasomal degradation [24–26]. However, the regulation of deubiquitinating enzymes (DUBs) that reverse the process of protein ubiquitination of ROS-generating enzymes is an equally important process that has not been given much attention. In this review, we mainly discuss the ROS-mediated regulatory functions of DUBs and their role in cancer progression.

2. ROS generation

Intracellular ROS generation is induced by various endogenous and exogenous agonists. Signaling-associated ROS is generated mainly inside the mitochondria or by growth factor signaling through the activation of NADPH oxidase enzyme (NOX). Mitochondria are a major site of ROS generation inside mammalian cells [27–29]. The mitochondrial electron transport chain (ETC) produces superoxide as the proximal ROS, which exists in the anionic form and is highly membrane impermeable [30]. The superoxide is dismutated into H_2O_2 either in the mitochondrial matrix (by MnSOD) or in the cytosol (by Cu/ZnSOD) [31,32]. The ETC encompasses five multi-subunit protein complexes (complexes I-IV and F_1–F_0 ATP synthase) as well as the mobile electron transporters ubiquinone and cytochrome *c* [33–35]. The sequential transfer of electrons is designed to prevent electron escape, but any delay at one location generates traffic and causes electron leakage inside cells [36]. These electrons leaking from the ETC react with oxygen and generate ROS inside cells, affecting various signaling pathways involved in the cell cycle and proliferation.

Under stress conditions, there are several oncogenes such as MYC, RAS, PI3K-AKT-mTOR and BCR/ABL, that are involved in modulating ROS-producing capacity of the ETC by increasing electron flow either by fueling the TCA cycle with carbon sources or by destabilizing electron flow through the ETC. These oncogene-mediated mechanisms reset ROS levels to a higher homoeostatic set point, sustaining the cancer cell phenotype [37–39]. For instance, MYC induces mitochondrial transcription factor A (TFAM) resulting in increased mitochondrial biomass and oxygen consumption indicating enhanced ETC activity [40]. RAS decrease complex I activity in digitonin-permeabilized fibroblasts by destabilizing the ETC, resulting in inefficient electron flow and ROS production [41]. Likewise, BCR/ABL impairs electron flow between ETC complexes I and II and complexes II and III resulting in increased ROS production [42].

The NOX and dual oxidase (DUOXs) family of enzymes is another important endogenous source of ROS in a variety of tissues [43–45]. NOX genes confer antagonistic pleiotropy and generate ROS as part of normal physiological functions, including signal transduction and biochemical reactions [46]. The NOX/DUOX-mediated generation of ROS involves activation of genes and transmembrane proteins that transfer electrons from NADPH to molecular oxygen, generating superoxide as the center for ROS production. NOX-derived ROS have a predisposition for causing molecular damage and are associated with chronic diseases such as hypertension, Alzheimer's disease, atherosclerosis, diabetic nephropathy, and cancer [46–48]. There is another major site of ROS generation inside cells via peroxisomes, where molecular oxygen is reduced to H_2O_2 and ultimately to H_2O through ROS-metabolizing enzymes such as xanthine oxidase [49]. Endogenous and exogenous components such as prostaglandins, fatty acids, and drugs also produce free radicals, especially $HO^{\bullet}$, inside cells [50].

3. The dual nature of ROS in cancers

Cancer cells exhibit higher ROS levels compared to their normal counterparts, producing elevated levels of antioxidant proteins to detoxify ROS and maintain redox homeostasis. Depending upon the cellular levels and duration of exposure, ROS have been shown to affect DNA, proteins, and lipids and activate oncogenic signaling cascades leading to genomic instability. Hydroxyl ions generated via the Fenton reaction result in DNA lesions such as oxidized DNA bases and single- or double-strand breaks [51–53]. ROS target lipids by reacting with polyunsaturated fatty acids to initiate lipid peroxidation [54,55]. The oxidation of lipids generates several genotoxic compounds, such as 4-hydroxy-2-alkenals, malondialdehyde, and 2-alkenals, which induce the formation of DNA adducts and cause DNA damage [56,57]. Moreover, ROS-induced lipid peroxidation might serve as a clinical marker in cancer progression. Higher lipid peroxidation and detection of thiobarbituric acid-reactive substances in the serum of colorectal carcinoma patients indicate increased peroxidation in tumor [58].

ROS influence the tumor microenvironment by regulating several cellular events in cancer, such as angiogenesis, metastasis, and maintenance of tumor stemness [10,59–62]. ROS regulate angiogenesis in tumors by the upregulation of vascular endothelial growth factor (VEGF) receptors or various angiogenic signaling cascades, such as PI3K/AKT and MAPK pathways [62–64]. In highly metastatic tumors, accumulated levels of ROS promote cancer invasion and metastasis [65]. ROS also regulate epithelial to mesenchymal transition (EMT) responsible for tumor metastasis. The NOX-dependent NF-κB signaling pathway enhances TGF-β1 and MMP expression to promote migration and invasion of MCG-10A and MDAMB-231C cells [66]. Treating colon carcinoma cells with ROS increases the production of MMP1/2/7/9 to enhance metastasis [67]. Oxidative stress can lead to chronic inflammation and cancer progression via activation of transcription factors, such as HIF-1α, β-catenin/Wnt and NF-κB [68–70]. ROS-mediated activation of NF-κB induces chemotherapeutic resistance against a variety of drugs, such as doxorubicin, cisplatin, and tamoxifen, through upregulation of B-cell lymphoma-extra-large (Bcl-xL), B-cell lymphoma 2 (Bcl-2), Akt, and X-linked inhibitor of apoptosis (XIAP) [71–73].

Paradoxically, ROS can also induce cancer cell death in biological systems, which can be exploited in cancer therapeutics [74–76]. Increased levels of intracellular ROS induce cancer cell senescence and apoptosis through a family of aspartate-directed and Cys-dependent proteases known as caspases [77–79]. In many cell types, H_2O_2 mediates the activation of autophagy through a beclin-1-dependent manner but can also induce autophagy, independent of beclin-1 in glutathione-depleted RAW264.7 cells [80]. In transformed U87 and HeLa cells, but not in non-transformed normal mouse astrocytes, H_2O_2 induces autophagy-mediated cell death [81]. Overall, enhanced ROS signaling has been implicated in cancer progression as well as cancer cell death.

3.1. ROS-mediated signaling pathways in cancer

An upsurge in ROS-sensitive signaling pathways is observed in different cancer types, leading to tumor growth and malignant progression. Such ROS-mediated oncogenic progression results either by the activation of several oncogenic pathways or through oncogenic mutations [82–85]. Here, we have briefly discussed the relevant signaling pathways mediated by ROS in cancer.

3.1.1. Nuclear Factor Kappa-B pathway

Nuclear Factor Kappa-B (NF-κB) is a redox-regulated sensor for oxidative stress that undergoes activation under low doses of H_2O_2 [86]. NF-κB is essential to cancer cell survival, proliferation, and cell cycle regulation along with the development of drug resistance [87]. Cytokine-based NF-κB stimulation activates the IκB kinase complex (IKKs) that phosphorylates NF-κB inhibitor (IκB), resulting in its ubiquitination and subsequent proteolysis. The IKK-mediated degradation of IκB releases bound NF-κB, which translocate to the nucleus and induces the expression of anti-apoptotic and anti-inflammatory genes [88,89]. The IKK-based NF-κB-inducing signaling process is activated by increased cellular oxidative stress [90,91]. Treating MCF-7 cells with TNF-α, IL-1β, or sodium arsenite generates free radicals that activate NF-κB and enhance cellular proliferation [92]. Knockdown of ROS scavenging enzyme, SOD increases the cellular levels of ROS and NF-κB activity in oral carcinoma cells [93]. RAC1-mediated ROS production

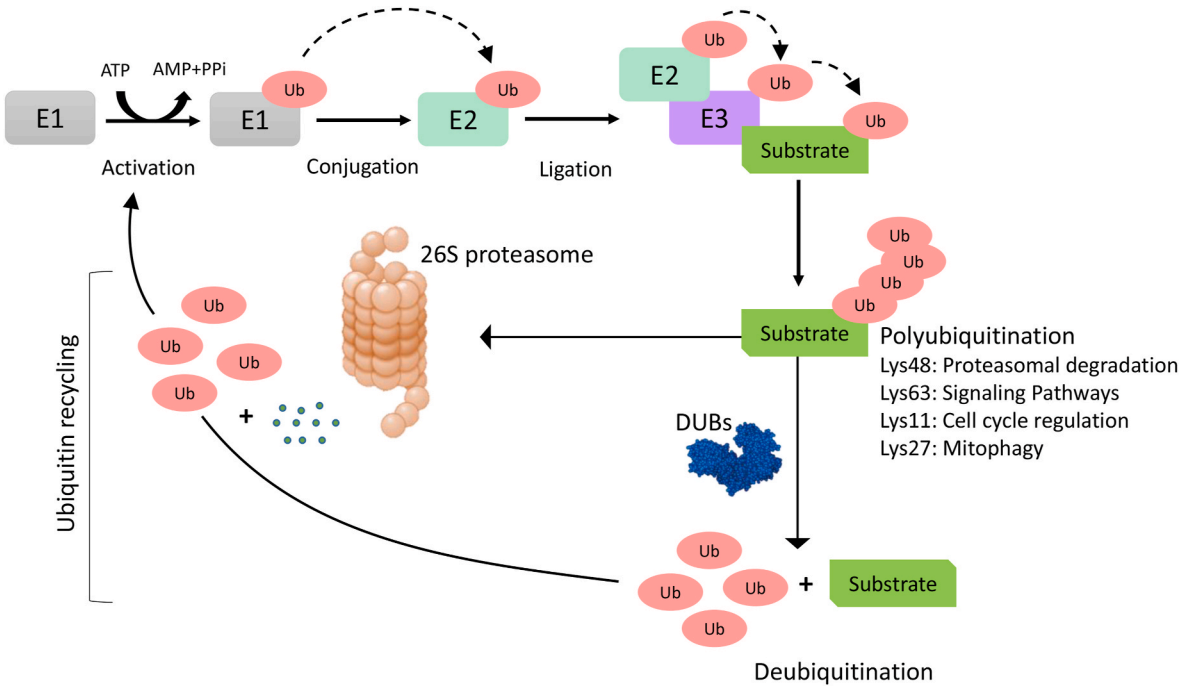

Fig. 1. The ubiquitin-proteasome system. Ubiquitin is attached to the E1 ubiquitin-activating enzyme in an ATP-dependent reaction, followed by its transfer to E2 ubiquitin-conjugating enzyme. Finally, in conjunction with E3 ubiquitin ligase, polyubiquitin chains are transferred to protein substrates, which are targeted for degradation by 26S proteasome. DUBs reverse the ubiquitination process, determining the fate of substrates, and ubiquitin molecules are recycled.

and NF-κB activation were found to facilitate WNT-driven intestinal stem cell proliferation and colorectal cancer initiation [94].

3.1.2. *Phosphoinositide-3-kinase/AKT signaling*

The phosphoinositide-3-kinase (PI3K)/AKT pathway regulates many critical cellular functions, including cell cycle progression, protein synthesis, autophagy, angiogenesis, and drug resistance [95–97]. The binding of ligands, such as VEGF, epidermal growth factor (EGF), and IL-6, to receptor tyrosine kinase activates class I PI3K. The activated PI3K produces phosphatidylinositol 3,4,5 triphosphate (PIP_3) from phosphatidylinositol 4,5 bisphosphate (PIP_2), which is reversed by tumor suppressor phosphatase and tensin homolog (PTEN) through the phosphorylation circuit [98,99]. Deregulation of PI3K/AKT signaling through ROS has been reported in various cancers [100–102]. ROS directly or indirectly activate PI3Ks either by amplifying various downstream signaling cascades or inhibiting the activity of PTEN. ROS promote the phosphorylation and proteolytic degradation of PTEN in breast cancer, glioblastomas, melanoma, and endometrial cancer [103–106]. H_2O_2 generated by EGF in human ovarian cancer activates AKT and its substrate p70S6K1 that regulates protein synthesis [107]. In breast cancer cells, PI3K/AKT signaling is upregulated by ROS generation through estrogen metabolism [108].

3.1.3. *Mitogen-activated protein kinase/ERK pathway*

The mitogen-activated protein kinase (MAPKs) play an important role in the transduction of signals required for cell survival [109]. Dysregulation of this crucial pathway has been linked to the pathogenesis of several cancer types. ROS act as a physiological modulator and activate MAP kinases extracellular signal-regulated kinase (ERK) 1/2 and p38 through various mechanisms, such as activation of Ras and p90RSK kinase [110–112]. Estrogen metabolism in breast carcinoma produces H_2O_2, which activates ERK1/2 and increases tumor growth [113]. Additionally, ROS initiate the oncogenic switch via activation of HRAS, NRAS, and KRAS [114,115]. In an animal model for Kras-driven pancreatic cancer, inhibiting cellular ROS levels using N-Acetyl-L-cysteine (NAC) and MitoQ reduced the progression of pre-cancerous lesions [115].

3.1.4. *Signal transducer and activator of transcription pathway*

The signal transducer and activator of transcription (STAT) pathway is associated with tumor formation and cell proliferation. STAT3 is activated in a number of malignancies and is the most extensively studied member of the STAT family in oncogenic signaling pathways. Unlike transient activation of STAT3 signaling in normal cells, many cancer types exhibit constitutively active STAT3 [116,117]. Several oncogenic pathways lead to STAT3, and many oncogenic and resistant tumors rely on ROS-mediated STAT signaling as an alternative mechanism for survival. Therefore, STAT3 serves as a therapeutic cancer target, and inhibiting STAT3 has the potential to block its upstream pathways and direct an apoptotic cancer cell fate [118–120]. In breast cancer cells, STAT3 inhibition using niclosamide inhibits BCL2 expression and sensitizes cancer cells. Radiotherapy treatment was shown to reduce ROS levels and increase phosphorylation of STAT3 in triple-negative breast cancer [121]. In acute myeloid leukemia, increased H_2O_2 level has been linked with FLT3/ITD expression in a NOX-dependent manner, leading to activation of STAT5 signaling. An FLT3 inhibitor (PKC412) and NOX inhibitors (DPI, VAS2870) are shown to regulate ROS levels in AML cells expressing FLT3/ITD [122]. Also, STAT5 expression and BCR/ABL mutation are associated with the progression of chronic myeloid leukemia (CML), where elevated STAT5 expression increases ROS production and BCR/ABL mutation in CML cells [123].

4. Ubiquitination and deubiquitination

The process of ubiquitination is an important PTM that involves the reversible covalent conjugation of ubiquitin moieties to substrate proteins to signal protein degradation, regulating their function. Ubiquitination is carried out by three enzymatic components that act in a sequential manner to attach mono-Ub or chains of Ub onto substrate proteins: (E1) Ub-activating enzyme, (E2) Ub-conjugating enzyme, and (E3) Ub-protein ligase. Lysine-48 (K48) along with K11- and K29-linked

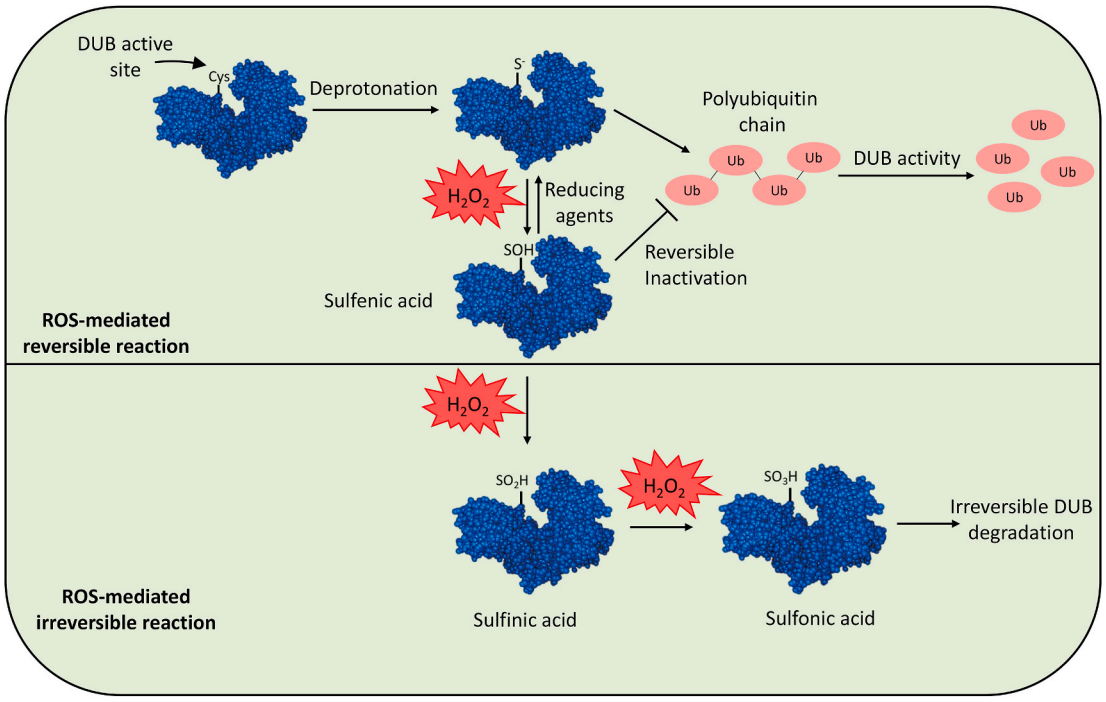

Fig. 2. Redox regulation on DUB catalytic activity. Many DUB enzymes contain a cysteine amino acid residue in their active site. Deprotonation of the cysteine amino acid forms a nucleophile (S^-), which activates the enzyme to deubiquitinate substrates. Nucleophilic cysteine residues are vulnerable to oxidation by reactive oxygen species such as H_2O_2 to sulfenic acid, which reversibly inhibits the DUB activity. Further ROS-mediated oxidation events lead to irreversible inhibition, by the formation of sulfinic and sulfonic acid intermediates that irreversibly inactivate DUB enzymes.

polyubiquitin chains mark proteins for degradation by the proteasome, while K63-linked poly-ubiquitination and multiple mono-ubiquitin conjugations are involved in lysosomal pathways. The ubiquitination marked at K27 is required for DNA damage response and mitochondrial clearance by mitophagy [124–127] (Fig. 1). In addition to labeling misfolded and damaged proteins for proteasomal degradation and determining the subcellular localization of proteins, ubiquitination regulates a wide array of cellular processes, such as transcription, translation, endocytosis, and receptor activity. Variations in the ubiquitin machinery or protein substrates that render proteins more susceptible to degradation are responsible for many disorders, including several types of cancer [128,129].

Deubiquitination is a process that counteracts ubiquitination by detaching Ub moieties or Ub-like conjugates from target proteins by DUBs, thereby emerging as a key regulator of ubiquitin-mediated signaling pathways by maintaining a balance of ubiquitin dynamics [130]. The human genome encodes more than 100 DUBs that have been categorized into seven families: Ubiquitin C-terminal hydrolases (UCHs), ubiquitin-specific proteases (USPs), ovarian tumor proteases (OTUs), Jab1/MPN domain-associated metalloisopeptidases (JAMM), Josephin or Machado-Joseph disease domain proteases (MJDs), motif interacting with Ub-containing novel DUB family (MINDY), and Zn-finger and UFSP domain proteins (ZUFSPs) [130–133]. Deubiquitination is a highly coordinated process that has implications in various cellular functions, such as cell-cycle regulation, DNA repair [22], proteasome- and lysosome-dependent protein degradation [134], kinase activation [135,136], microbial pathogenesis [137,138], and gene expression. Owing to the role of DUBs as key regulators of many ubiquitin-mediated processes, their localization, abundance, and catalytic activity are strongly controlled by a variety of mechanisms.

The regulated control of DUBs ensures appropriate responses and avoids inadvertent cleavage of non-substrate proteins in cells [130]. Dysregulation of such a process results in many physiological abnormalities, such as cancer, inflammatory diseases, and neurodegeneration [139–142]. Due to the involvement of DUBs in several physiological processes, it is important to unravel the different layers of DUB regulation in cellular functions. Modulation of DUB activity has been accomplished recently, and there are studies showing that the activity of these proteases is modified post-translationally by ubiquitination, phosphorylation, and SUMOylation [130,143–145]. In addition, the activity of DUBs also depends on the presence of scaffold proteins or substrates that impart conformational change towards catalytic competency [146,147]. Similar to other proteases like protein tyrosine phosphatases (PTPs), the activity of DUBs inside cells has been carefully monitored to avoid spurious cleavage of proteins; however, the development of reactive molecules to modify DUB function and related pathways is a new area that needs extensive research.

5. ROS-mediated regulation of DUB catalytic activity

The catalytic activity of many enzymes is carried out by a Cys residue present at the enzyme's active site. The regulation of enzyme activity by reversible oxidation of active site Cys residues is an intense area of research. The thiol group in Cys presumably is deprotonated first [148] and can adopt different oxidation states. This directs catalytic Cys to be a good target for oxidative control. Most DUBs along with E1 and E2 enzymes and some E3 ligases have catalytic Cys in their active site and tend to undergo ROS-mediated regulation.

Oxidation of proteins is considered a signature of permanent damage and is related to aging, cancer, and other chronic conditions. Cellular machinery and degradation pathways operate in unison to remove such damaged proteins from the cellular system. However, under conditions of stress, few Cys amino acid residues undergo reversible oxidation to modify protein activity in a manner analogous to protein regulation by phosphorylation [149]. Strikingly, it was found that Cys enzymes can be rapidly targeted by oxidative stress. Mechanistic and structural analysis revealed that ROS target catalytic Cys with low pKa values that are present more frequently in the active sites of enzymes [150,151]. The presence of catalytic diads or triads in Cys-dependent DUBs renders them more susceptible to oxidation. In the active site, histidine (His)

residues lower the pKa of nucleophilic Cys residues and activate them to disrupt the isopeptide linkage of a ubiquitinated substrate. Aspartic acid (Asp) or Asparagine (Asn) present in the triad align and polarize the His residue. Cys oxidation by H_2O_2 results in the formation of sulfenic (-SOH) acid, with one oxygen molecule in the reversible oxidized state of Cys. A combination of mass spectrometry, mutational analysis, and structural studies showed that reversible inhibition of DUB activity is due to sulfenic acid Cys intermediates at the enzymes' active site [152]. Further oxidation of sulfenylated Cys leads to the irreversible formation of sulfinic (-SO_2H) or sulfonic (-SO_3H) acids with two or three oxygen molecules, respectively [153]. For this modification to function as a reversible switch, further oxidation to sulfinic and sulfonic acid (-SO_2H and –SO_3H) must be avoided (Fig. 2). There are mechanisms that prevent over-oxidation of prone Cys residues to irreversible oxidation states. Formation of a disulfide bridge between two nearby Cys residues [154] or the formation of a cyclic sulfenamide as a result of a covalent bond formed between Cys and the main chain nitrogen of a neighboring residue [155,156] are two strategies by which this can be achieved.

Recent studies have portrayed oxidative and redox modification of DUBs as new aspects of further biological study. The majority of DUBs are Cys proteases and have a reactive Cys residue that is susceptible to reversible oxidation by ROS. Oxidation by ROS has been shown to inhibit sub-family members of DUBs, including USP, OTU, and UCH, both *in vitro* and *in vivo* [150]. In line, a reduction in overall DUB activity has been observed upon treatment of macrophages with exogenous and endogenous H_2O_2 [150]. Redox-driven DUB regulation is reversible, and even prolonged H_2O_2 exposure is unable to cause permanent DUB inhibition. Moreover, partial recovery of cellular DUB activity occurs in a time-dependent manner, even during H_2O_2 exposure, due to the upregulated activity of anti-oxidative genes in the cells [150].

6. DUBs and ROS regulation

The degree of DUB inhibition by ROS is specific for individual DUBs due to their differences in geometry and basal reactivity of their active sites. For example, partially active or inactive DUBs are less susceptible to Cys oxidation by ROS compared to fully active DUBs [143]. ROS-mediated regulation of several DUBs is discussed below.

6.1. USP1

USP1 is implicated in the DNA damage response and is critical for the maintenance of genomic stability [157,158]. It has been shown to deubiquitinate proliferating cell nuclear antigen (PCNA) and Fanconi anemia group D2 protein (FANCD2) [159,160]. PCNA has a strong role in regulating the response to DNA damage, and mono-ubiquitination of PCNA is essential for translesion DNA synthesis (TLS) across damaged bases [161]. Upon exposure to DNA-damaging agents, such as ultra-violet (UV) irradiation and associated USP1 degradation, higher PCNA mono-ubiquitination has been observed [162,163]. Additionally, H_2O_2-treated cells also show high intracellular levels of mono-ubiquitinated PCNA, indicating H_2O_2-mediated inhibition of USP1 [164]. H_2O_2 does not affect the interaction of USP1 with its co-activator USP1-associated factor 1 (UAF1), suggesting that the inhibition is likely caused by oxidation of the USP1 active site [150,165]. Unlike UV irradiation and other DNA-damaging agents, this redox-dependent inhibition of USP1 is rapid and reversible [164] and can be rescued by certain reducing agents, such as dithiothreitol (DTT). Additionally, enhanced PCNA mono-ubiquitination by oxidative stress is most active during S-phase and nearly non-existent in G0-or G1-phase of the cell cycle. USP1 is responsible for fine-tuning the PCNA mono-ubiquitination-dependent DNA damage tolerance in response to oxidative DNA damage during S-phase [143].

6.2. USP7

USP7 is a deubiquitinating enzyme that regulates many substrates involved in diverse cellular processes, such as DNA replication, tumor suppression, epigenetics, and the immune response [166–168]. Despite the importance of this enzyme, regulation of USP7 activity is still not well understood. A study on the effect of ROS on USP7 showed that H_2O_2 reversibly oxidizes the catalytic Cys present in the active site of USP7. Temporal studies in U2OS cells showed fully recovered USP7 activity in 2 h after oxidative stress. The inhibition of reversible USP7 oxidation with DTT is suggestive of the occurrence of some but not all active site Cys residues in a reversibly oxidized state, *i.e.* sulfenic acid form, Cys-SOH [143]. ROS-mediated inhibition of USP7 is higher at basic conditions (pH 8.2 or 8.8) than at pH 7.4 [150]. USP7 is known to have a disheveled active site in the absence of substrate or co-factors [169]. Sensitivity to DUB oxidation by ROS requires the catalytic Cys residue to have low pKa. Altering the environment by increasing pH augments DUB sensitivity towards ROS by facilitating Cys deprotonation [170,171]. Additionally, USP7 treatment with H_2O_2 in the presence of free ubiquitin having an unmodified carboxy-terminus led to increased sensitivity to ROS (~5 fold) similar to that caused by high pH condition [150].

6.3. USP19

USP19 is a member of the USP subfamily of DUBs and contains a C-terminal transmembrane domain. It is the first DUB reported to be regulated by heat shock protein, Hsp90, which binds with the catalytic domain of USP19 and promotes its substrate association. USP19 is involved in the endoplasmic reticulum-associated protein degradation (ERAD) pathway [172] that eliminates misfolded proteins from the endoplasmic reticulum of eukaryotic cells [173]. Additionally, hypoxia-inducible factor 1α (HIF-1α), a key player in the response to hypoxia, interacts with USP19 to prevent the degradation of HIF-1α in a non-catalytic manner [174]. USP19 contains several regulatory domains in addition to its conserved USP domain that harbors the catalytic triad residues Cys 506, His1165, and Asp1189. ROS inhibits USP19 by acting on the catalytic domain of USP19 (USP19CD) upon treatment with H_2O_2, while recovered by DTT treatment. Similar results were observed regarding the catalytic domain of deubiquitinase USP8 [150], suggesting that oxidation of Cys residues in the catalytic domain of DUBs can lead to their reversible inactivation.

6.4. USP28 and CYLD

USP28 has a dual role in carcinogenesis and functions both as a tumor suppressor as well as a tumor-promoting factor [175]. The oncogenic potential of USP28 has been associated with the stability of important oncogenes, such as LSD1, MYC, and c-Jun [142,176–179]. Moreover, USP28 is a positive regulator of HIF-1α protein stability, which also implies its pro-carcinogenic role. On the contrary, USP28 has been associated with p53 stabilization and tumor suppressor Chk2 stability [180,181]. Similarly, another DUB, cylindromatosis (CYLD), functions as a tumor suppressor and eliminates K63-linked Ub molecules from TNFR-associated factor 2 (TRAF2) [182]. CYLD also hampers the progression of cancer by inhibiting the activation of p65/p50 NF-κB [183] as well as c-Jun N-terminal kinase/Activator protein 1 (JNK/AP1) signaling [184].

USP28 and CYLD are both regulated by ROS-mediated oxidative stress. The steady-state mRNA levels of USP28 and CYLD are regulated negatively through superoxide radical- and H_2O_2-mediated ROS generation and enhanced by antioxidants such as NAC and glutathione [185]. Moreover, increased steady-state mRNA levels of USP28 and CYLD were observed in the mitochondrial glutaredoxin (Grx2a)-overexpressing cell line [185]. These studies provide a crucial association between oxidative stress and tumorigenesis through transcriptional downregulation of

tumor-regulating DUBs.

6.5. OTU sub-family DUBs

OTU DUBs are Cys proteases that cleave substrate polyubiquitin chains and can identify the associated linkage type [186,187]. The presence of Cys catalytic residues in the active site of OTU subfamily proteases makes them susceptible to reversible oxidation. Incubating purified OTUB1, OTUD1, OTUD2, OTUD3, OTUD5, and OTUD6A with H_2O_2 promoted –SOH modifications of these DUBs. Sulfenylation of OTU subfamily DUBs in response to varying concentrations of ROS indicated the ROS-mediated regulation of DUB activity [188].

Cezanne/OTUD7B has emerged as a negative regulator of NF-κB signaling through its role in the negative feedback loop in response to pro-inflammatory signaling. The role of ROS in NF-κB signaling is well understood, but their effects on the negative regulators of NF-κB have not received much attention [189–192]. In epithelial or endothelial cells, cezanne is induced in response to TNFα, which negatively regulates NF-κB translocation apart from its transcriptional activation. Cezanne functions at the level of the IκB kinase complex or upstream of TNF receptor (TNFR) signaling and prevents the degradation of RIP1 signal adapter protein [189]. However, the negative regulatory functions of Cezanne on NF-κB can be suppressed by H_2O_2, which promotes the oxidation of Cys residues of cezanne and prolongs NF-κB pathway activation in hepatocellular carcinoma cells. This ROS-mediated inactivation of cezanne was reversed by DTT treatment [193], suggesting the importance of oxidation-mediated regulation of cezzane activity in cancer.

A20 is also a well-characterized member of OTU Cys-proteases [186]. Several reports suggested that A20 has a dual behavior as both a pro-tumorigenic and an anti-tumorigenic enzyme in cancer progression [194]. The high-resolution crystal structure revealed a sulfenic acid intermediate in the catalytic site of A20 in four oxidation states, which are reversible and can establish a new mechanism to regulate DUB activity [188]. Otherwise, unstable hydroxylation intermediates (Cys sulfenic acid (-SOH)) are alleviated by interactions within the OTU domain, preventing permanent inhibition from irreversible oxidation to sulfinic ($-SO_2H$) or sulfonic ($-SO_3H$) acid [188].

6.6. UCHL1

Ubiquitin C-terminal hydrolase 1 (UCHL1) is predominantly expressed in many cancers and its high expression is linked with poor prognosis [195]. Upregulated expression of UCHL1 has been observed in different cancers, including lung cancer patients having a smoking history [196,197], colorectal cancer [198], and lymphoma [199], suggesting its role as an oncogene. Transgenic murine models with upregulated UCHL1 showed the development of tumors in many tissues [199]. Additionally, UCHL1 expression led to increased metastasis and tumor phenotype whereas its depletion showed anti-tumor effects in a lung cancer cell line [196].

Apart from its oncogenic functions, UCHL1 is also a neuron-specific DUB that constitutes around 1–5% of total brain protein. UCHL1 can both ligate and hydrolyze ubiquitin from proteins as a part of recycling into the ubiquitin pool required for the proteasomal pathway [200]. There are several neuronal functions of UCHL1 wherein it interacts with axonal, cytoskeletal, and synaptic proteins. In rodents, mutations in UCHL1 result in axonal and white matter abnormalities, suggesting the importance of UCHL1 in synaptic and axonal function. Aberrations in UCHL1 have been associated with a number of neurodegenerative diseases, such as familial Parkinson's disease and Alzheimer's disease [201,202]. Reactive lipid species, such as prostaglandins, are associated with the pathogenesis of stroke and many brain diseases. Reactive prostaglandin metabolites, such as 15dPGJ2, disrupt the UPS and lead to accumulation of ubiquitinated proteins [203,204]. 15dPGJ2 alters the structure and function of UCHL1 [205] through the interaction between the α, β-unsaturated carbonyl center of the cyclopentenone ring of 15dPGJ2 and the thiol group present in Cys 152 of UCHL1. Additionally, 15dPGJ2 can potentially inhibit UCH-L1, leading to hypoxic neuronal death, whereas overexpression of UCH-L1 protects neurons from hypoxia [206].

The Cys at the 152nd position of UCHL1 assumes a pivotal role in neuronal survival following hypoxic or ischemic injury. Knock-in mice with mutations at the 152nd position, Cys substituted by alanine (UCHL1-C152A), revealed fewer Ub-protein aggregates than mice with wild-type UCHL1 [207]. Also, the oxidation of parkinsonism-inducing dopamine derivative 3′,4′DHBnTIQ to its quinoid structure leads to its covalent conjugation to UCHL1 through Cys152 [202,207–209]. Thus, UCH-L1 modification by reactive lipid species highlights the potential significance of reversible oxidation in ischemic injury and neurodegenerative disease.

7. DUBs and cancer

The activity of DUBs is not limited to the removal of ubiquitin conjugates but encompasses multiple biological ramifications such as DNA repair, chromatin remodeling, cell-cycle control, and signaling pathways involved in cancer [7,17,130]. There are several lines of evidence that implicate the role of DUBs in tumor development at multiple levels that are briefly discussed below.

p53 is a tumor suppressor that is most frequently altered in several human cancers. p53 plays many pivotal roles including maintaining genome integrity, angiogenesis, autophagy, migration, aging, and apoptosis [210,211]. Many DUBs are directly or indirectly associated with p53 regulation. Ubiquitin-specific protease (USP) 7 and OTUB1 indirectly regulate p53 via suppression of Mdm2 and UbcH5s, respectively [166,212]. Compound 1, a selective inhibitor of USP7, elevates p53 levels and apoptosis in cancer cells and also exhibits tumor suppressive activity in xenograft multiple myeloma and B-cell leukemia models [213]. Many DUBs such as USP10, USP11, USP24, USP29, and USP42 directly contribute to p53 function by stabilizing p53 protein abundance [214–220]. On the contrary, USP2a negatively regulates p53 protein levels by promoting Mdm2-and MdmX-mediated p53 ubiquitination [221,222]. Several other DUBs such as USP5, USP15, and USP26 also negatively regulate p53 and its functions [223–225].

TGF-β is an oncogenic factor that plays a role in tissue homeostasis and cancer. The TGF-β signaling pathway is tightly regulated by both ubiquitination and deubiquitination [226,227]. E3 ligases such as SMAD7-SMAD specific E3 ubiquitin protein ligase 2 (SMURF2) interacts with the TGF-β receptor complex to facilitate TGF-β ubiquitination [227]. USP15 binds to the SMURF2 complex and prevents ubiquitination of the TGF-β receptor resulting in elevated TGF-β signaling. The expression profile of USP15 is amplified in breast cancer, ovarian cancer, and glioblastoma, which has been found to be correlated with high TGF-β signaling. Depleting USP15 showed reduced oncogenic capacity in patient-derived glioma-initiating cells, suggesting the therapeutic importance of USP15 [227]. UCH37 is another deubiquitinase that positively regulates type I TGF-β receptor and promotes TGF-β signaling in cancer [228]. USP2a, USP4, USP9X, and OTUB1 are additional deubiquitinases that are involved in the activation of TGF-β signaling and therefore TGF-β-mediated pathogenesis of different cancer types [229]. Thus, DUBs have been shown to regulate the activity of oncogenes and tumor suppressor proteins making DUBs a potential target of therapeutic interest.

7.1. DUBs and DNA repair

One hallmark of cancer is genomic instability, which is the predisposition to accumulate damaged DNA. Several exogenous and endogenous factors such as ROS, metabolic by-products, UV radiation, and other genotoxic chemicals generate different types of DNA defects [230]. DNA repair pathways and damage response mechanisms are

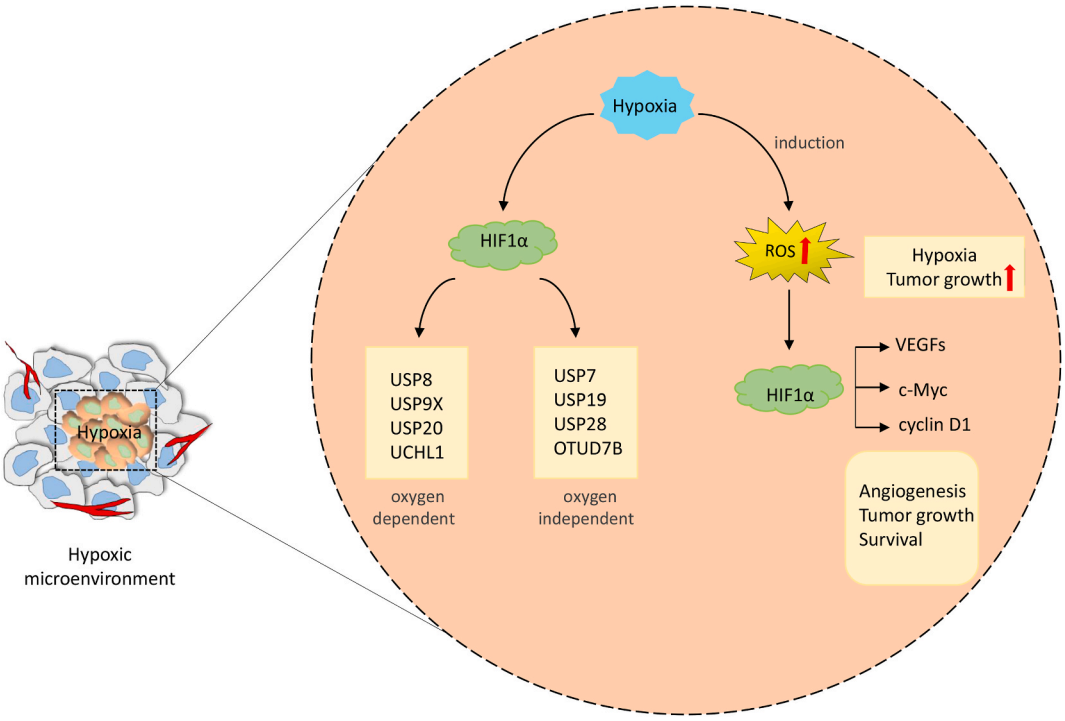

Fig. 3. Deubiquitinases regulate HIF1α stability in cancer. The hypoxic stress induces ROS production in the tumor microenvironment. Increased ROS leads to the activation of HIF1α and HIF1α-driven genes such as VEGF, c-Myc, and cyclin D1 contributing to tumor survival and proliferation. Several DUBs are responsible to regulate HIF1α stability in an oxygen-dependent and -independent manner.

broadly regulated by UPS and DUBs, which can be targeted for selective anticancer therapies [231,232]. USP1 selectively hydrolyses mono-ubiquitin adducts from FANCD2 and subsequently stabilizes Chk1 in the DNA damage response (DDR) [160,233]. The USP1/UAF1 complex also modulates PCNA monoubiquitination via UAF1 and ELG1 interaction [234]. Moreover, USP1 also regulates inhibitors of DNA (ID) binding protein stability that maintains the fate of stem cells [235,236]. The catalytic activity of USP1 also promotes *in vitro* transformation of osteosarcoma cells and *in vivo* tumor formation in murine models [235]. USP1 inhibitor screening showed ML323 as a potential USP1/UAF1 complex inhibitor that potentiates cisplatin cytotoxicity along with increased PCNA and FANCD2 monoubiquitination [237,238]. Another DUB, USP3, is a chromatin modifier that regulates ubiquitination of the H2A and H2B histones. RNAi-mediated ablation of USP3 leads to the accumulation of DNA breakage and thus replication stress by delaying progression of the S-phase during cell division [239]. USP9X is an interactor and stabilizer of CLASPIN protein that functions in checkpoint responses and replication fork stabilization [240]. It also prevents ubiquitin-mediated degradation of Mcl-1, resulting in enhanced radio resistance in glioblastoma cells [241]. Inhibition of USP9X increased cisplatin and doxorubicin sensitivity in estrogen receptor-negative breast cancer cells and hepatocellular carcinoma cells, respectively [215,242]. USP7 and USP11 are linked to oncogene-induced senescence wherein they modulate the ubiquitination status of Polycomb group (PcG) proteins that function in transcriptional regulation. Both USP7 and USP11 are recruited at chromatin sites and interact with PcG proteins to regulate the tumor suppressor gene locus p16 INK4A [243]. Additionally, USP11 regulates BRCA2 stability in the DSB repair pathway of homologous recombination, and USP11-depleted cells have been shown to be more sensitive to DNA damaging agents such as mitomycin [244,245]. USP47 has also been identified as a deubiquitinase critical for DNA repair and maintenance of genome integrity via DNA polymerase (Polβ) deubiquitination [246]. P22077-mediated inhibition of USP47 exerts cytotoxicity in leukemia cells both *in vitro* and *in vivo* [246].

7.2. DUBs and cell cycle regulation

The importance of DUBs in cell cycle progression is facilitated by the fact that DUBs are integral components of core cell cycle machinery and cell cycle checkpoints. DUBs control the activity of several E3 ligases in cell cycle progression. USP7 associates with the E3 ligase Mdm2 and its substrate p53, where depletion of USP7 triggers auto-ubiquitination and degradation of Mdm2. The premature degradation of Mdm2 impairs p53 ubiquitination leading to cell cycle arrest at either the G1 or G2 phases [247,248].

DUBs also regulate chromatin structure and transcription to exert cell cycle control. Under stress conditions, forkhead transcription factor (Foxo4) protein is ubiquitinated and translocated to the nucleus. The activated Foxo4 protein allows for transcription of the CDK-inhibitor p27 leading to cell cycle arrest. USP7 deubiquitinates Foxo4 protein under normal conditions, ensuring transient arrest of the cell cycle [249,250]. USP28 is a critical component of DNA damage checkpoints and also regulates the stability of c-Myc to maintain the proliferative functions of c-Myc protein in tumor cells [177,181]. Histone H2A deubiquitination by DUBs facilitate histone phosphorylation and chromosomal segregation. DUBs such as USP3, Usp16/Ubp-M, and Ubp8 deubiquitinate H2A and are required for mitotic progression [239,251–253]. USP13, USP39, and USP48 regulate Aurora B kinase levels and are therefore essential for spindle checkpoint integrity during mitosis [254–256].

8. Stress: DUBs activity and its association with cancer

Hypoxia is a common characteristic of cancer that results from increased oxygen consumption by proliferating cancer cells. Hypoxic tension in the tumor microenvironment initiates several signaling cascades, EMT and ROS production. A number of individual DUBs are independently regulated by hypoxia or ROS resulting in the progression of several disorders, particularly cancer.

8.1. Hypoxia: DUBs and cancer

Targeting hypoxia induced ROS in breast cancer cells using the antioxidant NAC reduced hypoxia-mediated cell adhesion and metastasis [257]. Treating cells with NAC also attenuated hypoxia-mediated EGFR activation, suggesting a potential role of redox signaling in hypoxic conditions [257]. Hypoxia-induced ROS also activates HIF1α via inactivation of the HIF1α inhibitor, Prolyl Hydroxylase Domain (PHD) protein [258]. ROS-activated HIF1α in sub-lethally damaged tumor cells contributes to their malignance and survival by promoting the expression of HIF1α-driven genes [259]. ROS activated HIF1α drives the expression of VEGF and allows tumor growth and angiogenesis [260]. Further, the oncogenic potential of HIF1α is attributed by the activation of proliferative genes such as c-Myc and cyclin D1 [261] (Fig. 3).

Several E3 ligases and DUBs regulate the cellular abundance of HIF1α protein in an oxygen-dependent and -independent manner [262]. The von Hippel-Lindau protein (VHL) E3 ligase mediates oxygen-dependent degradation of HIF proteins [263], while DUBs such as USP8, USP9X, USP20, and UCHL1 abrogate VHL-mediated protein degradation of HIF in an oxygen-dependent manner [264–266]. DUBs are involved in oxygen-independent HIF protein stability where hypoxia-induced K63-polyubiquitination of USP7 deubiquitinated HIF1α leading to metastasis and tumor progression [267]. Similarly, USP19 has been shown to regulate hypoxia pathways, including HIF1α, and regulate their abundance [174]. USP28 antagonizes Fbw7-mediated ubiquitination of HIF1α and influences HIF1α-dependent cellular events such as angiogenesis and cell migration [268]. Overall, the list of DUBs regulating HIF1α both in an oxygen-dependent and -independent manner is summarized in Fig. 3.

Conversely, hypoxia can also regulate DUBs by altering DUB mRNA levels. Several melanoma cell lines showed reduced USP13 mRNA and protein expression when exposed to 2% oxygen [269]. Cell-specific regulation of USP28 under hypoxic conditions has also been observed in A549 lung cancer cells [270]. Likewise, USP46 exhibited reduced mRNA expression under hypoxic conditions. USP46 reduction destabilizes the PHLPP phosphatase, which subsequently leads to hypoxia-induced chemoresistance in colon cancer [271]. Hypoxia-mediated induction of USP47 promotes EMT in colorectal cancer by transcriptional regulation of SNAIL expression [272]. Thus, the role of DUBs and hypoxia in cancer is also an important aspect in tumor biology and other hypoxia associated diseases. Further studies are necessary to forward the use of DUBs as a potential target for the development of DUB-based therapies.

8.2. ROS: DUBs and cancer

Oxidative stress and its influence on altering DUB activity have been associated with several diseases, especially neurological disorders such as Alzheimer's disease, Parkinson's disease, and epilepsy [273–276]. Reduced DUB activity is one of the main factors observed in neurodegenerative disorders that affect ubiquitin signal-mediated synaptic functions [276]. Another important factor is aging, where disorders become predominant due to the accumulation of ROS from damaged mitochondria and increased susceptibility of redox-sensitive DUBs towards oxidation [277]. However, the extent of oxidative stress that can alter DUB activity and its functions in disease progression are yet to be explored.

Apart from their role in neurological disorders, several redox-sensitive DUBs are also involved in cancer. For instance, redox-sensitive DUBs such as USP7 and A20 are associated with the progression of leukemia, liver, and metastatic cancers [278,279]. DUBs also regulate tumor progression by stabilizing potential cancer checkpoints and T-cell functions in cancer immunity. USP9X, CSN5, USP22, and OTUB1 have been found to regulate the crucial PD-1/PD-L1 immune checkpoint in cancer [280–283]. Many DUBs such as USP7, USP8, USP9X, USP11, USP15, CYLD, and A20 are involved in T-cell function and the immune response [284–287]. Moreover, studies understanding the impact of oxidative stress on PD-L1 have identified 15 drugs modulating ROS levels and PD-L1 in cancer cells [288]. The unified scenario integrating the regulation of DUBs by ROS in cancer immune checkpoints is still not understood. Additionally, DUBs such as CYLD, A20, OTUB1, USP7, and USP8, which are the main regulators of PD-1/PD-L1 cancer checkpoint and the immune response, are independently regulated by ROS suggesting a link between ROS regulation of DUBs and cancer checkpoints.

Table 1
Anticancer drugs targeting UPS and DUBs.

Drug	Mode of action	Cancer type	Reference
Bortezomib	Proteasome inhibitor, Increase ROS generation	Multiple myeloma, acute myeloid leukemia	[308, 309]
Curcumin	Increase ROS generation, Proteasome inhibitor, CSN5 mediated PD-L1 inhibition	Leukemia	[280, 310, 311]
Piperlongumine	Ubiquitin proteasome system inhibitor, Increase cellular ROS levels	Breast cancer	[312]
b-AP15	Proteasome inhibitor, inhibit USP14 and UCH37, Caspase activation, increase ROS generation	Prostate cancer, p53-deficient tumors	[298, 300, 313]
Pimozide	Increase ROS generation, ID1 degradation through USP1 inhibition	Prostate cancer, leukemia, lung cancer	[314-316]
beta-lapachone	Increase ROS generation, inhibit USP2	Prostate cancer, leukemia	[293, 295, 296]
Curcusone D	Ubiquitin proteasome system inhibitor, Increase ROS generation	Multiple myeloma	[292]
Spautin-1	Induce ROS-mediated DNA damage, target USP10 and USP13	Malignant melanoma	[317]
Pristimerin	ROS-dependent Ubiquitin-proteasomal degradation of BCL2	Prostate cancer	[318]

Therefore, DUBs are a promising target to design new anticancer therapies. Small molecule inhibitors (VLX1570) against DUBs such as USP14 and UCHL5 are under clinical trial for the treatment of multiple myeloma [289,290]. Malfunction of USP30 results in the accumulation of non-functional mitochondria in Parkinson's disease; however, the USP30 inhibitor was shown to be successful in the induction of mitophagy without side-effects [291]. Several drugs targeting the proteasome and DUBs in cancer therapy that are either under pre-clinical or clinical trials are summarized in Table 1. The proteasome inhibitor bortezomib has completed phase IV clinical trials in 18 Taiwanese participants with multiple myeloma (NCT02268890). Another study for bortezomib treatment in 50 participants with multiple myeloma has completed phase II clinical trials to evaluate the efficacy and safety of weekly administration of the drug (NCT01090921). Curcumin, which has been reported to dysregulate UPS has also been extensively studied under clinical settings for cancer (NCT03211104, NCT02944578, NCT03980509).

The natural compound 'Curcusone D' was found to have a synergistic effect with bortezomib and exhibits ROS-induced DUB inhibitory functions leading to the suppression of multiple myeloma cell growth [292]. Likewise, USP2 plays a key role in prostate and breast cancer cell survival [293,294]. Moreover, the small molecule inhibitor beta-lapachone is a potent drug that inhibits USP2 and is under clinical trial [295]. The beta-lapachone mechanism of action is based on selective and non-reversible oxidation of active site catalytic Cys moieties in DUBs [296]. Another DUB, USP14, is correlated with melanoma progression and low survival rate in metastatic melanoma patients [297]. Knockdown of USP14 rapidly accumulates poly-ubiquitinated proteins and chaperones, triggering mitochondrial dysfunction, ER stress, and ROS

Table 2
ROS-based anticancer drugs.

Drug	Mode of action	Target	Cancer type	Reference
Doxorubicin	Generates hydroxyl ion by inducing chelation of iron	Caspases, HIF1A, BCL2, PCNA, VEGFA, TP53, MAPK8/3/14, FAS, SOD1	Breast cancer, lung cancer, lymphoma, melanoma, colorectal cancer, hepatocellular carcinoma	[319, 320]
Cisplatin	Damages DNA and ETC	MAPK3/8/14, TP53, BCL2, SOD1, TNF, CASP3/8/9, IL6	Breast cancer, lung cancer, lymphoma, pancreatic cancer, colorectal cancer, hepatocellular carcinoma	[321, 322]
Motexafin gadolinium	Forms superoxide by accepting electrons	HMOX1, TXN	Glioblastoma, lung cancer, cerebral neoplasm	[323, 324]
2-Methoxyestradiol	Inhibits the Complex I of mETC	BAX, TP53, HIF1A, IL6, TNF, VEGFA, CASP9, BCL2, SOD2	Atherosclerosis, breast cancer, melanoma, hepatocellular carcinoma, pancreatic cancer	[325-327]
Buthionine sulfoximine	Binds to the enzyme related to GSH synthesis	BCL2, HMOX1, TNF, MAPK14, JUN, IL6	Lung cancer, Hepatocellular carcinoma	[328, 329]
Imexon	Binds to glutathione to induce oxidative stress	HIF1A, CASP3/9	Multiple myeloma, lymphoma, melanoma	[330, 331]
Alpha-lipoic acid (ALA)	Affects free radical scavenging in cells by increasing glutathione synthesis.	STAT3/MUC4	Gastric cancer	[299]
Peroxiredoxin 5 (PRDX5)	Regulate peroxide levels within cells	Bad, Bcl2, PARP	Gastric cancer, breast cancer, bladder cancer, prostate cancer, hepatocellular carcinoma	[332, 333]
PRDX1	Regulate peroxide levels within cells	MMP9, Bcl2, Bax, E-cadherin	Cervical cancer, breast cancer, hepatocellular carcinoma, ovarian cancer	[237, 334, 335]

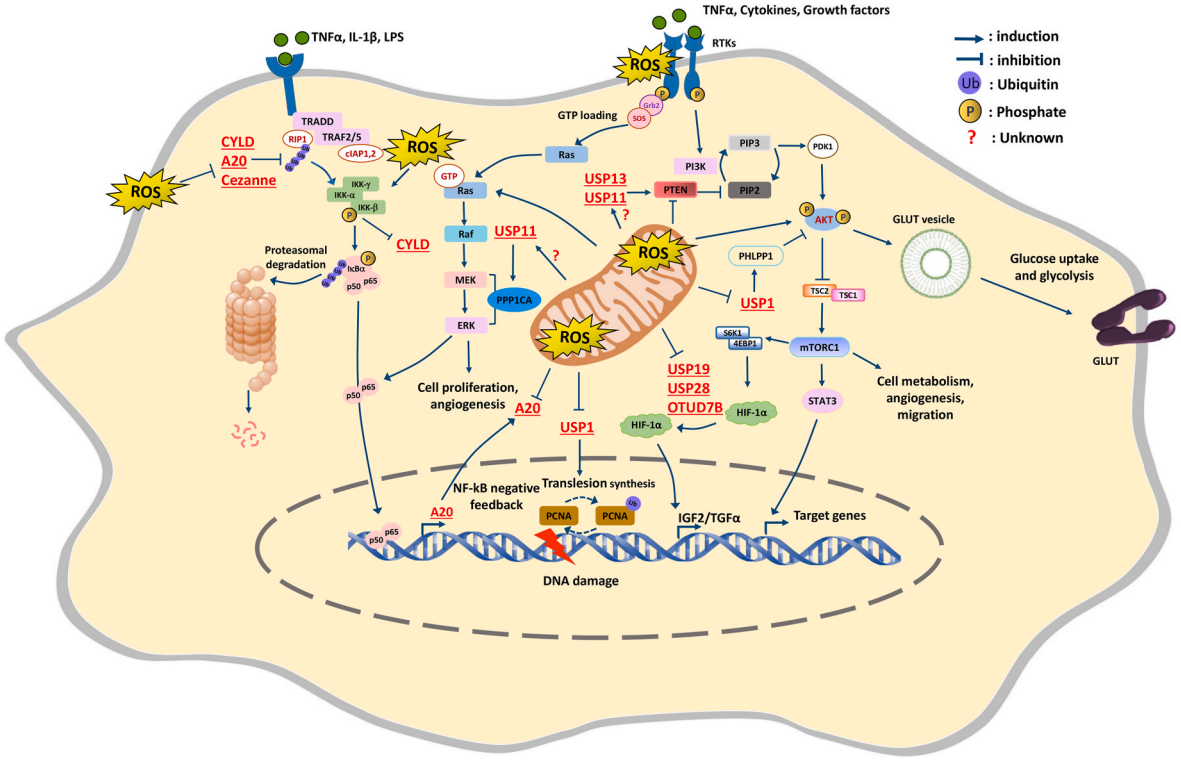

Fig. 4. ROS-regulated DUBs and its cellular signaling in cancer. Elevated ROS levels inside cells has been associated with pro-tumorigenic signaling and increased cell proliferation via many signaling cascades including NF-kB, MAPK/ERK and PI3K/AKT. Ubiquitination and deubiquitination events of downstream signaling molecules also regulate the fate of signaling cascades. ROS directly activates the IKK-based NF-κB-inducing signaling and also inactivate A20, Cezanne and CYLD which are negative regulators of NF-kB pathway. Binding of ligands to RTKs activate PI3K that produces PIP_3 from PIP_2, which is reversed by tumor suppressor PTEN through the phosphorylation circuit. PTEN is positively regulated by DUBs, USP11 and USP13. Direct ROS inhibition of PTEN or by ROS inactivation of USP11 and USP13 could be a possible DUB-mediated regulation of PI3K/AKT pathway in cancer. PHLPP1, a tumor suppressor inhibits AKT signaling and is positively regulated by USP1. ROS also regulate DUBs such as USP19, USP28 and OTUD7B that regulate HIF-1α. The MAPK/ERK pathway promote cell proliferation and cancer progression. The ROS-mediated control of the indicated DUBs such as USP11, USP13 and USP1 in several signaling cascades can also be a target of cancer therapeutics which need to be investigated.
All the DUBs are underlined and represented in red text.
PHLPP1, PH Domain and Leucine Rich Repeat Protein Phosphatase 1; PPP1CA, Protein Phosphatase 1 Catalytic Subunit Alpha; GLUT, Glucose transporters.

production that results in caspase-independent cell death [297]. Pharmacologic inhibition of USP14 using b-AP15 leads to apoptosis in several human cancer cell lines by decreasing cell viability and increasing ROS generation [298–300].

9. Future directions and conclusion

The altered cellular redox environment in cancer cells makes them more susceptible to redox manipulations and opens the door to the development of redox-based therapeutics to selectively target cancer

cells. Drug advances in anticancer therapies based on oxidative damage through the accumulation of ROS or defective antioxidant systems to alter redox homeostasis are summarized in Table 2. However, despite several pre-clinical and clinical trials of redox-mediated therapeutics, the significance of PTMs of redox-sensitive proteins and their therapeutic implications have not been well characterized. This review summarizes the pro-tumorigenic role of ROS in various cell signaling cascades and mainly emphasizes the ROS-mediated regulation of DUB activity in cancer progression (Fig. 4).

Advancements in 'omics' have identified many Cys-modified proteins, including kinases, SUMO, ubiquitin, and DUBs, regulated by oxidation [301,302]. Similar to that of PTPs, the transient and reversible oxidation of catalytic Cys residues in the active site of DUBs exhibits additional control over their activity. Oxidative regulation of DUB activity has several implications in microbial infection, developmental growth control, inflammation, neurodegenerative diseases, and cancer progression [140,273,303,304]. Several bodies of evidence suggest that oxidative stress-mediated DUB regulation can be exploited for therapeutic interventions of various disorders, including cancer. For instance, silencing of USP17, a critical regulator of the cell cycle [305], prevents the progression of lung, breast, and prostate cancer by inducing apoptosis [23,306]. Moreover, depletion of USP17 exerts anticancer effects by downregulation of NF-κB/p65 expression and tumor proliferation by enhancing ROS production, which were reversed using the ROS scavenger NAC [306]. Additionally, the monoubiquitination of PCNA recruits low-fidelity DNA polymerases and initiates DNA damage tolerance in response to oxidative stress in dividing cells [164,307]. The ROS-mediated reversible inactivation of USP1 deubiquitinating activity ensures the rapid accumulation of monoubiquitinated PCNA and subsequent DNA damage response during S-phase [143,150].

Altogether, DUBs belonging to the Cys protease family act as "ROS sensors" in human cells, wherein ROS-mediated DUB inactivation can serve as a critical mechanism for fine-tuning stress-activated signaling cascades. However, this area of research is in its infancy, and several criteria have to be considered in order to fully understand the implication of DUBs in redox-based therapeutics. Importantly, we need to understand how DUB activity is regulated by oxidative stress, particularly the structural information of DUBs revealing the extent of sensitivity towards oxidation or reduction. Secondly, specific information regarding DUBs localization and tissue expression could allow for the prediction of DUB sensitivity level towards stress. Lastly, development of allosteric drugs that modulate DUB function would increase the knowledge to protect any particular DUB from oxidative stress. Overall, the application of transcriptomic, protein structural analysis, and bioinformatics analysis could facilitate our understanding and reveal the mechanisms behind redox-based DUB regulation. Increasing progress in defining the regulation of Cys-based proteases and elucidating their role in human diseases would provide new insight into DUB-oriented therapeutics.

Authors' contributions

SR and AT conceived the idea. AT wrote the main manuscript along with the assistance of SR and SH. All authors read and approved the final draft of the manuscript.

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Declaration of competing interest

The authors declare that they have no competing interests.

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References

[1] Z.W. Ye, et al., Oxidative stress, redox regulation and diseases of cellular differentiation, Biochim. Biophys. Acta 1850 (8) (2015) 1607–1621.
[2] M. Valko, et al., Role of oxygen radicals in DNA damage and cancer incidence, Mol. Cell. Biochem. 266 (1–2) (2004) 37–56.
[3] M. Valko, et al., Free radicals and antioxidants in normal physiological functions and human disease, Int. J. Biochem. Cell Biol. 39 (1) (2007) 44–84.
[4] S.R. Maxwell, G.Y. Lip, Free radicals and antioxidants in cardiovascular disease, Br. J. Clin. Pharmacol. 44 (4) (1997) 307–317.
[5] W. Dröge, Free radicals in the physiological control of cell function, Physiol. Rev. 82 (1) (2002) 47–95.
[6] J. Kim, J. Kim, J.S. Bae, ROS homeostasis and metabolism: a critical liaison for cancer therapy, Exp. Mol. Med. 48 (11) (2016) e269.
[7] S.P. Hussain, L.J. Hofseth, C.C. Harris, Radical causes of cancer, Nat. Rev. Cancer 3 (4) (2003) 276–285.
[8] I. Afanas'ev, Signaling of reactive oxygen and nitrogen species in Diabetes mellitus, Oxid. Med. Cell. Longev. 3 (6) (2010) 361–373.
[9] B.N. Ames, M.K. Shigenaga, T.M. Hagen, Oxidants, antioxidants, and the degenerative diseases of aging, Proc. Natl. Acad. Sci. U. S. A. 90 (17) (1993) 7915–7922.
[10] T.P. Szatrowski, C.F. Nathan, Production of large amounts of hydrogen peroxide by human tumor cells, Cancer Res. 51 (3) (1991) 794–798.
[11] N.K. Tonks, Redox redux: revisiting PTPs and the control of cell signaling, Cell 121 (5) (2005) 667–670.
[12] F. Bassermann, R. Eichner, M. Pagano, The ubiquitin proteasome system - implications for cell cycle control and the targeted treatment of cancer, Biochim. Biophys. Acta 1843 (1) (2014) 150–162.
[13] R.W. King, M. Glotzer, M.W. Kirschner, Mutagenic analysis of the destruction signal of mitotic cyclins and structural characterization of ubiquitinated intermediates, Mol. Biol. Cell 7 (9) (1996) 1343–1357.
[14] Y.C. Wang, S.E. Peterson, J.F. Loring, Protein post-translational modifications and regulation of pluripotency in human stem cells, Cell Res. 24 (2) (2014) 143–160.
[15] A.M. Antao, et al., Advances in deubiquitinating enzyme inhibition and applications in cancer therapeutics, Cancers 12 (6) (2020).
[16] D. Nandi, et al., The ubiquitin-proteasome system, J. Biosci. 31 (1) (2006) 137–155.
[17] D. Komander, M. Rape, The ubiquitin code, Annu. Rev. Biochem. 81 (2012) 203–229.
[18] R. Yau, M. Rape, The increasing complexity of the ubiquitin code, Nat. Cell Biol. 18 (6) (2016) 579–586.
[19] K.N. Swatek, D. Komander, Ubiquitin modifications, Cell Res. 26 (4) (2016) 399–422.
[20] C.M. Pickart, Ubiquitin enters the new millennium, Mol. Cell. 8 (3) (2001) 499–504.
[21] C.M. Pickart, M.J. Eddins, Ubiquitin: structures, functions, mechanisms, Biochim. Biophys. Acta 1695 (1–3) (2004) 55–72.
[22] P. Schwertman, S. Bekker-Jensen, N. Mailand, Regulation of DNA double-strand break repair by ubiquitin and ubiquitin-like modifiers, Nat. Rev. Mol. Cell Biol. 17 (6) (2016) 379–394.
[23] C. McFarlane, et al., The deubiquitinating enzyme USP17 is associated with non-small cell lung cancer (NSCLC) recurrence and metastasis, Oncotarget 4 (10) (2013) 1836–1843.
[24] J.H. Joo, et al., NADPH oxidase 1 activity and ROS generation are regulated by grb2/cbl-mediated proteasomal degradation of NoxO1 in colon cancer cells, Cancer Res. 76 (4) (2016) 855–865.
[25] H. Qian, et al., Structure and function of HECT E3 ubiquitin ligases and their role in oxidative stress, J. Transl. Int. Med. 8 (2) (2020) 71–79.
[26] M. Daugaard, et al., Hace1 controls ROS generation of vertebrate Rac1-dependent NADPH oxidase complexes, Nat. Commun. 4 (2013) 2180.
[27] B. Chance, H. Sies, A. Boveris, Hydroperoxide metabolism in mammalian organs, Physiol. Rev. 59 (3) (1979) 527–605.
[28] P.K. Jensen, Antimycin-insensitive oxidation of succinate and reduced nicotinamide-adenine dinucleotide in electron-transport particles. I. pH dependency and hydrogen peroxide formation, Biochim. Biophys. Acta 122 (2) (1966) 157–166.
[29] R.S. Balaban, S. Nemoto, T. Finkel, Mitochondria, oxidants, and aging, Cell 120 (4) (2005) 483–495.
[30] R.A. Gus'kova, et al., Permeability of bilayer lipid membranes for superoxide (O2-.) radicals, Biochim. Biophys. Acta 778 (3) (1984) 579–585.
[31] M.P. Murphy, How mitochondria produce reactive oxygen species, Biochem. J. 417 (1) (2009) 1–13.
[32] M.D. Brand, The sites and topology of mitochondrial superoxide production, Exp. Gerontol. 45 (7–8) (2010) 466–472.
[33] R.Z. Zhao, et al., Mitochondrial electron transport chain, ROS generation and uncoupling (Review), Int. J. Mol. Med. 44 (1) (2019) 3–15.
[34] Y.S. Bae, et al., Regulation of reactive oxygen species generation in cell signaling, Mol. Cell. 32 (6) (2011) 491–509.

[35] R. Guo, et al., Architecture of human mitochondrial respiratory megacomplex I(2)III(2)IV(2), Cell 170 (6) (2017) 1247–1257, e12.
[36] M. Jastroch, et al., Mitochondrial proton and electron leaks, Essays Biochem. 47 (2010) 53–67.
[37] P.E. Porporato, et al., Mitochondrial metabolism and cancer, Cell Res. 28 (3) (2018) 265–280.
[38] J. Zhang, et al., ROS and ROS-Mediated Cellular Signaling, vol. 2016, Oxid Med Cell Longev, 2016, p. 4350965.
[39] V. Raimondi, F. Ciccarese, V. Ciminale, Oncogenic pathways and the electron transport chain: a dangeROS liaison, Br. J. Cancer 122 (2) (2020) 168–181.
[40] F. Li, et al., Myc stimulates nuclearly encoded mitochondrial genes and mitochondrial biogenesis, Mol. Cell Biol. 25 (14) (2005) 6225–6234.
[41] A. Baracca, et al., Mitochondrial Complex I decrease is responsible for bioenergetic dysfunction in K-ras transformed cells, Biochim. Biophys. Acta 1797 (2) (2010) 314–323.
[42] M. Nieborowska-Skorska, et al., Rac2-MRC-cIII-generated ROS cause genomic instability in chronic myeloid leukemia stem cells and primitive progenitors, Blood 119 (18) (2012) 4253–4263.
[43] J.M. Li, A.M. Shah, ROS generation by nonphagocytic NADPH oxidase: potential relevance in diabetic nephropathy, J. Am. Soc. Nephrol. 14 (8 Suppl 3) (2003) S221–S226.
[44] U. Weyemi, et al., NADPH Oxidases NOXs and DUOXs as putative targets for cancer therapy, Anti Cancer Agents Med. Chem. 13 (3) (2013) 502–514.
[45] X. Cui, Reactive oxygen species: the achilles' heel of cancer cells? Antioxidants Redox Signal. 16 (11) (2012) 1212–1214.
[46] K. Bedard, K.H. Krause, The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology, Physiol. Rev. 87 (1) (2007) 245–313.
[47] J.D. Lambeth, NOX enzymes and the biology of reactive oxygen, Nat. Rev. Immunol. 4 (3) (2004) 181–189.
[48] J.D. Lambeth, Nox enzymes, ROS, and chronic disease: an example of antagonistic pleiotropy, Free Radic. Biol. Med. 43 (3) (2007) 332–347.
[49] T.B. Dansen, K.W. Wirtz, The peroxisome in oxidative stress, IUBMB Life 51 (4) (2001) 223–230.
[50] D.T. Wright, et al., Interactions of oxygen radicals with airway epithelium, Environ. Health Perspect. 102 (Suppl 10) (1994) 85–90. Suppl 10.
[51] J.A. Imlay, S.M. Chin, S. Linn, Toxic DNA damage by hydrogen peroxide through the Fenton reaction in vivo and in vitro, Science 240 (4852) (1988) 640–642.
[52] S. Maynard, et al., Base excision repair of oxidative DNA damage and association with cancer and aging, Carcinogenesis 30 (1) (2009) 2–10.
[53] H. Wiseman, B. Halliwell, Damage to DNA by reactive oxygen and nitrogen species: role in inflammatory disease and progression to cancer, Biochem. J. 313 (Pt 1) (1996) 17–29. Pt 1.
[54] J.A. North, A.A. Spector, G.R. Buettner, Cell fatty acid composition affects free radical formation during lipid peroxidation, Am. J. Physiol. 267 (1 Pt 1) (1994) C177–C188.
[55] H.W. Gardner, Oxygen radical chemistry of polyunsaturated fatty acids, Free Radic. Biol. Med. 7 (1) (1989) 65–86.
[56] A. Catalá, Lipid peroxidation of membrane phospholipids generates hydroxy-alkenals and oxidized phospholipids active in physiological and/or pathological conditions, Chem. Phys. Lipids 157 (1) (2009) 1–11.
[57] P.C. Burcham, Genotoxic lipid peroxidation products: their DNA damaging properties and role in formation of endogenous DNA adducts, Mutagenesis 13 (3) (1998) 287–305.
[58] H. Lauschke, et al., Lipid peroxidation as additional marker in patients with colorectal cancer. Results of a preliminary study, Eur. Surg. Res. 34 (5) (2002) 346–350.
[59] P. Storz, Reactive oxygen species in tumor progression, Front. Biosci. 10 (2005) 1881–1896.
[60] S.Y. Lee, et al., Reactive oxygen species induce epithelial-mesenchymal transition, glycolytic switch, and mitochondrial repression through the Dlx-2/Snail signaling pathways in MCF-7 cells, Mol. Med. Rep. 20 (3) (2019) 2339–2346.
[61] A. Nasir Kansestani, et al., High glucose-reduced apoptosis in human breast cancer cells is mediated by activation of NF-κB, Iran. J. Allergy, Asthma Immunol. 18 (2) (2019) 153–162.
[62] D. Zhu, et al., The ROS-mediated activation of STAT-3/VEGF signaling is involved in the 27-hydroxycholesterol-induced angiogenesis in human breast cancer cells, Toxicol. Lett. 264 (2016) 79–86.
[63] C. Xia, et al., Reactive oxygen species regulate angiogenesis and tumor growth through vascular endothelial growth factor, Cancer Res. 67 (22) (2007) 10823–10830.
[64] N. Wang, et al., Increased expression of RRM2 by human papillomavirus E7 oncoprotein promotes angiogenesis in cervical cancer, Br. J. Cancer 110 (4) (2014) 1034–1044.
[65] N. Kundu, S. Zhang, A.M. Fulton, Sublethal oxidative stress inhibits tumor cell adhesion and enhances experimental metastasis of murine mammary carcinoma, Clin. Exp. Metastasis 13 (1) (1995) 16–22.
[66] B. Zhang, Z. Liu, X. Hu, Inhibiting cancer metastasis via targeting NAPDH oxidase 4, Biochem. Pharmacol. 86 (2) (2013) 253–266.
[67] S. Verma, et al., Matrix metalloproteinases and gastrointestinal cancers: impacts of dietary antioxidants, World J. Biol. Chem. 5 (3) (2014) 355–376.
[68] S. Reuter, et al., Oxidative stress, inflammation, and cancer: how are they linked? Free Radic. Biol. Med. 49 (11) (2010) 1603–1616.
[69] Y. Wu, et al., Molecular mechanisms underlying chronic inflammation-associated cancers, Cancer Lett. 345 (2) (2014) 164–173.
[70] S.J. Forrester, et al., Reactive oxygen species in metabolic and inflammatory signaling, Circ. Res. 122 (6) (2018) 877–902.
[71] H.C. Zheng, The molecular mechanisms of chemoresistance in cancers, Oncotarget 8 (35) (2017) 59950–59964.
[72] S.K. Manna, et al., Morin (3,5,7,2',4'-Pentahydroxyflavone) abolishes nuclear factor-kappaB activation induced by various carcinogens and inflammatory stimuli, leading to suppression of nuclear factor-kappaB-regulated gene expression and up-regulation of apoptosis, Clin. Cancer Res. 13 (7) (2007) 2290–2297.
[73] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (5) (2011) 646–674.
[74] B. Perillo, et al., ROS in cancer therapy: the bright side of the moon, Exp. Mol. Med. 52 (2) (2020) 192–203.
[75] S.J. Kim, H.S. Kim, Y.R. Seo, Understanding of ROS-inducing strategy in anticancer therapy, Oxid. Med. Cell. Longev. 2019 (2019) 5381692.
[76] Y. Wang, et al., The double-edged roles of ROS in cancer prevention and therapy, Theranostics 11 (10) (2021) 4839–4857.
[77] E.S. Alnemri, et al., Human ICE/CED-3 protease nomenclature, Cell 87 (2) (1996) 171.
[78] J. Chandra, A. Samali, S. Orrenius, Triggering and modulation of apoptosis by oxidative stress, Free Radic. Biol. Med. 29 (3–4) (2000) 323–333.
[79] A. Baker, B.D. Santos, G. Powis, Redox control of caspase-3 activity by thioredoxin and other reduced proteins, Biochem. Biophys. Res. Commun. 268 (1) (2000) 78–81.
[80] G. Seo, et al., Hydrogen peroxide induces Beclin 1-independent autophagic cell death by suppressing the mTOR pathway via promoting the ubiquitination and degradation of Rheb in GSH-depleted RAW 264.7 cells, Free Radic. Res. 45 (4) (2011) 389–399.
[81] Y. Chen, S.B. Gibson, Is mitochondrial generation of reactive oxygen species a trigger for autophagy? Autophagy 4 (2) (2008) 246–248.
[82] B.N. Ames, Dietary carcinogens and anticarcinogens. Oxygen radicals and degenerative diseases, Science 221 (4617) (1983) 1256–1264.
[83] S. Loft, H.E. Poulsen, Cancer risk and oxidative DNA damage in man, J. Mol. Med. (Berl.) 74 (6) (1996) 297–312.
[84] J.N. Moloney, T.G. Cotter, ROS signalling in the biology of cancer, Semin. Cell Dev. Biol. 80 (2018) 50–64.
[85] V. Nogueira, N. Hay, Molecular pathways: reactive oxygen species homeostasis in cancer cells and implications for cancer therapy, Clin. Cancer Res. 19 (16) (2013) 4309–4314.
[86] G.Y. Liou, P. Storz, Reactive oxygen species in cancer, Free Radic. Res. 44 (5) (2010) 479–496.
[87] K.M. Ahmed, N. Cao, J.J. Li, HER-2 and NF-kappaB as the targets for therapy-resistant breast cancer, Anticancer Res. 26 (6b) (2006) 4235–4243.
[88] S. Singh, B.G. Darnay, B.B. Aggarwal, Site-specific tyrosine phosphorylation of IkappaBalpha negatively regulates its inducible phosphorylation and degradation, J. Biol. Chem. 271 (49) (1996) 31049–31054.
[89] M. Karin, The IkappaB kinase - a bridge between inflammation and cancer, Cell Res. 18 (3) (2008) 334–342.
[90] P. Storz, A. Toker, Protein kinase D mediates a stress-induced NF-kappaB activation and survival pathway, EMBO J. 22 (1) (2003) 109–120.
[91] P. Storz, H. Döppler, A. Toker, Protein kinase Cdelta selectively regulates protein kinase D-dependent activation of NF-kappaB in oxidative stress signaling, Mol. Cell Biol. 24 (7) (2004) 2614–2626.
[92] R. Ruiz-Ramos, et al., Sodium arsenite induces ROS generation, DNA oxidative damage, HO-1 and c-Myc proteins, NF-kappaB activation and cell proliferation in human breast cancer MCF-7 cells, Mutat. Res. 674 (1–2) (2009) 109–115.
[93] Y. Wang, et al., The endogenous reactive oxygen species promote NF-kappaB activation by targeting on activation of NF-kappaB-inducing kinase in oral squamous carcinoma cells, Free Radic. Res. 41 (9) (2007) 963–971.
[94] K.B. Myant, et al., ROS production and NF-κB activation triggered by RAC1 facilitate WNT-driven intestinal stem cell proliferation and colorectal cancer initiation, Cell Stem Cell 12 (6) (2013) 761–773.
[95] A. Arcaro, A.S. Guerreiro, The phosphoinositide 3-kinase pathway in human cancer: genetic alterations and therapeutic implications, Curr. Genom. 8 (5) (2007) 271–306.
[96] R. Liu, et al., PI3K/AKT pathway as a key link modulates the multidrug resistance of cancers, Cell Death Dis. 11 (9) (2020) 797.
[97] F. Xu, et al., Roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours, Cell Biosci. 10 (2020) 54.
[98] F. Luongo, et al., PTEN tumor-suppressor: the dam of stemness in cancer, Cancers 11 (8) (2019).
[99] T. Maehama, G.S. Taylor, J.E. Dixon, PTEN and myotubularin: novel phosphoinositide phosphatases, Annu. Rev. Biochem. 70 (2001) 247–279.
[100] D. Presti, E. Quaquarini, The PI3K/AKT/mTOR and CDK4/6 pathways in endocrine resistant HR+/HER2- metastatic breast cancer: biological mechanisms and new treatments, Cancers 11 (9) (2019).
[101] S.M. Nur Husna, et al., Inhibitors targeting CDK4/6, PARP and PI3K in breast cancer: a review, Ther. Adv. Med. Oncol. 10 (2018), 1758835918808509.
[102] Y. Zhou, et al., Effect of microRNA-135a on cell proliferation, migration, invasion, apoptosis and tumor angiogenesis through the IGF-1/PI3K/Akt signaling pathway in non-small cell lung cancer, Cell. Physiol. Biochem. 42 (4) (2017) 1431–1446.
[103] H. Wu, V. Goel, F.G. Haluska, PTEN signaling pathways in melanoma, Oncogene 22 (20) (2003) 3113–3122.
[104] Y. Kitagishi, S. Matsuda, Redox regulation of tumor suppressor PTEN in cancer and aging (Review), Int. J. Mol. Med. 31 (3) (2013) 511–515.
[105] S.R. Lee, et al., Reversible inactivation of the tumor suppressor PTEN by H2O2, J. Biol. Chem. 277 (23) (2002) 20336–20342.

[106] Y.Y. Huo, et al., PTEN deletion leads to deregulation of antioxidants and increased oxidative damage in mouse embryonic fibroblasts, Free Radic. Biol. Med. 44 (8) (2008) 1578–1591.
[107] L.Z. Liu, et al., Reactive oxygen species regulate epidermal growth factor-induced vascular endothelial growth factor and hypoxia-inducible factor-1alpha expression through activation of AKT and P70S6K1 in human ovarian cancer cells, Free Radic. Biol. Med. 41 (10) (2006) 1521–1533.
[108] V.O. Okoh, et al., Reactive oxygen species via redox signaling to PI3K/AKT pathway contribute to the malignant growth of 4-hydroxy estradiol-transformed mammary epithelial cells, PLoS One 8 (2) (2013) e54206.
[109] P.P. Roux, J. Blenis, ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions, Microbiol. Mol. Biol. Rev. 68 (2) (2004) 320–344.
[110] J.A. McCubrey, et al., Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance, Biochim. Biophys. Acta 1773 (8) (2007) 1263–1284.
[111] M. Cargnello, P.P. Roux, Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases, Microbiol. Mol. Biol. Rev. 75 (1) (2011) 50–83.
[112] Y. Son, et al., Mitogen-activated protein kinases and reactive oxygen species: how can ROS activate MAPK pathways? J. Signal Transduct. 2011 (2011) 792639.
[113] K. Irani, et al., Mitogenic signaling mediated by oxidants in Ras-transformed fibroblasts, Science 275 (5306) (1997) 1649–1652.
[114] S. Messina, G. De Simone, P. Ascenzi, Cysteine-based regulation of redox-sensitive Ras small GTPases, Redox Biol. 26 (2019) 101282.
[115] G.Y. Liou, et al., Mutant KRas-induced mitochondrial oxidative stress in acinar cells upregulates EGFR signaling to drive formation of pancreatic precancerous lesions, Cell Rep. 14 (10) (2016) 2325–2336.
[116] X. Wang, et al., STAT3 inhibition, a novel approach to enhancing targeted therapy in human cancers (review), Int. J. Oncol. 41 (4) (2012) 1181–1191.
[117] M. Lee, et al., Targeting STAT3 and oxidative phosphorylation in oncogene-addicted tumors, Redox Biol. 25 (2019) 101073.
[118] H. Yu, D. Pardoll, R. Jove, STATs in cancer inflammation and immunity: a leading role for STAT3, Nat. Rev. Cancer 9 (11) (2009) 798–809.
[119] C. Kim, et al., Formononetin-induced oxidative stress abrogates the activation of STAT3/5 signaling axis and suppresses the tumor growth in multiple myeloma preclinical model, Cancer Lett. 431 (2018) 123–141.
[120] G. Sethi, et al., Inhibition of STAT3 dimerization and acetylation by garcinol suppresses the growth of human hepatocellular carcinoma in vitro and in vivo, Mol. Cancer 13 (2014) 66.
[121] L. Lu, et al., Activation of STAT3 and Bcl-2 and reduction of reactive oxygen species (ROS) promote radioresistance in breast cancer and overcome of radioresistance with niclosamide, Oncogene 37 (39) (2018) 5292–5304.
[122] J. Stanicka, et al., NADPH oxidase-generated hydrogen peroxide induces DNA damage in mutant FLT3-expressing leukemia cells, J. Biol. Chem. 290 (15) (2015) 9348–9361.
[123] J.F. Woolley, et al., H2O2 production downstream of FLT3 is mediated by p22phox in the endoplasmic reticulum and is required for STAT5 signalling, PLoS One 7 (7) (2012) e34050.
[124] A. Hershko, et al., Components of ubiquitin-protein ligase system. Resolution, affinity purification, and role in protein breakdown, J. Biol. Chem. 258 (13) (1983) 8206–8214.
[125] F. Ikeda, I. Dikic, Atypical ubiquitin chains: new molecular signals. 'Protein Modifications: beyond the Usual Suspects' review series, EMBO Rep. 9 (6) (2008) 536–542.
[126] E.B. Dammer, et al., Polyubiquitin linkage profiles in three models of proteolytic stress suggest the etiology of Alzheimer disease, J. Biol. Chem. 286 (12) (2011) 10457–10465.
[127] M. van Huizen, M. Kikkert, The role of atypical ubiquitin chains in the regulation of the antiviral innate immune response, Front. Cell. Dev. Biol. 7 (2019) 392.
[128] S.H. Lecker, A.L. Goldberg, W.E. Mitch, Protein degradation by the ubiquitin-proteasome pathway in normal and disease states, J. Am. Soc. Nephrol. 17 (7) (2006) 1807–1819.
[129] J. Heideker, I.E. Wertz, DUBs, the regulation of cell identity and disease, Biochem. J. 467 (1) (2015) 191.
[130] F.E. Reyes-Turcu, K.H. Ventii, K.D. Wilkinson, Regulation and cellular roles of ubiquitin-specific deubiquitinating enzymes, Annu. Rev. Biochem. 78 (2009) 363–397.
[131] S.A. Abdul Rehman, et al., MINDY-1 is a member of an evolutionarily conserved and structurally distinct new family of deubiquitinating enzymes, Mol. Cell. 63 (1) (2016) 146–155.
[132] T. Hermanns, et al., A family of unconventional deubiquitinases with modular chain specificity determinants, Nat. Commun. 9 (1) (2018) 799.
[133] J. Liang, et al., MCP-induced protein 1 deubiquitinates TRAF proteins and negatively regulates JNK and NF-kappaB signaling, J. Exp. Med. 207 (13) (2010) 2959–2973.
[134] A. Guterman, M.H. Glickman, Complementary roles for Rpn11 and Ubp6 in deubiquitination and proteolysis by the proteasome, J. Biol. Chem. 279 (3) (2004) 1729–1738.
[135] C. Grabbe, K. Husnjak, I. Dikic, The spatial and temporal organization of ubiquitin networks, Nat. Rev. Mol. Cell Biol. 12 (5) (2011) 295–307.
[136] B. Skaug, X. Jiang, Z.J. Chen, The role of ubiquitin in NF-kappaB regulatory pathways, Annu. Rev. Biochem. 78 (2009) 769–796.
[137] H.A. Lindner, Deubiquitination in virus infection, Virology 362 (2) (2007) 245–256.
[138] A. Rytkönen, D.W. Holden, Bacterial interference of ubiquitination and deubiquitination, Cell Host Microbe 1 (1) (2007) 13–22.
[139] S.V. Todi, H.L. Paulson, Balancing act: deubiquitinating enzymes in the nervous system, Trends Neurosci. 34 (7) (2011) 370–382.
[140] G. Lopez-Castejon, M.J. Edelmann, Deubiquitinases: novel therapeutic targets in immune surveillance? Mediat. Inflamm. (2016) 3481371, 2016.
[141] A. Pinto-Fernandez, B.M. Kessler, DUBbing cancer: deubiquitylating enzymes involved in epigenetics, DNA damage and the cell cycle as therapeutic targets, Front. Genet. 7 (2016) 133.
[142] S. Haq, B. Suresh, S. Ramakrishna, Deubiquitylating enzymes as cancer stem cell therapeutics, Biochim. Biophys. Acta Rev. Canc 1869 (1) (2018) 1–10.
[143] X.M. Cotto-Rios, et al., Deubiquitinases as a signaling target of oxidative stress, Cell Rep. 2 (6) (2012) 1475–1484.
[144] R.P. Kommaddi, P.Y. Jean-Charles, S.K. Shenoy, Phosphorylation of the deubiquitinase USP20 by protein kinase A regulates post-endocytic trafficking of β2 adrenergic receptors to autophagosomes during physiological stress, J. Biol. Chem. 290 (14) (2015) 8888–8903.
[145] T. Das, et al., Regulation of deubiquitinating enzymes by post-translational modifications, Int. J. Mol. Sci. 21 (11) (2020).
[146] M.A. Cohn, et al., A UAF1-containing multisubunit protein complex regulates the Fanconi anemia pathway, Mol. Cell. 28 (5) (2007) 786–797.
[147] T. Yao, et al., Proteasome recruitment and activation of the Uch37 deubiquitinating enzyme by Adrm1, Nat. Cell Biol. 8 (9) (2006) 994–1002.
[148] H. Walden, et al., The structure of the APPBP1-UBA3-NEDD8-ATP complex reveals the basis for selective ubiquitin-like protein activation by an E1, Mol. Cell. 12 (6) (2003) 1427–1437.
[149] H.S. Chung, et al., Cysteine oxidative posttranslational modifications: emerging regulation in the cardiovascular system, Circ. Res. 112 (2) (2013) 382–392.
[150] J.G. Lee, et al., Reversible inactivation of deubiquitinases by reactive oxygen species in vitro and in cells, Nat. Commun. 4 (2013) 1568.
[151] N. Stankovic-Valentin, F. Melchior, Control of SUMO and ubiquitin by ROS: signaling and disease implications, Mol. Aspect. Med. 63 (2018) 3–17.
[152] J.M. Denu, K.G. Tanner, Specific and reversible inactivation of protein tyrosine phosphatases by hydrogen peroxide: evidence for a sulfenic acid intermediate and implications for redox regulation, Biochemistry 37 (16) (1998) 5633–5642.
[153] A. Claiborne, et al., Protein-sulfenic acids: diverse roles for an unlikely player in enzyme catalysis and redox regulation, Biochemistry 38 (47) (1999) 15407–15416.
[154] G. Buhrman, et al., Structural mechanism of oxidative regulation of the phosphatase Cdc25B via an intramolecular disulfide bond, Biochemistry 44 (14) (2005) 5307–5316.
[155] R.L. van Montfort, et al., Oxidation state of the active-site cysteine in protein tyrosine phosphatase 1B, Nature 423 (6941) (2003) 773–777.
[156] J. Asai, Y. Fukushima, Y. Makino, Isolation, purification, and characterization of an acidic protein in the cerebrospinal fluid of central nervous system disease, Neurol. Med.-Chir. 32 (11) (1992) 811–817.
[157] H. Kim, A.D. D'Andrea, Regulation of DNA cross-link repair by the Fanconi anemia/BRCA pathway, Genes Dev. 26 (13) (2012) 1393–1408.
[158] J. Niraj, A. Färkkilä, A.D. D'Andrea, The Fanconi anemia pathway in cancer, Annu. Rev. Cell Biol. 3 (2019) 457–478.
[159] T.T. Huang, et al., Regulation of monoubiquitinated PCNA by DUB autocleavage, Nat. Cell Biol. 8 (4) (2006) 339–347.
[160] S.M. Nijman, et al., A genomic and functional inventory of deubiquitinating enzymes, Cell 123 (5) (2005) 773–786.
[161] S. Bergink, S. Jentsch, Principles of ubiquitin and SUMO modifications in DNA repair, Nature 458 (7237) (2009) 461–467.
[162] A. Niimi, et al., Regulation of proliferating cell nuclear antigen ubiquitination in mammalian cells, Proc. Natl. Acad. Sci. U. S. A. 105 (42) (2008) 16125–16130.
[163] X.M. Cotto-Rios, et al., APC/CCdh1-dependent proteolysis of USP1 regulates the response to UV-mediated DNA damage, J. Cell Biol. 194 (2) (2011) 177–186.
[164] A. Zlatanou, et al., The hMsh2-hMsh6 complex acts in concert with monoubiquitinated PCNA and Pol η in response to oxidative DNA damage in human cells, Mol. Cell. 43 (4) (2011) 649–662.
[165] F. Liang, et al., DNA requirement in FANCD2 deubiquitination by USP1-UAF1-RAD51AP1 in the Fanconi anemia DNA damage response, Nat. Commun. 10 (1) (2019) 2849.
[166] Y. Sheng, et al., Molecular recognition of p53 and MDM2 by USP7/HAUSP, Nat. Struct. Mol. Biol. 13 (3) (2006) 285–291.
[167] Z. Wang, et al., USP7: novel drug target in cancer therapy, Front. Pharmacol. 10 (2019) 427.
[168] S.V. Khoronenkova, G.L. Dianov, Regulation of USP7/HAUSP in response to DNA damage: yet another role for ATM, Cell Cycle 11 (13) (2012) 2409–2410.
[169] M. Hu, et al., Crystal structure of a UBP-family deubiquitinating enzyme in isolation and in complex with ubiquitin aldehyde, Cell 111 (7) (2002) 1041–1054.
[170] K.D. Wilkinson, et al., Synthesis and characterization of ubiquitin ethyl ester, a new substrate for ubiquitin carboxyl-terminal hydrolase, Biochemistry 25 (21) (1986) 6644–6649.
[171] A.C. Faesen, et al., Mechanism of USP7/HAUSP activation by its C-terminal ubiquitin-like domain and allosteric regulation by GMP-synthetase, Mol. Cell. 44 (1) (2011) 147–159.
[172] G.C. Hassink, et al., The ER-resident ubiquitin-specific protease 19 participates in the UPR and rescues ERAD substrates, EMBO Rep. 10 (7) (2009) 755–761.
[173] J.G. Lee, et al., Characterization of the deubiquitinating activity of USP19 and its role in endoplasmic reticulum-associated degradation, J. Biol. Chem. 289 (6) (2014) 3510–3517.

[174] M. Altun, et al., Ubiquitin-specific protease 19 (USP19) regulates hypoxia-inducible factor 1α (HIF-1α) during hypoxia, J. Biol. Chem. 287 (3) (2012) 1962–1969.
[175] K. Richter, et al., USP28 deficiency promotes breast and liver carcinogenesis as well as tumor angiogenesis in a HIF-independent manner, Mol. Cancer Res. 16 (6) (2018) 1000–1012.
[176] Y. Wu, et al., The deubiquitinase USP28 stabilizes LSD1 and confers stem-cell-like traits to breast cancer cells, Cell Rep. 5 (1) (2013) 224–236.
[177] N. Popov, et al., The ubiquitin-specific protease USP28 is required for MYC stability, Nat. Cell Biol. 9 (7) (2007) 765–774.
[178] M.E. Diefenbacher, et al., The deubiquitinase USP28 controls intestinal homeostasis and promotes colorectal cancer, J. Clin. Invest. 124 (8) (2014) 3407–3418.
[179] G. Guo, et al., USP28 is a potential prognostic marker for bladder cancer, Tumour Biol. 35 (5) (2014) 4017–4022.
[180] F. Meitinger, et al., 53BP1 and USP28 mediate p53 activation and G1 arrest after centrosome loss or extended mitotic duration, J. Cell Biol. 214 (2) (2016) 155–166.
[181] D. Zhang, et al., A role for the deubiquitinating enzyme USP28 in control of the DNA-damage response, Cell 126 (3) (2006) 529–542.
[182] E. Trompouki, et al., CYLD is a deubiquitinating enzyme that negatively regulates NF-kappaB activation by TNFR family members, Nature 424 (6950) (2003) 793–796.
[183] S.C. Sun, CYLD: a tumor suppressor deubiquitinase regulating NF-kappaB activation and diverse biological processes, Cell Death Differ. 17 (1) (2010) 25–34.
[184] P. Miliani de Marval, et al., CYLD inhibits tumorigenesis and metastasis by blocking JNK/AP1 signaling at multiple levels, Cancer Prev. Res. 4 (6) (2011) 851–859.
[185] S.J. Kim, H.J. Jung, C.J. Lim, Reactive oxygen species-dependent down-regulation of tumor suppressor genes PTEN, USP28, DRAM, TIGAR, and CYLD under oxidative stress, Biochem. Genet. 51 (11–12) (2013) 901–915.
[186] M.Y. Balakirev, et al., Otubains: a new family of cysteine proteases in the ubiquitin pathway, EMBO Rep. 4 (5) (2003) 517–522.
[187] T.E. Mevissen, et al., OTU deubiquitinases reveal mechanisms of linkage specificity and enable ubiquitin chain restriction analysis, Cell 154 (1) (2013) 169–184.
[188] Y. Kulathu, et al., Regulation of A20 and other OTU deubiquitinases by reversible oxidation, Nat. Commun. 4 (2013) 1569.
[189] K. Enesa, et al., NF-kappaB suppression by the deubiquitinating enzyme Cezanne: a novel negative feedback loop in pro-inflammatory signaling, J. Biol. Chem. 283 (11) (2008) 7036–7045.
[190] M.J. Morgan, Z.G. Liu, Crosstalk of reactive oxygen species and NF-κB signaling, Cell Res. 21 (1) (2011) 103–115.
[191] P.C. Evans, et al., A novel type of deubiquitinating enzyme, J. Biol. Chem. 278 (25) (2003) 23180–23186.
[192] X.C. Bai, et al., Reactive oxygen species stimulates receptor activator of NF-kappaB ligand expression in osteoblast, J. Biol. Chem. 280 (17) (2005) 17497–17506.
[193] Z. Yin, et al., Reactive oxygen species-mediated cezanne inactivation by oxidation of its catalytic cysteine residue in hepatocellular carcinoma, Oncol. Res. 27 (9) (2019) 1069–1077.
[194] A.B. Hjelmeland, et al., Targeting A20 decreases glioma stem cell survival and tumor growth, PLoS Biol. 8 (2) (2010) e1000319.
[195] J. Hurst-Kennedy, L.S. Chin, L. Li, Ubiquitin C-terminal hydrolase l1 in tumorigenesis, Biochem. Res. Int. 2012 (2012) 123706.
[196] H.J. Kim, et al., Ubiquitin C-terminal hydrolase-L1 is a key regulator of tumor cell invasion and metastasis, Oncogene 28 (1) (2009) 117–127.
[197] P. D'Arcy, X. Wang, S. Linder, Deubiquitinase inhibition as a cancer therapeutic strategy, Pharmacol. Ther. 147 (2015) 32–54.
[198] Y. Akishima-Fukasawa, et al., Significance of PGP9.5 expression in cancer-associated fibroblasts for prognosis of colorectal carcinoma, Am. J. Clin. Pathol. 134 (1) (2010) 71–79.
[199] S. Hussain, et al., The de-ubiquitinase UCH-L1 is an oncogene that drives the development of lymphoma in vivo by deregulating PHLPP1 and Akt signaling, Leukemia 24 (9) (2010) 1641–1655.
[200] R. Setsuie, K. Wada, The functions of UCH-L1 and its relation to neurodegenerative diseases, Neurochem. Int. 51 (2–4) (2007) 105–111.
[201] T. Kabuta, K. Wada, Insights into links between familial and sporadic Parkinson's disease: physical relationship between UCH-L1 variants and chaperone-mediated autophagy, Autophagy 4 (6) (2008) 827–829.
[202] J. Choi, et al., Oxidative modifications and down-regulation of ubiquitin carboxyl-terminal hydrolase L1 associated with idiopathic Parkinson's and Alzheimer's diseases, J. Biol. Chem. 279 (13) (2004) 13256–13264.
[203] Z. Wang, et al., Prostaglandin J2 alters pro-survival and pro-death gene expression patterns and 26 S proteasome assembly in human neuroblastoma cells, J. Biol. Chem. 281 (30) (2006) 21377–21386.
[204] Z. Li, et al., Delta12-Prostaglandin J2 inhibits the ubiquitin hydrolase UCH-L1 and elicits ubiquitin-protein aggregation without proteasome inhibition, Biochem. Biophys. Res. Commun. 319 (4) (2004) 1171–1180.
[205] L.M. Koharudin, et al., Cyclopentenone prostaglandin-induced unfolding and aggregation of the Parkinson disease-associated UCH-L1, Proc. Natl. Acad. Sci. U. S. A. 107 (15) (2010) 6835–6840.
[206] H. Liu, et al., Modification of ubiquitin-C-terminal hydrolase-L1 by cyclopentenone prostaglandins exacerbates hypoxic injury, Neurobiol. Dis. 41 (2) (2011) 318–328.
[207] S.H. Graham, Modification of ubiquitin C-terminal hydrolase L1 by reactive lipid species: role in neural regeneration and diseases of aging, Neural Regen. Res. 11 (6) (2016) 908–909.
[208] E. Leroy, et al., The ubiquitin pathway in Parkinson's disease, Nature 395 (6701) (1998) 451–452.
[209] H. Shen, et al., Oxidative stress regulated expression of ubiquitin Carboxyl-terminal Hydrolase-L1: role in cell survival, Apoptosis 11 (6) (2006) 1049–1059.
[210] S.M. Reed, D.E. Quelle, p53 acetylation: regulation and consequences, Cancers 7 (1) (2014) 30–69.
[211] A. Rufini, et al., Senescence and aging: the critical roles of p53, Oncogene 32 (43) (2013) 5129–5143.
[212] X.X. Sun, K.B. Challagundla, M.S. Dai, Positive regulation of p53 stability and activity by the deubiquitinating enzyme Otubain 1, EMBO J. 31 (3) (2012) 576–592.
[213] J. Weinstock, et al., Selective dual inhibitors of the cancer-related deubiquitylating proteases USP7 and USP47, ACS Med. Chem. Lett. 3 (10) (2012) 789–792.
[214] S.K. Kwon, M. Saindane, K.H. Baek, p53 stability is regulated by diverse deubiquitinating enzymes, Biochim. Biophys. Acta Rev. Canc 1868 (2) (2017) 404–411.
[215] H. Liu, et al., WP1130 increases doxorubicin sensitivity in hepatocellular carcinoma cells through usp9x-dependent p53 degradation, Cancer Lett. 361 (2) (2015) 218–225.
[216] J. Yuan, et al., USP10 regulates p53 localization and stability by deubiquitinating p53, Cell 140 (3) (2010) 384–396.
[217] T. Yamaguchi, et al., The deubiquitinating enzyme USP11 controls an IkappaB kinase alpha (IKKalpha)-p53 signaling pathway in response to tumor necrosis factor alpha (TNFalpha), J. Biol. Chem. 282 (47) (2007) 33943–33948.
[218] L. Zhang, F. Gong, Involvement of USP24 in the DNA damage response, Mol. Cell. Oncol. 3 (1) (2016) e1011888.
[219] J. Liu, et al., JTV1 co-activates FBP to induce USP29 transcription and stabilize p53 in response to oxidative stress, EMBO J. 30 (5) (2011) 846–858.
[220] A.K. Hock, et al., Regulation of p53 stability and function by the deubiquitinating enzyme USP42, EMBO J. 30 (24) (2011) 4921–4930.
[221] N. Allende-Vega, et al., MdmX is a substrate for the deubiquitinating enzyme USP2a, Oncogene 29 (3) (2010) 432–441.
[222] L.F. Stevenson, et al., The deubiquitinating enzyme USP2a regulates the p53 pathway by targeting Mdm2, EMBO J. 26 (4) (2007) 976–986.
[223] S. Dayal, et al., Suppression of the deubiquitinating enzyme USP5 causes the accumulation of unanchored polyubiquitin and the activation of p53, J. Biol. Chem. 284 (8) (2009) 5030–5041.
[224] Q. Zou, et al., USP15 stabilizes MDM2 to mediate cancer-cell survival and inhibit antitumor T cell responses, Nat. Immunol. 15 (6) (2014) 562–570.
[225] S. Lahav-Baratz, et al., The testis-specific USP26 is a deubiquitinating enzyme of the ubiquitin ligase Mdm2, Biochem. Biophys. Res. Commun. 482 (1) (2017) 106–111.
[226] A. Hata, Y.G. Chen, TGF-β signaling from receptors to smads, Cold Spring Harb. Perspect. Biol. 8 (9) (2016).
[227] P.J. Eichhorn, et al., USP15 stabilizes TGF-β receptor I and promotes oncogenesis through the activation of TGF-β signaling in glioblastoma, Nat. Med. 18 (3) (2012) 429–435.
[228] S.J. Wicks, et al., The deubiquitinating enzyme UCH37 interacts with Smads and regulates TGF-beta signalling, Oncogene 24 (54) (2005) 8080–8084.
[229] S.Y. Kim, K.H. Baek, TGF-β signaling pathway mediated by deubiquitinating enzymes, Cell. Mol. Life Sci. 76 (4) (2019) 653–665.
[230] N.J. Curtin, DNA repair dysregulation from cancer driver to therapeutic target, Nat. Rev. Cancer 12 (12) (2012) 801–817.
[231] S.P. Jackson, D. Durocher, Regulation of DNA damage responses by ubiquitin and SUMO, Mol. Cell. 49 (5) (2013) 795–807.
[232] X. Jacq, et al., Deubiquitylating enzymes and DNA damage response pathways, Cell Biochem. Biophys. 67 (1) (2013) 25–43.
[233] J.H. Guervilly, et al., USP1 deubiquitinase maintains phosphorylated CHK1 by limiting its DDB1-dependent degradation, Hum. Mol. Genet. 20 (11) (2011) 2171–2181.
[234] N. Sikdar, et al., DNA damage responses by human ELG1 in S phase are important to maintain genomic integrity, Cell Cycle 8 (19) (2009) 3199–3207.
[235] S.A. Williams, et al., USP1 deubiquitinates ID proteins to preserve a mesenchymal stem cell program in osteosarcoma, Cell 146 (6) (2011) 918–930.
[236] A. Lasorella, T. Uo, A. Iavarone, Id proteins at the cross-road of development and cancer, Oncogene 20 (58) (2001) 8326–8333.
[237] T.S. Dexheimer, et al., Synthesis and structure-activity relationship studies of N-benzyl-2-phenylpyrimidin-4-amine derivatives as potent USP1/UAF1 deubiquitinase inhibitors with anticancer activity against nonsmall cell lung cancer, J. Med. Chem. 57 (19) (2014) 8099–8110.
[238] Q. Liang, et al., A selective USP1-UAF1 inhibitor links deubiquitination to DNA damage responses, Nat. Chem. Biol. 10 (4) (2014) 298–304.
[239] F. Nicassio, et al., Human USP3 is a chromatin modifier required for S phase progression and genome stability, Curr. Biol. 17 (22) (2007) 1972–1977.
[240] E. McGarry, et al., The deubiquitinase USP9X maintains DNA replication fork stability and DNA damage checkpoint responses by regulating CLASPIN during S-phase, Cancer Res. 76 (8) (2016) 2384–2393.
[241] D. Trivigno, et al., Deubiquitinase USP9x confers radioresistance through stabilization of Mcl-1, Neoplasia 14 (10) (2012) 893–904.
[242] P. Fu, et al., WP1130 increases cisplatin sensitivity through inhibition of usp9x in estrogen receptor-negative breast cancer cells, Am. J. Transl. Res. 9 (4) (2017) 1783–1791.

[243] G.N. Maertens, et al., Ubiquitin-specific proteases 7 and 11 modulate Polycomb regulation of the INK4a tumour suppressor, EMBO J. 29 (15) (2010) 2553–2565.
[244] A.R. Schoenfeld, et al., BRCA2 is ubiquitinated in vivo and interacts with USP11, a deubiquitinating enzyme that exhibits prosurvival function in the cellular response to DNA damage, Mol. Cell Biol. 24 (17) (2004) 7444–7455.
[245] K.J. Patel, et al., Involvement of Brca2 in DNA repair, Mol. Cell. 1 (3) (1998) 347–357.
[246] J.L. Parsons, et al., USP47 is a deubiquitylating enzyme that regulates base excision repair by controlling steady-state levels of DNA polymerase β, Mol. Cell. 41 (5) (2011) 609–615.
[247] M. Li, et al., A dynamic role of HAUSP in the p53-Mdm2 pathway, Mol. Cell. 13 (6) (2004) 879–886.
[248] E. Meulmeester, et al., Loss of HAUSP-mediated deubiquitination contributes to DNA damage-induced destabilization of Hdmx and Hdm2, Mol. Cell. 18 (5) (2005) 565–576.
[249] A. van der Horst, et al., FOXO4 transcriptional activity is regulated by monoubiquitination and USP7/HAUSP, Nat. Cell Biol. 8 (10) (2006) 1064–1073.
[250] D. Hoeller, C.M. Hecker, I. Dikic, Ubiquitin and ubiquitin-like proteins in cancer pathogenesis, Nat. Rev. Cancer 6 (10) (2006) 776–788.
[251] R.S. Wu, K.W. Kohn, W.M. Bonner, Metabolism of ubiquitinated histones, J. Biol. Chem. 256 (11) (1981) 5916–5920.
[252] H.Y. Joo, et al., Regulation of cell cycle progression and gene expression by H2A deubiquitination, Nature 449 (7165) (2007) 1068–1072.
[253] A. Wyce, et al., H2B ubiquitylation acts as a barrier to Ctk1 nucleosomal recruitment prior to removal by Ubp8 within a SAGA-related complex, Mol. Cell. 27 (2) (2007) 275–288.
[254] M. Esposito, et al., USP13 controls the stability of Aurora B impacting progression through the cell cycle, Oncogene 39 (37) (2020) 6009–6023.
[255] R.J. van Leuken, et al., Usp39 is essential for mitotic spindle checkpoint integrity and controls mRNA-levels of aurora B, Cell Cycle 7 (17) (2008) 2710–2719.
[256] A.M. Antao, et al., USP48 governs cell cycle progression by regulating the protein level of aurora B, Int. J. Mol. Sci. 22 (16) (2021).
[257] I. Azimi, et al., Hypoxia-induced reactive oxygen species mediate N-cadherin and SERPINE1 expression, EGFR signalling and motility in MDA-MB-468 breast cancer cells, Sci. Rep. 7 (1) (2017) 15140.
[258] R.A. Gatenby, R.J. Gillies, Why do cancers have high aerobic glycolysis? Nat. Rev. Cancer 4 (11) (2004) 891–899.
[259] M. Tafani, et al., The Interplay of Reactive Oxygen Species, Hypoxia, Inflammation, and Sirtuins in Cancer Initiation and Progression, vol. 2016, Oxid Med Cell Longev, 2016, p. 3907147.
[260] Y. Kondo, et al., Enhancement of angiogenesis, tumor growth, and metastasis by transfection of vascular endothelial growth factor into LoVo human colon cancer cell line, Clin. Cancer Res. 6 (2) (2000) 622–630.
[261] Y.G. Yoo, et al., An essential role of the HIF-1alpha-c-Myc axis in malignant progression, Ann. N. Y. Acad. Sci. 1177 (2009) 198–204.
[262] D. Mennerich, K. Kubaichuk, T. Kietzmann, DUBs, hypoxia, and cancer, Trends Canc. 5 (10) (2019) 632–653.
[263] I. Groulx, S. Lee, Oxygen-dependent ubiquitination and degradation of hypoxia-inducible factor requires nuclear-cytoplasmic trafficking of the von Hippel-Lindau tumor suppressor protein, Mol. Cell Biol. 22 (15) (2002) 5319–5336.
[264] Z. Li, et al., VHL protein-interacting deubiquitinating enzyme 2 deubiquitinates and stabilizes HIF-1alpha, EMBO Rep. 6 (4) (2005) 373–378.
[265] A. Troilo, et al., HIF1α deubiquitination by USP8 is essential for ciliogenesis in normoxia, EMBO Rep. 15 (1) (2014) 77–85.
[266] C. Zhang, et al., USP9X destabilizes pVHL and promotes cell proliferation, Oncotarget 7 (37) (2016) 60519–60534.
[267] H.T. Wu, et al., K63-polyubiquitinated HAUSP deubiquitinates HIF-1α and dictates H3K56 acetylation promoting hypoxia-induced tumour progression, Nat. Commun. 7 (2016) 13644.
[268] D. Flügel, A. Görlach, T. Kietzmann, GSK-3β regulates cell growth, migration, and angiogenesis via Fbw7 and USP28-dependent degradation of HIF-1α, Blood 119 (5) (2012) 1292–1301.
[269] M. Scortegagna, et al., USP13 enzyme regulates Siah2 ligase stability and activity via noncatalytic ubiquitin-binding domains, J. Biol. Chem. 286 (31) (2011) 27333–27341.
[270] Q. Li, et al., Mechanisms of c-myc degradation by nickel compounds and hypoxia, PLoS One 4 (12) (2009) e8531.
[271] Y.A. Wen, et al., Downregulation of PHLPP expression contributes to hypoxia-induced resistance to chemotherapy in colon cancer cells, Mol. Cell Biol. 33 (22) (2013) 4594–4605.
[272] B.J. Choi, et al., Hypoxia induces epithelial-mesenchymal transition in colorectal cancer cells through ubiquitin-specific protease 47-mediated stabilization of Snail: a potential role of Sox9, Sci. Rep. 7 (1) (2017) 15918.
[273] S. Das, S. Ramakrishna, K.S. Kim, Critical roles of deubiquitinating enzymes in the nervous system and neurodegenerative disorders, Mol. Cell. 43 (3) (2020) 203–214.
[274] J. Chakraborty, E. Ziviani, Deubiquitinating enzymes in Parkinson's disease, Front. Physiol. 11 (2020) 535.
[275] L. Paemka, et al., Seizures are regulated by ubiquitin-specific peptidase 9 X-linked (USP9X), a de-ubiquitinase, PLoS Genet. 11 (3) (2015) e1005022.
[276] J.R. Kowalski, P. Juo, The role of deubiquitinating enzymes in synaptic function and nervous system diseases, Neural Plast. 2012 (2012) 892749.
[277] P.R. Angelova, A.Y. Abramov, Role of mitochondrial ROS in the brain: from physiology to neurodegeneration, FEBS Lett. 592 (5) (2018) 692–702.
[278] H. Shan, et al., USP7 deubiquitinates and stabilizes NOTCH1 in T-cell acute lymphoblastic leukemia, Signal Transduct. Target Ther. 3 (2018) 29.
[279] J. Ma, et al., A20 promotes melanoma progression via the activation of Akt pathway, Cell Death Dis. 11 (9) (2020) 794.
[280] S.O. Lim, et al., Deubiquitination and stabilization of PD-L1 by CSN5, Cancer Cell 30 (6) (2016) 925–939.
[281] W. Jingjing, et al., Deubiquitination and stabilization of programmed cell death ligand 1 by ubiquitin-specific peptidase 9, X-linked in oral squamous cell carcinoma, Canc. Med. 7 (8) (2018) 4004–4011.
[282] Y. Wang, et al., The deubiquitinase USP22 regulates PD-L1 degradation in human cancer cells, Cell Commun. Signal. 18 (1) (2020) 112.
[283] D. Zhu, et al., Deubiquitinating enzyme OTUB1 promotes cancer cell immunosuppression via preventing ER-associated degradation of immune checkpoint protein PD-L1, Cell Death Differ. 28 (6) (2021) 1773–1789.
[284] C. Vlasschaert, et al., Evolution of the highly networked deubiquitinating enzymes USP4, USP15, and USP11, BMC Evol. Biol. 15 (2015) 230.
[285] H. Hu, et al., Otud7b facilitates T cell activation and inflammatory responses by regulating Zap70 ubiquitination, J. Exp. Med. 213 (3) (2016) 399–414.
[286] W. Sun, et al., USP11 negatively regulates TNFalpha-induced NF-kappaB activation by targeting on IkappaBalpha, Cell. Signal. 22 (3) (2010) 386–394.
[287] M. Zhao, et al., Non-proteolytic ubiquitination of OTULIN regulates NF-κB signaling pathway, J. Mol. Cell Biol. 12 (3) (2020) 163–175.
[288] C. Bailly, Regulation of PD-L1 expression on cancer cells with ROS-modulating drugs, Life Sci. 246 (2020) 117403.
[289] E.K. Rowinsky, et al., Phase 1 study of the protein deubiquitinase inhibitor VLX1570 in patients with relapsed and/or refractory multiple myeloma, Invest. N. Drugs 38 (5) (2020) 1448–1453.
[290] X. Wang, et al., Synthesis and evaluation of derivatives of the proteasome deubiquitinase inhibitor b-AP15, Chem. Biol. Drug Des. 86 (5) (2015) 1036–1048.
[291] H. Luo, et al., Pharmacological inhibition of USP30 activates tissue-specific mitophagy, Acta Physiol. 232 (3) (2021) e13666.
[292] M.N. Cao, et al., Curcusone D, a novel ubiquitin-proteasome pathway inhibitor via ROS-induced DUB inhibition, is synergistic with bortezomib against multiple myeloma cell growth, Biochim. Biophys. Acta 1840 (6) (2014) 2004–2013.
[293] C. Priolo, et al., The isopeptidase USP2a protects human prostate cancer from apoptosis, Cancer Res. 66 (17) (2006) 8625–8632.
[294] E. Graner, et al., The isopeptidase USP2a regulates the stability of fatty acid synthase in prostate cancer, Cancer Cell 5 (3) (2004) 253–261.
[295] R.E. Savage, et al., Identification of a novel glucosylsulfate conjugate as a metabolite of 3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]pyran-5,6-dione (ARQ 501, beta-lapachone) in mammals, Drug Metab. Dispos. 36 (4) (2008) 753–758.
[296] S. Ohayon, et al., Harnessing the oxidation susceptibility of deubiquitinases for inhibition with small molecules, Angew Chem. Int. Ed. Engl. 54 (2) (2015) 599–603.
[297] R. Didier, et al., Targeting the proteasome-associated deubiquitinating enzyme USP14 impairs melanoma cell survival and overcomes resistance to MAPK-targeting therapies, Mol. Cancer Therapeut. 17 (7) (2018) 1416–1429.
[298] J. Cai, et al., A novel deubiquitinase inhibitor b-AP15 triggers apoptosis in both androgen receptor-dependent and -independent prostate cancers, Oncotarget 8 (38) (2017) 63232–63246.
[299] Y. Yang, et al., The antioxidant alpha-lipoic acid inhibits proliferation and invasion of human gastric cancer cells via suppression of STAT3-mediated MUC4 gene expression, Oxid. Med. Cell. Longev. 2019 (2019) 3643715.
[300] Y.T. Oh, et al., The proteasome deubiquitinase inhibitor b-AP15 enhances DR5 activation-induced apoptosis through stabilizing DR5, Sci. Rep. 7 (1) (2017) 8027.
[301] S.E. Leonard, K.G. Reddie, K.S. Carroll, Mining the thiol proteome for sulfenic acid modifications reveals new targets for oxidation in cells, ACS Chem. Biol. 4 (9) (2009) 783–799.
[302] J.W. Baty, M.B. Hampton, C.C. Winterbourn, Proteomic detection of hydrogen peroxide-sensitive thiol proteins in Jurkat cells, Biochem. J. 389 (Pt 3) (2005) 785–795.
[303] N. Poondla, et al., Deubiquitinating enzymes as cancer biomarkers: new therapeutic opportunities? BMB Rep. 52 (3) (2019) 181–189.
[304] S.C. Sun, Deubiquitylation and regulation of the immune response, Nat. Rev. Immunol. 8 (7) (2008) 501–511.
[305] M. de la Vega, et al., The deubiquitinating enzyme USP17 is essential for GTPase subcellular localization and cell motility, Nat. Commun. 2 (2011) 259.
[306] X. Baohai, F. Shi, F. Yongqi, Inhibition of ubiquitin specific protease 17 restrains prostate cancer proliferation by regulation of epithelial-to-mesenchymal transition (EMT) via ROS production, Biomed. Pharmacother. 118 (2019) 108946.
[307] N. Acharya, et al., Roles of PCNA-binding and ubiquitin-binding domains in human DNA polymerase eta in translesion DNA synthesis, Proc. Natl. Acad. Sci. U. S. A. 105 (46) (2008) 17724–17729.
[308] J.R. Berenson, Bortezomib in newly diagnosed multiple myeloma, Nat. Rev. Clin. Oncol. 6 (5) (2009) 255–256.
[309] S.V. Rajkumar, S. Kumar, Multiple myeloma current treatment algorithms, Blood Cancer J. 10 (9) (2020) 94.
[310] Y.A. Larasati, et al., Curcumin targets multiple enzymes involved in the ROS metabolic pathway to suppress tumor cell growth, Sci. Rep. 8 (1) (2018) 2039.
[311] N.R. Jana, et al., Inhibition of proteasomal function by curcumin induces apoptosis through mitochondrial pathway, J. Biol. Chem. 279 (12) (2004) 11680–11685.
[312] M. Jarvius, et al., Piperlongumine induces inhibition of the ubiquitin-proteasome system in cancer cells, Biochem. Biophys. Res. Commun. 431 (2) (2013) 117–123.

[313] Y.S. Ma, et al., Inhibition of USP14 and UCH37 deubiquitinating activity by b-AP15 as a potential therapy for tumors with p53 deficiency, Signal Transduct. Target Ther. 5 (1) (2020) 30.
[314] U. Kim, et al., Pimozide inhibits the human prostate cancer cells through the generation of reactive oxygen species, Front. Pharmacol. 10 (2019) 1517.
[315] J. Chen, et al., Selective and cell-active inhibitors of the USP1/UAF1 deubiquitinase complex reverse cisplatin resistance in non-small cell lung cancer cells, Chem. Biol. 18 (11) (2011) 1390–1400.
[316] H. Mistry, et al., Small-molecule inhibitors of USP1 target ID1 degradation in leukemic cells, Mol. Cancer Therapeut. 12 (12) (2013) 2651–2662.
[317] J. Guo, et al., Potent USP10/13 antagonist spautin-1 suppresses melanoma growth via ROS-mediated DNA damage and exhibits synergy with cisplatin, J. Cell Mol. Med. 24 (7) (2020) 4324–4340.
[318] Y.B. Liu, et al., Pristimerin induces apoptosis in prostate cancer cells by down-regulating bcl-2 through ROS-dependent ubiquitin-proteasomal degradation pathway, J. Carcinog. Mutagen. (Suppl 6) (2013), 005.
[319] S. Kotamraju, et al., Transferrin receptor-dependent iron uptake is responsible for doxorubicin-mediated apoptosis in endothelial cells: role of oxidant-induced iron signaling in apoptosis, J. Biol. Chem. 277 (19) (2002) 17179–17187.
[320] J. Lankelma, et al., Doxorubicin gradients in human breast cancer, Clin. Cancer Res. 5 (7) (1999) 1703–1707.
[321] R. Marullo, et al., Cisplatin induces a mitochondrial-ROS response that contributes to cytotoxicity depending on mitochondrial redox status and bioenergetic functions, PLoS One 8 (11) (2013) e81162.
[322] S. Dasari, P.B. Tchounwou, Cisplatin in cancer therapy: molecular mechanisms of action, Eur. J. Pharmacol. 740 (2014) 364–378.
[323] D. Magda, R.A. Miller, Motexafin gadolinium: a novel redox active drug for cancer therapy, Semin. Cancer Biol. 16 (6) (2006) 466–476.
[324] G.M. Richards, M.P. Mehta, Motexafin gadolinium in the treatment of brain metastases, Expet Opin. Pharmacother. 8 (3) (2007) 351–359.
[325] T. Hagen, et al., Inhibition of mitochondrial respiration by the anticancer agent 2-methoxyestradiol, Biochem. Biophys. Res. Commun. 322 (3) (2004) 923–929.
[326] M. Fukui, B.T. Zhu, Mechanism of 2-methoxyestradiol-induced apoptosis and growth arrest in human breast cancer cells, Mol. Carcinog. 48 (1) (2009) 66–78.
[327] S. Qanungo, et al., 2-Methoxyestradiol induces mitochondria dependent apoptotic signaling in pancreatic cancer cells, Oncogene 21 (26) (2002) 4149–4157.
[328] O.W. Griffith, A. Meister, Potent and specific inhibition of glutathione synthesis by buthionine sulfoximine (S-n-butyl homocysteine sulfoximine), J. Biol. Chem. 254 (16) (1979) 7558–7560.
[329] M. Lee, et al., 3-bromopyruvate and buthionine sulfoximine effectively kill anoikis-resistant hepatocellular carcinoma cells, PLoS One 12 (3) (2017) e0174271.
[330] S. Moulder, et al., A phase I trial of imexon, a pro-oxidant, in combination with docetaxel for the treatment of patients with advanced breast, non-small cell lung and prostate cancer, Invest. N. Drugs 28 (5) (2010) 634–640.
[331] E.V. Sheveleva, et al., Imexon induces an oxidative endoplasmic reticulum stress response in pancreatic cancer cells, Mol. Cancer Res. 10 (3) (2012) 392–400.
[332] B. Kim, et al., Peroxiredoxin 5 overexpression enhances tumorigenicity and correlates with poor prognosis in gastric cancer, Int. J. Oncol. 51 (1) (2017) 298–306.
[333] A. Nicolussi, et al., The role of peroxiredoxins in cancer, Mol. Clin. Oncol. 6 (2) (2017) 139–153.
[334] E. Lu, et al., Up-regulation of peroxiredoxin-1 promotes cell proliferation and metastasis and inhibits apoptosis in cervical cancer, J. Cancer 11 (5) (2020) 1170–1181.
[335] W. Fiskus, et al., SIRT2 deacetylates and inhibits the peroxidase activity of peroxiredoxin-1 to sensitize breast cancer cells to oxidant stress-inducing agents, Cancer Res. 76 (18) (2016) 5467–5478.