Targeting Nrf2-Mediated Oxidative Stress Response Signaling Pathways as New Therapeutic Strategy for Pituitary Adenomas

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Oxidative stress and oxidative damage are the common pathophysiological characteristics in pituitary adenomas (PAs), which have been confirmed with many omics studies in PA tissues and cell/animal experimental studies. Nuclear factor erythroid 2 p45-related factor 2 (Nrf2), the core of oxidative stress response, is an oxidative stress sensor. Nrf2 is synthesized and regulated by multiple factors, including Keap1, ERK1/2, ERK5, JNK1/2, p38 MAPK, PKC, PI3K/AKT, and ER stress, in the cytoplasm. Under the oxidative stress status, Nrf2 quickly translocates from cytoplasm into the nucleus and binds to antioxidant response element /electrophile responsive element to initiate the expressions of antioxidant genes, phases I and II metabolizing enzymes, phase III detoxifying genes, chaperone/stress response genes, and ubiquitination/proteasomal degradation proteins. Many Nrf2 or Keap1 inhibitors have been reported as potential anticancer agents for different cancers. However, Nrf2 inhibitors have not been studied as potential anticancer agents for PAs. We recommend the emphasis on in-depth studies of Nrf2 signaling and potential therapeutic agents targeting Nrf2 signaling pathways as new therapeutic strategies for PAs. Also, the use of Nrf2 inhibitors targeting Nrf2 signaling in combination with ERK inhibitors plus p38 activators or JNK activators targeting MAPK signaling pathways, or drugs targeting mitochondrial dysfunction pathway might produce better anti-tumor effects on PAs. This perspective article reviews the advances in oxidative stress and Nrf2-mediated oxidative stress response signaling pathways in pituitary tumorigenesis, and the potential of targeting Nrf2 signaling pathways as a new therapeutic strategy for PAs.

Keywords: pituitary adenoma, oxidative stress, Nrf2, signaling pathway, biomarker, therapeutic target and drug

INTRODUCTION

Pituitary adenoma (PA) is a common intracranial neoplasm that occurs in the central regulatory organ pituitary gland in the hypothalamic-pituitary-target organ axis system, which seriously affects human endocrine system and health. PAs account for 10–25% of all intracranial tumors, and are classified into benign (~65%), invasive (~35%), and malignant (carcinoma; only 0.1–0.2%) PAs according to the malignancy level (Stalla et al., 2019). PAs are divided into macroadenomas...
(≥10 mm) and microadenomas (<10 mm) according to tumor size (Lopes, 2017). They are also divided into clinically functional and nonfunctional PAs (FPAs and NFPAs) according to the level of hormone secretion (Zhan et al., 2016). FPAs are hormone-secreting PAs, which result in hyperpituitarism, including acromegaly derived from growth hormone (GH)-secreting PAs, hyperprolactinemia derived from prolactin (PRL)-secreting PAs, and Cushing’s syndrome derived from adrenocorticotropin (ACTH)-secreting PAs. NFPAs are non-hormone-secreting PAs (Qian et al., 2018). The main clinical symptoms of PAs include inappropriate hormone secretion syndrome, and compression of the neighboring tissues and structures such as headache, visual field defect, and increased intracranial pressure (Reimondo et al., 2019). PA is a multi-factor, multi-process, and multi-consequence complex disease, which is involved in a series of molecular alterations at the levels of genome, transcriptome, proteome, peptidome, metabolome, and radiome; and these molecules mutually associate and function in a molecular network system (Zhan and Desiderio, 2010b; Hu et al., 2013; Grech et al., 2015; Cheng and Zhan, 2017; Lu and Zhan, 2018). Thus, one must shift the research and practice strategy from a single-factor model to a multi-parameter systematic model for predictive, preventive, and personalized medicine in PAs (Hu et al., 2013; Grech et al., 2015; Cheng and Zhan, 2017). Multomics is an effective approach to realize this multi-parameter systematic strategy model shift, which can establish signaling pathway systems for in-depth understanding of molecular mechanisms of PAs, identify molecular network-based biomarkers for prediction, diagnosis, and prognostic assessment of PAs, and discover signaling pathway network-based therapeutic targets for effective treatment of PAs (Grech et al., 2015; Cheng and Zhan, 2017; Lu and Zhan, 2018).

A series of omics analyses have been performed in PAs to reach our long-term goals that clarify molecular mechanisms and discover effective biomarkers and therapeutic targets for PAs (Zhan and Desiderio, 2010a; Long et al., 2019; Cheng et al., 2019; Wang Y. et al., 2019), including NFPA quantitative transcriptomics (differentially expressed genes, DEGs) (Moreno et al., 2005; Cheng et al., 2019), NFPA quantitative proteomics (differentially expressed proteins, DEPs) (Moreno et al., 2005), NFPA proteomic mapping (Zhan and Desiderio, 2003; Wang X. et al., 2015; Cheng et al., 2019), NFPA nitroproteomics (Zhan and Desiderio, 2006), invasive NFPA quantitative transcriptomics (Galland et al., 2010; Zhou et al., 2011; Wang et al., 2019), invasive NFPA quantitative proteomics (Zhan et al., 2014b), control pituitary proteomic mapping (Beranova-Giorgianni et al., 2002; Giorgianni et al., 2003; Zhao et al., 2005), pituitary control nitroproteomics (Zhan and Desiderio, 2004; Zhan and Desiderio, 2007), control pituitary phosphoproteomics (Giorgianni et al., 2004; Beranova-Giorgianni et al., 2006), PRL-secreting adenoma proteomics and transcriptomics (Evans et al., 2008), and ACTH-secreting adenoma proteomics and metabolomics (Feng et al., 2018). Integrative analysis of these omics data has revealed some important signaling pathway network alterations in PA pathogenesis, including mitochondrial dysfunction, oxidative stress, cell cycle dysregulation, and mitogen-activated protein kinase (MAPK) signaling pathway alteration (Zhan and Desiderio, 2010a; Long et al., 2019). Mitochondrial dysfunction pathway network and mitochondrial dynamics (Li and Zhan, 2019), and MAPK signaling pathway-based drug therapeutic targets (Lu et al., 2019) have been discussed in detail in PAs. It is well-known that mitochondria are the energy factories of the body, and mitochondrial metabolism is the source of reactive oxygen species (ROS). The imbalance between free radicals reactive oxygen/nitrogen species (ROS/RNS) and antioxidant system leads to oxidative stress, which plays an important role in diseases. Many studies focus on oxidative stress system as therapeutic strategy; for example, benfotiamine is an efficient antioxidant, which could prevent oxidative stress in the anterior tibialis muscle and heart of mice (Gonçalves et al., 2019). Another research shows that pancreatic oxidative damage in the diabetic state is caused by ROS, and scavenging the various ROS generated in the disease is one of effective ways to treat this disease (Afolabi et al., 2018). Studies have clearly demonstrated that mitochondrial dysfunction and oxidative stress pathway changes operate in PAs (Zhan and Desiderio, 2010a), and nuclear factor erythroid 2 p45-related factor 2 (Nrf2)-mediated oxidative stress response significantly impacts the pathogenesis of PAs and modulates the energy metabolism reprogramming for PAs (Sabatino et al., 2018). It is well-known that PAs can lead to abnormal hormone secretion, which might affect oxidative stress and Nrf2 signaling in PAs; for example, human growth hormone (hGH) can attenuate inflammation and oxidative stress attained by Cisplatin probably through inhibition of Nrf2/heme oxygenase 1 (HO-1) pathway (Mahan, 2020). More studies show that Nrf2 signaling and oxidative stress can be regulated by cortisol (Wu et al., 2019), thyroid hormone (Mishra et al., 2019), follicle-stimulating hormone (FSH) (Li et al., 2020), luteinizing hormone (LH) (Li et al., 2020), GH (Mahan, 2020), ACTH (Benloch et al., 2016), and PRL (Ebokaiwe et al., 2020). These findings clearly demonstrate the importance of oxidative stress in PAs. This present review article will focus on oxidative stress response signaling pathway network in PA pathogenesis.

**REDOX HOMEOSTASIS AND NRF2 AS THE HEART OF OXIDATIVE STRESS RESPONSE**

Oxidative stress is derived from the imbalance between the upload of free radicals ROS/RNS from in vivo and in vitro environmental approaches and the ability of endogenous antioxidants to detoxify these ROS/RNS (Prasad et al., 2016; Klaunig, 2018; Sajadimajd and Khazaei, 2018). It results in the injuries of multiple biomacromolecules such as DNAs, RNAs, proteins, and membrane lipids to significantly associate with a wide spectrum of diseases including cancers. Many studies demonstrate that the increased ROS/RNS productions promote carcinogenesis development (Kudryavtseva et al., 2016; Kruk and Aboul-Enein, 2017), and oxidative stress-mediated chronic inflammation is the risk factor of tumorigenesis (Reuter et al., 2010; Qian et al., 2019). The oxidative phosphorylation system in
mitochondrial respiratory chain is the central machine that generates ROS products such as superoxide radical (O$_2^-$). One study shows that ROS levels and signs of oxidative damage are significantly increased in PAs (Sabatino et al., 2018). One of the most important RNS, nitric oxide (NO), is generated by inducible nitric synthase (iNOS) in many pathogenesis conditions, which can rapidly react with superoxide radical (O$_2^-$) to generate more toxic peroxynitrite anion (ONOO$^-$) and highly reactive hydroxyl radical (OH) to attack DNAs, RNAs, proteins, and membrane lipids. iNOS has been extensively found in rat and human pituitaries (Ceccatelli et al., 1993; Lloyd et al., 1995; Ueta et al., 1998; Kruse et al., 2002; Pawlikowski et al., 2003) and has the elevated activities in PAs compared to those in controls (Vankelecom et al., 1997; Kruse et al., 2002). Another study shows that NO functions in the hypothalamic-pituitary-adrenocortical axis (Riedel, 2002) by promoting the release of follicle-stimulating hormone-releasing hormone (FSHRH) and luteinizing hormone-releasing hormone (LHRH) from hypothalamus (McCann et al., 2001; Pinilla et al., 2001; McCann et al., 2003), and regulating secretion of PRL (Duvilanski et al., 1995) and GH in pituitaries and PAs (Cuttica et al., 1997; Pinilla et al., 1999; Bocca et al., 2000). Peroxynitrite anion (ONOO$^-$) is a key factor in vivo that causes protein tyrosine nitration and alters protein functions. Nine nitrotyrosine-containing proteins have been identified in NFPA tissues, and tyrosine nitration occurs in important structural and functional domains to change protein functions (Zhan and Desiderio, 2006).

With the generation of ROS/RNS, the in vivo antioxidant detoxification system is correspondingly initiated to adapt against the increased ROS/RNS (Valko et al., 2006; Obrador et al., 2019). The endogenous antioxidant detoxification system is a very complex system, including i) enzymatic antioxidants such as superoxide dismutases (CuZnSOD and MnSOD), glutathione peroxidase, and catalase; ii) non-enzymatic antioxidants such as vitamin E, vitamin C, carotenoid, flavonoid, selenium, thiol antioxidant (thioredoxin, lipoic acid, and glutathione), and others; and iii) multiple regulatory factors [Nrf2, NF-kB (nuclear factor kB), and AP-1 (activator protein-1), etc.] that interact with antioxidants (Valko et al., 2006; Obrador et al., 2019). CuZnSOD exists in most parts of cells, while MnSOD is only found in mitochondrial matrix; and both of them are able to effectively scavenge O$_2^-$ and generate H$_2$O$_2$ (Li et al., 1995; Melov et al., 2001; Elchuri et al., 2005). H$_2$O$_2$ can be scavenged by GPX’s (glutathione peroxidases) and peroxiredoxins (thioredoxin-independent peroxidases) (Chu et al., 2004; Kang et al., 2005). Studies have found that the levels of CuZnMOD and MnSOD are significantly lower in PAs compared to those of controls (Kurisaka et al., 2004; Yang et al., 2012; Ilhan et al., 2018). The abnormal activities of these antioxidant enzymes and non-enzymatic antioxidants are directly associated with carcinogenesis (Neumann et al., 2003; Chu et al., 2004; Harris et al., 2015). The transcription factor Nrf2 is pivotal to the antioxidant response, which is a sensor of oxidative stress in redox homeostasis, and is mainly located in the cytoplasm under basal conditions (Li and Kong, 2009; Furfaro et al., 2016a). When the upload of free radicals ROS/RNS is increased to cause oxidative stress, Nrf2 quickly translocates from cytoplasm into the nucleus to initiate the antioxidant response, protecting against oxidative/nitrative damages (Dhakshinamoorthy and Porter, 2004; Osburn et al., 2006; Mann et al., 2007; Pi et al., 2008).

The Nrf2 signaling regulatory system contains at least four components, including Nrf2, Kelch-like ECH-associated protein 1 (Keap1), small muscleaponeurotic fibrosarcoma (Maf), and antioxidant response element (ARE) or electrophile responsive element (EpRE), which in combination are necessary for the antioxidant response (Kwak and Kensler, 2010; Furfaro et al., 2016; de la Vega et al., 2018). Nrf2 signaling pathways regulate multiple biological processes, including i) the expressions of antioxidant genes, ii) ubiquitin-proteasome system, iii) molecular chaperone/stress-response system, and iv) anti-inflammatory response (Kwak and Kensler, 2010; Furfaro et al., 2016). The accumulated evidence clearly demonstrates that Nrf2 signaling pathways are involved in 12 hallmarks of cancer, including sustained proliferative signaling, insensitivity to antigrowth signals, resistance to apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, metabolic reprogramming, avoiding immune destruction, tumor-promoting inflammation, genome instability, altered redox homeostasis, and proteotoxic stress (de la Vega et al., 2018). Thereby, any decreased capability of the antioxidant protective system in the redox homeostasis might cause more susceptibility to carcinogen toxicity, tumor inflammatory response, oxidative stress, and carcinogenesis (Yates and Kensler, 2007).

MULTIOMICS REVEALS OXIDATIVE STRESS-RELATED PATHWAY ALTERATIONS IN PAs

Our multiomics studies in PAs (Zhan and Desiderio, 2010a; Long et al., 2019) clearly demonstrate oxidative stress-related pathway changes in PAs. For example, i) Nrf2-mediated oxidative stress response pathway is significantly changed in NFPA with evidence of upregulation of key molecules [upregulated DEPs: GST (glutathione S-transferase) or GSTM2 (glutathione S-transferase mu 2), and ERP29 (endoplasmic reticulum protein 29), and downregulation of key molecules [downregulated DEPs: HSP22 (heat shock protein 22), HSP27, and HSP90 or GRP94 (94 kD glucose-regulated protein)]) in this pathway. ii) Mitochondrial dysfunction pathway is significantly changed in NFPA with evidence of upregulation of key molecules [upregulated DEPs: NDUF8 (NADH ubiquinone oxido reductase core subunit S8), COX6B (cytochrome c oxidase subunit 6B), CAT (catalase), β-secret2, and ATP5B (ATP synthase, H+ transporting mitochondrial F1 complex, subunit b)].

Mitochondrial dysfunction can increase ROS production in cancer cells to mediate tumor-related signaling pathways and activate pro-oncogenic signaling (Li and Zhan, 2019). iii) Oxidative phosphorylation pathway is significantly changed in NFPA with evidence of upregulation of key molecules (upregulated DEPs: NDUF8,
increase in oxidative stress and damage in human PAs. Recently, these findings are also confirmed with experiments in cell models and animal models, which demonstrate that increased mitochondrial fusion results in bigger mitochondria, increased ROS levels, and oxidative damage in PAs, and that Nrf2 signaling pathway is activated in PAs as an antioxidant response (Sabatino et al., 2018). Thus, it suggests that Nrf2 is the master regulator of the cellular antioxidant response (de la Vega et al., 2018).

NRF2-MEDIATED OXIDATIVE STRESS RESPONSE SIGNALING PATHWAYS IN PAs

Nrf2 signaling pathway in response to oxidative stress is shown (Figure 1). Multiple in vivo and in vitro environmental factors, including inflammatory cytokines, prostaglandins, growth factors, low-density lipoproteins, bacterial and viral infection, heavy metals, ultraviolet (UV) radiation, ionizing radiation, drugs, xenobiotics, antioxidants, oxidants, and chemopreventive agents, cause the increased upload of free radicals ROS/RNS and electrophiles to result in oxidative stress (Hetland et al., 2020; Mehnati et al., 2020). The increased ROS or electrophiles will activate the Nrf2/Keap1 complex in the cytoplasm through ERK1/2, ERK5, JNK1/2, p38 MAPK, PKC, and PI3K-AKT signaling pathways, and these signaling pathways will communicate with each other (Roy Chowdhury et al., 2014; Tian et al., 2014; Wang K.-C. et al., 2019). The activated Nrf2 is phosphorylated and separated from Keap1 (Hambright et al., 2015; Sánchez-Martín et al., 2020). The separated and phosphorylated Nrf2 quickly translocates into the nucleus to interact with ARE or EpRE, which will initiate at least five types of gene expressions to exert the corresponding biological functions (Furfaro et al., 2016; Sánchez-Martín et al., 2020): i) reduction of the oxidative damage via antioxidant proteins such as Nrf2, small MAF, ATF4, SQSTM1, HO-1, PRDX1, FTL, FTH1, CAT, GPX5, SOD, TXN, GSR, and TRXR1 (Sun et al., 2019; Saad El-Din et al., 2020; Yu et al., 2020); ii) detoxification and metabolism of xenobiotics to regulate cell survival, or production of reactive metabolites to promote tumorigenesis via phase I and II metabolizing enzymes such as CYP1A2/2A3/3A4/2C, FMO, GST, NQD, UGT, AFAH, EPHX1, GCLC, GCLN, CB4, AKR, and AOX4 (Zhao et al., 2015; Huang et al., 2018); iii) transportation of xenobiotics and metabolites via phase III detoxifying proteins such as SR-B1 and MRPI (Sivils et al., 2013; Lubelska et al., 2016); iv) repairment and removal of the damaged proteins via chaperone and stress response proteins such as HSP22/40/90, STIP1, PTPLAD1, HERPUD1, CCT7, CLPP, FKBP5, PP1B, and ERP29 (Nitoue and Jaiswal, 2010; Sahin et al., 2012); and v) repairment and removal of the damaged proteins via ubiquitination and proteasomal degradation proteins such as PSMD17, B2R1, VCP, Usp14, UBB, and HIP2 (Liu et al., 2019; Song et al., 2019). This clearly demonstrates that while the Nrf2-mediated oxidative stress response signaling pathways are regulated by multiple factors, Nrf2 is the essential component. In the cytoplasm, Keap1, the main regulator of Nrf2, is a substrate adaptor protein for the Cul3-Keap1-E3 ligase complex that ubiquinates Nrf2, marking it for proteasomal degradation in the cytoplasm under basal conditions (Baird and Yamamoto, 2020; Dayalan Naidu and Dinkova-Kostova, 2020). To reduce its inhibitory effects on Nrf2, Keap1 can be ubiquitinated for degradation, leading to
FIGURE 1 | Nrf2-mediated oxidative stress response signaling pathways in human pituitary adenomas. AKR, Palmitoyltransferase; AKT, Protein kinase B; AOX4, Aldehyde oxidase 4; ARE, Antioxidant response element; ASK1, Apoptosis signal-regulating kinase 1; ATF4, Activating transcription factor 4; BACH1, Transcription regulator protein; BAK1, CAT, catalase; CBP, CREB-binding protein; CB4, carbonyl reductase 4; CCT7, T-complex protein 1 subunit eta; c-FOS, Proto-oncogene protein c-FOS; CLPP, Caseinolytic protease; Cul3, Cullin 3-based ubiquitin E3 ligase complex; Cyp, cytochrome P; EPRE, Electrophile responsive element; ER, endoplasmic reticulum; ERK, Extracellular signal-related kinase; ERP29: endoplasmic reticulum protein 29; FMO, Dimethylaniline monooxygenase [N-oxide-forming]; FRA1, Fos-related antigen 1; FTH1, Ferritin heavy polypeptide 1; FTL1, ferritin light polypeptide; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate-cysteine ligase modifier subunit; GPX, Glutathione peroxidases; GSK3β, glycogen synthase kinase 3β; GST, glutathione reductase; GST, glutathione S-transferase; HSP22/40/90, heat shock proteins 22, 40 and 90; JNK, Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; Maf, Musculoaponeurotic fibrosarcoma; MAPK, Mitogen-activated protein kinase; MEK, Mitogen-activated protein kinase kinase (MAPKK); MRP1, multidrug-resistant protein-1; NQO1, NAD(P)H:quinone oxidoreductase 1; Nrf2, Nuclear factor erythroid 2 p45-related factor 2; NQO1, NAD(P)H:quinone oxidoreductase 1; Nrf2, Nuclear factor erythroid 2 p45-related factor 2; PERK, the double-stranded RNA (PKR)-activated protein kinase; Pim1, 3-hydroxyacyl-CoA dehydratase 3; c-Raf, RAF proto-oncogene serine/threonine-protein kinase; Ras, GTPase Ras; ROS, reactive oxygen species; SOD, Superoxide dismutase; SQSTM1, sequestosome-1 protein; SOD1, Scavenger receptor class B member 1; STIP1, Stress induced phosphoprotein 1; TAK1, TGF beta-Activated Kinase 1; TXN1, thioredoxin 1; TRX1, thioredoxin reductase 1; UbB, Polyubiquitin-B; UBZ/R1, Ubiquitin-conjugating enzyme E2 R1; UGT, UDP glucuronosyl transferase; USP14, ubiquitin-specific peptidase 14; and VCP, valosin-containing protein. Modified from Zhan et al. (2010) (Zhan and Desiderio, 2010a), copyright permission from BioMed Central publisher open-access article, copyright 2010; and modified from Long et al. (2019) (Long et al., 2019), copyright permission from Frontiersin publisher open-access article, copyright 2019.
an increase in Nrf2 phosphorylation (activation) (Villeneuve et al., 2010). The phosphorylated Nrf2 can then interact with actin to form an Nrf2/actin complex that then translocates into the nucleus. After Nrf2 translocates into the nucleus, there are additional regulatory systems in place that include multiple factors such as ATF4, JUN, ERK1/2-CBP/P300, small MAF, BACH1, c-FOS, FRA1, and c-MAF, to influence the binding of Nrf2 and ARE/EpRE. The detailed regulatory mechanism system of Nrf2 has been extensively reviewed (Kwak and Kensler, 2010; Hybertson et al., 2011; Furfaro et al., 2016a; Lu et al., 2016; Menegon et al., 2016; Taguchi and Yamamoto, 2017; Bellezza et al., 2018; Chen and Maltagliati, 2018; de la Vega et al., 2018; Ryoo and Kwak, 2018; Sajadimajd and Khazaee, 2018; Cloer et al., 2019; Cuadrado et al., 2019; Qin et al., 2019) response signaling pathways have also been studied in pituitaries and PAs. One study shows that Nrf2, phosphorylated Nrf2 (p-Nrf2) protein, and mRNA expressions are increased in PAs, and the Nrf2 downstream effector HO-1 is also increased in PAs (Sabatino et al., 2018). This clearly demonstrates the activation of the Nrf2 signaling pathway, likely causing the extensive surviving capability of pituitary tumor cells. The Nrf2/PTEN-induced putative kinase protein 1 (PINK1)/Parkin pathway and mitophagy are activated in T-2 toxin-induced toxicities in rat pituitary GH3 cells (Deyu et al., 2018). Antioxidants N-acetylcysteine (NAC) and vitamin E can decrease the expressions of Nrf2 and HO-1 in rat pituitaries (Prevatto et al., 2017). Genetically induced Nrf2 overexpression in melanoma cells promotes tumor growth and increases antioxidant defense in malignant cells, which can be inhibited by anticancer agent pterostilbene (Pter, a natural dimethoxylated analog of resveratrol) through the downregulation of p38 MAPK, and ERK pathways (An et al., 2003). Therefore, oxidative stress and antioxidative stress response extensively exist in PA pathogenesis. Nrf2, as the core of oxidative stress response, could be the novel target used to develop effective therapeutic agents for human PAs (Kwak and Kensler, 2010; Furfaro et al., 2016; de la Vega et al., 2018).

## THERAPEUTIC STATUS TARGETING NRF2 SIGNALING PATHWAYS IN CANCERS

Nrf2 signaling, as the heart of oxidative stress response, is extensively related to cancer pathogenesis, which has attracted tremendous attention as possible anticancer therapeutic target. Nrf2 signaling-based anticancer therapeutic studies have been extensively carried out in multiple cancers, including acute myeloid leukemia, gallbladder cancer, renal carcinoma, pancreatic cancer, melanoma, hepatocellular carcinoma, lung cancer, colon cancer, ovarian cancer, breast cancer, esophageal cancer, and glioblastoma (Table 1). i) In acute myeloid leukemia, studies found that Nrf2 activators [dimethyl fumarate (DMF), tert-butylhydroquinone, or carnosic acid] and vitamin D derivatives can cooperatively induce acute myeloid leukemia cell differentiation to inhibit leukemia progression in a xenograft mouse model via activating the Nrf2/ARE signaling pathway (Nachlielly et al., 2019). Novel pyrazolyl hydroxamic acid derivative (4f) can inhibit Nrf2 activity to induce apoptosis of human acute myeloid leukemia cells (Zhang et al., 2017). ii) In gallbladder cancer, one study found that atypical protein kinase Cι (aPKCι) can promote gallbladder tumorigenesis and chemoresistance of anticancer agent gemcitabine by competing with Nrf2 for binding to Keap1, implying that inhibiting the aPKCι-Keap1-Nrf2 axis might overcome drug resistance for the treatment of gallbladder cancer (Tian et al., 2019). iii) In renal carcinoma, one study found that the natural product chitosan oligosaccharide (COS) can inhibit human renal carcinoma cell proliferation in vitro and in vivo by promoting the expressions of Nrf2 and Nrf2 target genes such as HO-1, the modifier subunit of
| Cancer type       | Experimental model                                      | Chemical reagents or potential drugs                                                                                           | Possible mechanisms                                                                                                                                                                                                 | References                                      |
|------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Acute myeloid leukemia | Acute myeloid leukemia cells in a xenograft mouse model | Nrf2 activators: dimethyl fumarate (DMF), tert-butylhydroquinone, or carnosic acid                                            | Cooperate with vitamin D derivatives to induce acute myeloid leukemia cell differentiation to inhibit leukemia progression in a xenograft mouse model via activating the Nrf2/ARE signaling pathway | Nachliely et al. (2019)                       |
| Gallbladder cancer | Human acute myeloid leukemia cells                    | Novel pyrazolyl hydroxyamic acid derivative (4f)                                                                             | Inhibit Nrf2 activity to induce apoptosis of human acute myeloid leukemia cells. A typical protein kinase C (pPKC) can promote gallbladder tumorigenesis and chemoresistance of anticancer agent gemcitabine by competing with Nrf2 for binding to Keap1, implying that inhibiting the pPKC-Keap1-Nrf2 axis might overcome drug resistance for the gallbladder cancer treatment | Zhang et al. (2019)                           |
| Gallbladder cancer | Gallbladder cancer cells                               | The aPKC-ι inhibitors, Nrf2 activators, or gemcitabine                                                                      | Atypical protein kinase C (aPKC-ι) can promote gallbladder tumorigenesis and chemoresistance of anticancer agent gemcitabine by competing with Nrf2 for binding to Keap1, implying that inhibiting the pPKC-Keap1-Nrf2 axis might overcome drug resistance for the gallbladder cancer treatment | Tian et al. (2019)                            |
| Renal carcinoma  | Human renal carcinoma cells                            | Chitosan oligosaccharide (COS)                                                                                               | Inhibit human renal carcinoma cell proliferation in vitro and in vivo by promoting the expressions of Nrf2 and Nrf2 target genes such as HO-1, the modifier subunit of glutamate cysteine ligase, solute carrier family 7 member 11, glucose-regulated protein 78, protein RNA-like endoplasmic reticulum kinase, and cytochrome C, etc. | Zhai et al. (2019)                            |
| Pancreatic cancer | Pancreatic cancer cells                                | Resveratrol                                                                                                                  | Enhance the sensitivity of pancreatic cancer cells to gemcitabine via suppressing NAF-1 expression, inducing ROS accumulation, and activating Nrf2 signaling pathways | Cheng et al. (2018)                           |
| Melanoma         | Melanoma cells                                         | Nrf2 inhibitor: Brusatol (BR)                                                                                                 | The co-treatment of brusatol and UVA irradiation can effectively inhibit melanoma growth by regulating the AKT-Nrf2 pathway                                                                                           | Wang et al. (2018)                            |
| Hepatocellular carcinoma | Hepatocellular carcinoma (HCC) cells                | Vitamin C (VC), all-trans retinoic acid (ATRA), ochratoxin A (OTA), bexarotene, flavonoids (including brusatol, luteolin, apigenin and chrysins), ruthenium (Ru) metal complexes, ursoic acid (UA), halofuginone, trigonelline, quercetin, and isorhizaid | Sensitize chemotherapy drugs in hepatocellular carcinoma                                                                                                                                                    | Tian et al. (2018)                            |
| Liver injury model | Cordycepin (CA)                                        | Activate the Nrf2/HD-1/NF-κB pathway for its anti-hepatocarcinoma effect in N-nitrosodiethylamine (NDEA)-induced mouse hepatocellular carcinomas. | Induce apoptosis and inhibit the Nrf2/ARE signaling pathway in Hep3B cells, and IQ-7 was suggested a degree of specificity against cancer cells. Protect against carbon tetrachloride (CCl4)-induced liver injury by activating Nrf2 signaling via JNK, AMF, and calcium signaling | Zeng et al. (2017); Zhang et al. (2016)         |
| Lung cancer      | Lung cancer cells                                     | The potent anticancer agent: Isodeoxyelephantopin                                                                           | Induce protective autophagy in lung cancer cells via the Nrf2-p62-keap1 pathway                                                                                                                                   | Wang et al. (2017)                            |
| RAW 264.7 mouse macrophage-like cells, in VC1 lung cancer cells, and in the A/J model of lung cancer | Two clinically relevant classes of Nrf2 activators: DMF, and the synthetic oleandrene triterpenoids –C-28 methyl ester of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO)-Imidazole (CDDO-Im) and CDDO-Methyl ester (CDDO-Me) | Activate the Nrf2 pathway as well as regulate different subsets of Nrf2 target genes and Nrf2-independent genes                                                                                             | Chian et al. (2014); To et al. (2015)          |

(Continued on following page)
| Cancer type | Experimental model | Chemical reagents or potential drugs | Possible mechanisms | References |
|-------------|-------------------|-------------------------------------|---------------------|------------|
| Colon cancer | SFN-treated human colon cancer cells and non-transformed colonic epithelial cells | Anticancer agent: Sulforaphane (SFN) | Regulate the activity of antioxidant and the detoxification of carcinogens via Nrf2 signaling to suppress human colon cancer | Johnson et al. (2017) |
| | 1, 2-dimethyl hydrazine (DMH)-induced mouse colon model | Taxifolin (TAX) | Induce antioxidant response pathway, enhance level of Nrf2 proteins, and act as effective chemopreventive agent capable of modulating inflammatory response | Manigandan et al. (2015) |
| Ovarian cancer | Human ovarian cancer cell lines: PEO4, OVCAR4, and SKOV3 | Anti-HER2 drugs: Trastuzumab and Pertuzumab | HER2 targeting by antibodies inhibited growth in association with persistent ROS generation, glutathione (GSH) depletion, reduction in Nrf2 levels, and inhibition of Nrf2 function in ovarian cancer cell lines | Khall et al. (2016) |
| | Human epithelial ovarian cancer (EOC) cell lines | Keap1 mutation reagent | Activation of Nrf2 pathway in EOC seems to be related to Keap1 mutations within highly conserved domains of the Keap1 gene; and Nrf2 may serve as an important therapeutic target for novel drugs capable of preventing or reversing resistance to chemotherapy in EOC | Konstantinopoulos et al. (2011) |
| Breast cancer | Breast cancer cells, and mouse model | Target antioxidant enzymes: GCLC and GCLM | Nrf2 serves as a key regulator in chemotherapeutic resistance under hypoxia through ROS-Nrf2-GCLC-GSH pathway, and can be a potential treatment for hypoxia-induced drug resistance in breast cancer cells. | Syu et al. (2016) and Song et al. (2011) |
| Esophageal cancer | Esophageal squamous cancer cells (ESCC): Ec109 and KYSE70 cells | CDDO-Me | Protects the cells against oxidative stress via inhibition of ROS generation, while CDDO-Me at low micromolar concentrations induces apoptosis by increasing ROS and decreasing intracellular glutathione levels | Wang X. et al. (2015) |
| Glioblastoma | Glioblastoma cells | Potential anti-cancer agents | Targeting Nrf2 signaling for chemotherapy and chemoresistance | Zhu et al. (2014) |
| Osteosarcoma | Human osteosarcoma 143B and MG63 cells | The bioengineered Nrf2-siRNA | Interferes with the Nrf2 signaling pathway to reduce the expression of Nrf2-regulated oxidative enzymes and lead to higher intracellular ROS levels; knocking down Nrf2 with bioengineered siRNA agent improves chemosensitivity of cancer cells, which is related to the suppression of Nrf2-regulated efflux ABC transporters. | Li et al. (2018) |
| Other cancers | prostate cancer cell PC4-LN4; colon cancer cell HCT-116; breast cancer cells MB-MDA-231 and MB-MDA-231-ARE-Luc Mammalian cancer cells | PIM kinases inhibitors | Inhibit Nrf2 signaling and increase ROS to kill hypoxic tumor cells in a HIF-1-independent manner by controlling its cellular localization | Warfel et al. (2016) |
| | Mouse epidermal cells (J76 P+), Gallic acid (GA), Z-ligustilide (LIG), and senkyunolide A (SA) | Proteasome inhibitors | In response to proteasome inhibition, several responses are activated, such as the ALP, proteaphagy, the transcriptional upregulation of the autophagy Ub receptor p62/SQSTM1, and proteasome genes, by Nrf1 and Nrf1/Nrf2 transcription factors, respectively, GA, LIG, and SA in Si-Wu-Tang (SWT) can individually or cooperatively target the Nrf2/ARE pathway to prevent cancer. | Alborno et al. (2019) |
glutamate cysteine ligase, solute carrier family 7 member 11, glucose-regulated protein 78, protein RNA-like endoplasmic reticulum kinase, and cytochrome C. (Zhai et al., 2019). iv) In pancreatic cancer, one study found that antioxidant agent resveratrol enhances the sensitivity of pancreatic cancer cells to gemcitabine via suppressing NAF-1 (nutrient-deprivation autophagy factor-1) expression, inducing ROS accumulation, and activating Nrf2 signaling pathways (Cheng et al., 2018). v) In melanoma, the co-treatment of Nrf2 inhibitor (brusatol, BR) and UVA irradiation can effectively inhibit melanoma growth by regulating AKT-Nrf2 pathway (Wang et al., 2018). vi) In hepatocellular carcinoma, one study found that potential Nrf2 inhibitors can sensitize chemotherapy drugs in hepatocellular carcinoma (Tian et al., 2018). Cordycepin (CA) can activate the Nrf2/HO-1/OF-xB pathway for its anti-hepatocarcinoma effect in N-nitrosodiethylamine (NDEA)-induced mouse hepatocellular carcinomas (Zeng et al., 2017). The novel indazolo[3,2-b]quinazolinone (IQ) derivatives, IQ-7 and IQ-12, can induce apoptosis of human hepatoma cells Hep3B and inhibit the Nrf2/ARE signaling pathway in Hep3B cells, and IQ-7 is suggested as a degree of specificity against cancer cells (Zhang et al., 2016). Also, dibenzoylmethane (DBM) can protect against carbon tetrachloride (CCL4)-induced liver injury by activating Nrf2 signaling via JNK, AMPK, and calcium signaling (Cao et al., 2017). vii) In lung cancer, one study found that the potent anticancer agent isodeoxyelephantopin can induce protective autophagy in lung cancer cells via the Nrf2-p62-keap1 pathway (Wang et al., 2017). The Nrf2 activators, DMF and the synthetic oleanane triterpenoids, activate the Nrf2 pathway as well as regulate different subsets of Nrf2 target genes and Nrf2-independent genes in lung cancer (Chian et al., 2014; To et al., 2015). viii) In colon cancer, one study found that anticancer agent sulforaphane (SFN) can activate Nrf2 signaling to suppress human colon cancer (Johnson et al., 2017). Also, taxifolin (TAX) can induce antioxidant response pathway and enhance level of Nrf2 protein, and act as effective chemopreventive agent capable of modulating inflammation in colon cancer (Manigandan et al., 2015). ix) In ovarian cancer, one study found that Nrf2 can mediate the response of cancer cells to the anti-HER2 drugs, trastuzumab and pertuzumab, in ovarian cancer cells (Khalil et al., 2016). Also, activation of Nrf2 pathway in ovarian cancer seems to be related to Keap1 mutations within highly conserved domains of Keap1 gene and that Nrf2 may serve as an important therapeutic target for novel drugs capable of preventing or reversing resistance to chemotherapy in ovarian cancer (Konstantinopoulos et al., 2011). x) In breast cancer, Nrf2 serves as a key regulator in chemotherapeutic resistance under hypoxia through ROS-Nrf2-GCLC-GSH pathway and can be a potential treatment for hypoxia induced drug resistance in breast cancer cells (Song et al., 2011; Syu et al., 2016). xi) In esophageal cancer, C-28 methyl ester of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO-Me) can protect the cells against oxidative stress via inhibition of ROS generation, while CDDO-Me at low micromolar concentrations induces apoptosis by increasing ROS and decreasing intracellular glutathione levels in esophageal squamous cancer cells (Wang Y. Y. et al., 2015). xii) In glioblastoma, there are many potent anti-cancer agents targeting Nrf2 signaling for chemotherapy and chemoresistance in glioblastoma (Zhu et al., 2014). xiii) In osteosarcoma, the bioengineered Nrf2-siRNA can effectively interfere with the Nrf2 signaling pathway to improve chemosensitivity of human cancer cells (Li et al., 2018). Moreover, the PIM (provilair integration site for moloney murine leukemia virus) kinase inhibitors can reduce Nrf2 signaling and increase ROS to kill hypoxic tumor cells such as prostate cancer cells (PC4-LN4), colon cancer cells (HCT-116), and breast cancer cells (MB-MDA-231 and MB-MDA-231-ARE-Luc) (Warfel et al., 2016). One study shows that proteasome biogenesis is dependent on the Nrf2 transcriptional factor, thus proteasome inhibitors have been actively developed as potential anticancer drugs (Albornoz et al., 2019). Gallic acid (GA), Z-ligustilide (LIG), and senkyunolide A (SA) can individually or cooperatively target Nrf2/ARE pathway to prevent cancer (Liu et al., 2018). Therefore, it can be said that Keap1-Nrf2 signaling pathways have different roles at different stages of cancer (Leinonen et al., 2014; Furfaro et al., 2016; de la Vega et al., 2018). Multiple Nrf2 or Keap1 inhibitors have been reported; and some of them are in the stages of pre- and clinical trial towards the Nrf2 signaling for cancers. For example, sulforaphane can target Nrf2 and the Nrf2 target genes NQO1 and GCLC to prevent oral cancer, and a preclinical trial has been performed to study its chemopreventive activity for oral cancer (Bauman et al., 2016). A single centre, single arm prospective phase II clinical trial has been performed for phytochrome complex of curcumin targeting Nrf2 signaling as a the complementary therapy of gemcitabine on pancreatic cancer (Pastorelli et al., 2018). However, none of these Nrf2 or Keap1 inhibitors have currently entered into real clinical applications, which suggests that the sole inhibition of Nrf2 might not be sufficient for anticancer. A rational combination of Nrf2 inhibitors with other chemical agents would be a better strategy to treat cancers (Zhang et al., 2019).

**POTENTIAL OF TARGETING NRF2 SIGNALING AS NEW THERAPEUTIC STRATEGY FOR PAs**

As described above, many omics studies in human PA tissues and experimental studies in PA cells and animal models demonstrate that oxidative stress and oxidative damage is the important hallmark of PA pathogenesis. Nrf2-mediated oxidative stress response signaling pathways are at the heart of oxidative stress response, and many chemical agents targeting Nrf2 signaling pathways have been developed and tested as potential anticancer drugs for different cancers. This clearly demonstrates the potential of targeting Nrf2 signaling pathways as new therapeutic strategies for PAs. However, the use of Nrf2 signaling as a therapeutic target for PAs has not been studied. We strongly believe that the Nrf2-mediated oxidative stress response signaling pathways are the promising targets for novel therapeutic strategies for PAs. Furthermore, MAPK signaling pathways including ERK, JNK, and p38 MAPK clearly regulate Nrf2 signaling (Figure 1). Moreover, MAPK signaling pathways have been recognized as potential therapeutic targets for PAs (Lu et al., 2019). The combined
use of Nrf2 inhibitors targeting Nrf2 signaling and ERK inhibitors [e.g., somatostatin analogs pasireotide (SOM230) and octreotide (OCT), or dopamine] plus p38 activators (e.g., cabergoline, bromocriptine, and fulvestrant) or JNK activators (e.g., ursolic acid, UA) targeting MAPK signaling pathways (Lu et al., 2019) might produce better anti-tumor effects on PAs. In addition, oxidative stress is tightly associated with mitochondrial dysfunctions, both operate in PAs (Zhan and Desiderio, 2010a; Li and Zhan, 2019; Long et al., 2019). Some drugs targeting mitochondria are also recognized as a therapeutic strategy for PAs, including pyrimethamine, temozolomide, melatonin, mitochondria are also recognized as a therapeutic strategy for PAs. Furthermore, the combined use of Nrf2 inhibitors targeting Nrf2 signaling and ERK inhibitors plus p38 activators or JNK activators targeting MAPK signaling pathways, or drugs targeting mitochondria dysfunction pathway might produce better anti-tumor effects on PAs.

**CONCLUSION**

Pituitary adenoma (PA) is a common and important disease that occurs in the hypothalamic-pituitary-target organ axis system and seriously affects human endocrine system and health. The imbalance between oxidative stress and the antioxidant defense system is an important pathophysiological characteristic in PAs, which has been evidenced by many omics analysis in PA tissues and experimental studies in PA cells and animal models. Nrf2 signaling is at the heart of oxidative stress response signaling pathways. Multiple anticancer agents targeting Nrf2-mediated oxidative stress response pathways have been developed and tested as potential therapeutic drugs for different cancers. However, Nrf2 signaling and targeting Nrf2 signaling as a therapeutic strategy has not yet been extensively studied in PAs. We strongly recommend the emphasis on in-depth studies of Nrf2 signaling and potential therapeutic agents targeting Nrf2 signaling pathways in PAs. Furthermore, the combined use of Nrf2 inhibitors targeting Nrf2 signaling and ERK inhibitors plus p38 activators or JNK activators targeting MAPK signaling pathways, or drugs targeting mitochondria dysfunction pathway might produce better anti-tumor effects on PAs.

**AUTHOR CONTRIBUTIONS**

XZ conceived the concept, collected and analyzed literature, designed, coordinated, wrote and revised manuscript, and was responsible for its financial supports and the corresponding works. JL and TZ participated in literature collection and analysis, and prepared figures. All authors approved the final manuscript.

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# GLOSSARY

| Term          | Description                                      |
|---------------|-------------------------------------------------|
| ACTH          | Adrenocorticotropin                             |
| AFAR          | aldo-keto reductase family 7 member A2         |
| AIP           | Aryl hydrocarbon receptor interacting protein gene |
| AKR           | Palmitoyltransferase AKT                       |
| AKR1B1        | aldo-keto reductase family 1 member B          |
| AKT           | Protein kinase B                               |
| AOX4          | Aldehyde oxidase 4                             |
| AP-1          | Activator protein-1                            |
| aPKC1         | Atypical protein kinase C                      |
| ARE           | Antioxidant response element                    |
| ARS           | Acute restraint stress                         |
| ASK1          | Apoptosis signal-regulating kinase 1           |
| ATF4          | Activating transcription factor 4              |
| ATP5A1        | ATP synthase subunit alpha, mitochondrial      |
| ATP5B         | ATP synthase, H+ transporting mitochondrial F1 complex, beta subunit |
| BACH1         | Transcription regulator protein BACH1          |
| Bax           | BCL2 associated X, apoptosis regulator          |
| BCL2          | BCL2 apoptosis regulator                       |
| BR            | Brusatol                                        |
| CALM          | Calmodulin                                     |
| CAT           | Catalase                                        |
| CBP           | CREB-binding protein                            |
| CBR4          | carboxyl reductase 4                           |
| CCL2          | C-C motif chemokine ligand 2                   |
| CCT7          | T-complex protein 1 subunit eta                |
| c-FOS         | Proto-oncogene protein c-FOS                   |
| CLPP          | Caseinolytic protease                          |
| COS           | Chitosan oligosaccharide                       |
| COX6B         | cytochrome c oxidase subunit 6B                |
| c-MAF (MAF)   | MAF bZIP transcription factor                  |
| c-Raf         | RAF proto-oncogene serine/threonine-protein kinase |
| CRS           | Chronic restraint stress                       |
| Cul3          | Cullin 3-based ubiquitin E3 ligase complex     |
| Cyp           | cytochrome P                                   |
| CYP1A         | cytochrome P450 family 1 subfamily A           |
| CYP2A         | cytochrome P450 family 2 subfamily A           |
| CYP2C         | cytochrome P450 family 2 subfamily C           |
| CYP3A         | cytochrome P450 family 3 subfamily A           |
| CYP4A         | cytochrome P450 family 4 subfamily A           |
| DBM           | Dibenzoylmethane                               |
| DEG           | Differentially expressed gene                  |
| DEP           | Differentially expressed protein               |
| DMF           | Dimethyl fumarate                              |
| EPHX1         | Epoxide hydrolase 1                            |
| EpRE          | Electrophile responsive element                |
| ER            | endoplasmic reticulum                          |
| ERK           | Extracellular signal-related kinase            |
| ERK1/2        | mitogen-activated protein kinase               |
| ERK5          | mitogen-activated protein kinase               |
| ERP29         | endoplasmic reticulum protein 29               |
| ESR1          | estrogen receptor 1                            |
| ESR2          | estrogen receptor 2                            |
| FKBPs         | FK506-binding protein 5                        |
| FMO           | Dimethylamin monooxygenase [N-oxide-forming]    |
| FPA           | Functional pituitary adenoma                   |
| FRA1          | Fos-related antigen 1                          |
| FSH           | Follicle-stimulating hormone                   |
| FSHRH         | Follicle-stimulating hormone-releasing hormone |
| FTH1          | Ferritin heavy polypeptide                     |
| FTL1          | ferritin light polypeptide                     |
| GA            | Gallic acid                                    |
| GCLC          | glutamate-cysteine ligase catalytic subunit     |
| GCLM          | glutamate-cysteine ligase modifier subunit     |
| GH            | Growth hormone                                 |
| GPX4          | glutathione peroxidase 4                       |
| GPX’s          | Glutathione peroxidases                        |
| GRP94         | 94 kD glucose-regulated protein                |
| GSK3β         | glycogen synthase kinase 3β                   |
| GSR           | glutathione reductase                          |
| GST           | glutathione S-transferase                      |
| GSTM2         | glutathione S-transferase mu 2                 |
| HERPUD1       | Homocysteine-responsive endoplasmic reticulum-resident ubiquitin-like domain member 1 protein |
| HIP2          | Ubiquitin-conjugating enzyme E2 K              |
| HO-1          | heme oxygenase 1                               |
| HSP22/40/90   | heat shock proteins 22, 40 and 90              |
| HSP27         | heat shock protein 27                          |
| HSP70         | (HSPA4) heat shock protein family A member 4    |
| HSP90         | heat shock protein 90                          |
| HSP90AA1      | heat shock protein 90 alpha family class A member 1 |
| HSP90AB1      | heat shock protein 90 alpha family class B member 1 |
| HSP94         | heat shock protein 94                          |
| HSPA5         | heat shock protein family A (Hsp70) member 5    |
| HSPA8         | heat shock protein family A (Hsp70) member 8    |
| HSPA9         | heat shock protein family A (Hsp70) member 9    |
HSPCA (HSP90AA1) heat shock protein 90 alpha family class A member 1
HSPCB (HSP90AB1) heat shock protein 90 alpha family class B member 1
IL-1β interleukin 1 beta
IL-6 interleukin 6
iNOS Inducible nitric synthase
IP3R (ITPR1) inositol 1,4,5-trisphosphate receptor type 1
Ipt Iptakalim
JNK Jun N-terminal kinase
JNK1 (MAPK8) mitogen-activated protein kinase 8
JNK 2 (MAPK9) mitogen-activated protein kinase 9
JUN Jun proto-oncogene, AP-1 transcription factor subunit
K-ATP ATP-sensitive potassium
Keap1 Kelch-like ECH-associated protein 1
LH Luteinizing hormone
LHRH Luteinizing hormone-releasing hormone
LIG Z-ligustilide
Maf Musculoaponeurotic fibrosarcoma
MAPKs Mitogen-activated protein kinases
MEK Mitogen-activated protein kinase kinase (MAPKK)
MEKK Mitogen-activated protein kinase kinase kinase (MAPKKK)
MN Micronucleus
MRP1 multidrug-resistant protein-1
NAC N-acetylcysteine
NAF-1 Nutrient-deprivation autophagy factor-1
NDEA N-nitrosodimethylamine
NDUFS8 (NADH) ubiquinone oxidoreductase core subunit S8
NF-kB Nuclear factor kB
NFPA Nonfunctional pituitary adenoma
NME1 NME/NM23 nucleoside diphosphate kinase 1
NO Nitric oxide
NQO1 NAD(P)H:quinone oxidoreductase 1
Nrf2 Nuclear factor erythroid 2 p45-related factor 2
Nur77 (NR4A1) nuclear receptor subfamily 4 group A member 1
O2.- Superoxide radical
8-OHdG 8-hydroxy-2'-deoxyguanosine
OCT octreotide
OH hydroxyl radical
ONOO- Peroxy nitrite anion
PA Pituitary adenoma
PACAP38 Pituitary adenylate cyclase-activating polypeptide 38
PDK1 pyruvate dehydrogenase kinase 1
PERK the double-stranded RNA (PKR)-activated protein kinase-like eukaryotic initiation factor 2 kinase
PKA cAMP dependent protein kinase
PKC protein kinase C
POMC proopiomelanocortin
PP1B Peptidyl-prolyl cis-trans isomerase B
PP2C putative protein phosphatase
PRDX1 peroxiredoxin 1
PRL Prolactin
PSM multiple subunits of the 20S proteasome
Pter Pterostilbene
PTPLAD1 3-hydroxyacyl-CoA dehydratase 3
Ras GTPase Ras
RNS Reactive nitrogen species
ROS Reactive oxygen species
SA Senkyunolide A
SFN Sulforaphane
SOD Superoxide dismutase
SOD1 superoxide dismutase 1
SOM230 somatostatin analogs pasireotide
SQSTM1 sequestosome-1 protein
SR-B1 Scavenger receptor class B member 1
STIP1 stress induced phosphoprotein 1
TAC Total antioxidant capability
TAK1 TGF beta-Activated Kinase 1
TGM2 transglutaminase 2
TLR4 toll like receptor 4
TNFα tumor necrosis factor alpha
TRXR1 thioredoxin reductase 1
TUBB tubulin beta class I
TUBB2A tubulin beta 2A class IIa
TXN1 thioredoxin
UBB Polyubiquitin-B
UB2R1 Ubiquitin-conjugating enzyme E2 R1
UGT UDP glucuronosyl transferase
USP14 ubiquitin-specific peptidase 14
UV ultraviolet
VCP valosin-containing protein