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Review article

The Role of Nrf2 signaling in cancer stem cells: From stemness and self-renewal to tumorigenesis and chemoresistance

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ABSTRACT

Cancer stem cells (CSCs) are subpopulation of tumor mass with exclusive abilities in self-renewing, stemness maintaining, and differentiation into the various non-stem cancer cells to provoke tumorigenesis, metastasis dissemination, drug-resistant, and cancer recurrence. Reactive oxygen species (ROS) impair cellular function by oxidizing cell components containing proteins, lipids, and DNA. Tumor oxidant status is elevated due to high metabolic activity under influence of abnormal growth factors, cytokines and function ROS-producing enzymes, including nitric oxide synthases, cyclooxygenases, and lipoxygenases. Nuclear factor-erythroid 2-related factor 2 (NRF2) is a transcriptional master regulator element which is believed to recognize cellular oxidative stress followed by binding to promoter of cyto-protective and anti-oxidative genes to maintain cellular redox status through promoting antioxidant response participants (glutathione peroxidase, glutathione reductase, thioredoxin reductase, ferritin, NADPH: quinone oxidoreductase 1). However, Nrf2 signaling protects malignant cells from ROS damage against tumor growth and chemoresistance. In addition, Nrf2 is able to participate in differentiation of certain stem cells by modulating autophagy procedure, also NRF2 provokes DNA damage response and facilitates drug metabolism and drug resistance by controlling of downstream enzyme and transporter members. In this review, we discuss the role of NRF2 in stemness, self-renewal ability, tumorigenesis and chemoresistance of CSCs.

1. Introduction

Cancer is a disease with a high mortality rate which shows dynamic nature due to heterogeneous cell population in tumor mass that harboring unique cellular and molecular signatures in inter-tumoral and/or intra-tumoral sites [1]. Cancer stem cells (CSCs) comprise small subpopulation of cancerous cells (both hematological and non-hematological) which have exclusive abilities in self-renewing, stemness maintaining and differentiation into the multitude non-stem cancer cell linages to promote tumorigenesis, cancer dissemination, drug-resistant, and cancer recurrence [2,3]. CSCs represent analogous characteristics with normal stem or progenitor cells in self-renewal and differentiation signaling pathways. Line of evidences support the role of epigenetic alternations in induction of key signaling pathways for development and function of CSCs [4].

Intra-cellular and extra-cellular oxidative stresses impair cellular functions by oxidizing cell compartments (proteins, lipids, DNA) that results in production of reactive oxygen species (ROSs) as bio-reactions byproduct. ROS accumulation in the cells is able to trigger carcinogenesis, cellular senescence or cell death. Oxidative stresses mainly cause DNA damages in genome including base lesions, single- and double-strand breaks and abasic sites which are commonly found in cancer cells [5–7]. ROS, as the main oxidative stress, plays a dual role to establish p53 mediated apoptosis or inhibition of apoptosis via stimulation of certain oncogenes (Akt, ERK and c-MYC) to support cell proliferation, malignant transformation and eventually metastasis [8]. CSCs-specific antioxidant response mechanisms mainly depend on redox buffer glutathione and glucose metabolism which promote

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pentose phosphate pathway cycle to reduce the ROS concentration [9,10].

Nuclear factor-erythroid 2-related factor 2 (NRF2) is a transcriptional master regulator which senses the status of cellular oxidative stress and regulates cell redox hemostasis by stimulating activity of antioxidant responses elements (glutathione peroxidase, glutathione reductase, thioredoxin reductase, ferritin, NADPH: quinone oxidoreductase 1) [8,11]. Protective function of Nrf2 is utilized by malignant cells to establish a pro-survival tumoral environment for tumor growth and supports the cancer cells for establishment of chemoresistance. Notably, Nrf2 maintains the stemness of CSCs as a key factor for improvement of aggressiveness and chemoresistance of tumor cells [12–15]. In this review, we summarized the role of Nrf2 signaling in stemness and self-renewal characteristics of CSCs to promote tumorigenesis and chemoresistance.

2. Cancer stem cells

CSCs comprise tiny sub-group of cancerous cells in tumor bulk and show similar characteristics with normal stem cells except in self-renewal ability and differentiation capability into the certain cell linages [16]. Several main sources are considered for origin of CSCs including mutated adult stem cells (by accumulation of carcinogenic mutations), de-differentiation and reprograming of normal somatic cells, beside originating from progenitor cells with partial self-renewal ability [16–18]. Embryonic stem cell markers (octamer-binding transcription factor 4 (oct4), Nanog homeobox, and sex determining region Y-box 2 (SRY)) are also reported to be expressed on CSCs. They implicate Wnt/β-catenin, Hedgehog, and Notch pathways predominantly to maintain self-renewal capacity as none-CSCs [19].

This small population is able to participate in tumorigenesis, cancer dissemination, drug-resistant and also cancer recurrence [2]. Cellular stemness in both CSCs and non-CSCs is established through activation of certain molecular signaling networks including canonical Wnt, PI3K and PTEN, Jagged/Notch, JAK/STAT, Hedgehog/GLI, and NF-κB pathways. Also, the differentiation ability of stem cells is under influence of bone morphogenetic protein (BMP) and retinoic acid induced pathways [2,20]. Recent studies also have revealed the role of Nrf2 in preserving stemness, promoting aggressive tumorigenic and launching chemoresistance in CSCs [13–15].

3. Structure and physio-pathological role of Nrf2

Nrf2 as a basic-region leucine zipper cytosolic transcription factor (member of cap′n′collar (CNC) and/or CNC-bZIP family) senses oxidative stress status of the cells (electrophilic, chemical and radiation-induced) to regulate antioxidant responses through modulating expression of antioxidant and phase II detoxificant genes [21].

Nrf2 cooperates with small Maf family (MafF, MafG, MafK) or Jun proteins to facilitate Nrf2 binding to the promoters of cyto-protective and anti-oxidative genes for boosting transcription activity [22]. In physiological condition, Nrf2 couples to its cytoplasmic inhibitory molecule known as Kelch Like ECH Associated Protein 1 (Keap1) to enable subsequent ubiquitination within Cullin E3 ligase for reducing the activity. However, in stress condition, conformational alternation in cysteine residues of Keap1 releases Nrf2 and provides Nrf2 translocation into the nucleus to induce the expression of anti-stress genes [23]. Protein kinase C (PKC) dependent signaling is an alternative mechanism for direct regulation of Nrf2 activity through phosphorylation of Ser40 to upregulate Nrf2 activity. Dysregulated activity of PKC is reported to provoke cancer initiation and progression in Nrf2 depended manner [24].

Mitochondrial ROS status as the main intrinsic is the main activator of Nrf2 function, also Nrf2 in a bidirectional communication is able to mediate mitochondria biogenesis and mitochondria depended apoptosis in a mutual manner [25]. In addition, Nrf2 participates in differentiation of adipose derived stem cells into the osteoblasts by modulating autophagy procedure. NRF2 is able to stimulate DNA damage response and also mediates drug metabolizing and -resistance through regulation and induction of downstream drug-metabolism-specific enzymes and transporters [26–29]. Despite transient activation of Nrf2 in normal cells to overcome oxidative insults, prolonged upregulation of Nrf2 in cancer cells not only causes reduction of ROS but also provokes carcinogenesis and chemoresistance through alternation of metabolic profile of malignant cells by upregulation of certain enzymes involved in glycolysis, anti-apoptotic activity (BCl2 and Bcl-XL) and K-Ras, B-Raf, and Myc oncogenes to promote cancer progression [30,31].

4. The role of Nrf2 in CSCs tumorigenicity and cancer progression

NRF2 gene (NFE2L2) is often mutated in cancers (in gain of function manner), which causes over activation of Nrf2 to protect the cells against undesired oxidative stresses. These mutations are associated with therapy resistance which lead to poor clinical outcomes for patients [32]. Also, certain mutations of Keap1 are able to initiate cancer by constant inhibition of Nrf2 which reduces the cellular ability in removing of chemical carcinogenesis [33]. Long term exposure of breast cancer cells to the anti-cancer drugs is reported to result in generation of CSC-like cells with low ROS levels besides upregulated glutathione peroxidase and superoxide dismutase under influence of activated Nrf2 expression that suggest possible role of Nrf2 in establishment of CSCs [34,35]. Examination of colon CSC-like cells revealed high concentration of NRF2-induced antioxidant and detoxifying proteins in total secretome which demonstrates the key role of Nrf2 in maintenance of CSCs metabolic status [36]. The results from both human and animal models confirmed that airway basal stem cells change ROS content from low to moderate to maintain self-renewal and proliferation ability by stimulating Nrf2 to provoke Notch pathway [37]. Homozygous inactivation of murine Keap1 (inhibitor of Nrf2) provokes self-renewal ability in airway basal stem cells which leads to proliferation, dissemination, and resistance to oxidative stresses and irradiation which is due to over activated Nrf2 and subsequent dropping of intracellular ROS content [38]. Nrf2 and Notch signaling pathways are commonly mutated in cancers. Mutant Nrf2 and Notch mutual crosstalk in lung tissue cells is considered as an important mechanism for carcinogenesis [39].

Spheroid culture of ovarian cancer cells provides formation of stem cell-like cells by obtaining stem cell features through positive-feedback regulation loop. Nrf2 is responsible for optimum ROS levels which are essential for self-renewal activity. Cytoplasmic and nuclear Nrf2 protein levels indicates intense elevation in ovarian cancer spheroids independent of mRNA level to regulate autophagy activity for stimulating self-renewal and preserving the quiescence of ovarian cancer spheroid cells with stem cell-like characteristics [40]. CD44 is considered as a CSC marker which is associated with high expression level of Nrf2. CD44 modulates Nrf2 activation through expression of p62 in breast CSCs to establish stem cell properties [41,42].

5. Nrf2 role in stemness and self-renewal of CSCs

The self-renewal capability in CSCs is mainly related to upregulated expression of antioxidant enzymes, drug transporters, cell cycle quiescence, and enhanced DNA repair capacity [43]. ROS plays a significant role in stem cell maintenance by promoting redox status to maintain cellular quiescence self-renewal ability [19]. ROS are produced through intracellular (mainly mitochondria) and/or extracellular sources. Interaction of ROS and antioxidant system activity results in three distinct signaling pathways for cell proliferation, apoptosis, or differentiation [8]. Redox homeostasis is reported to be an important regulatory factor for cancer stemness which is predominantly under control of NRF2 signaling. CSCs comprise low levels of endogenous ROS in comparison

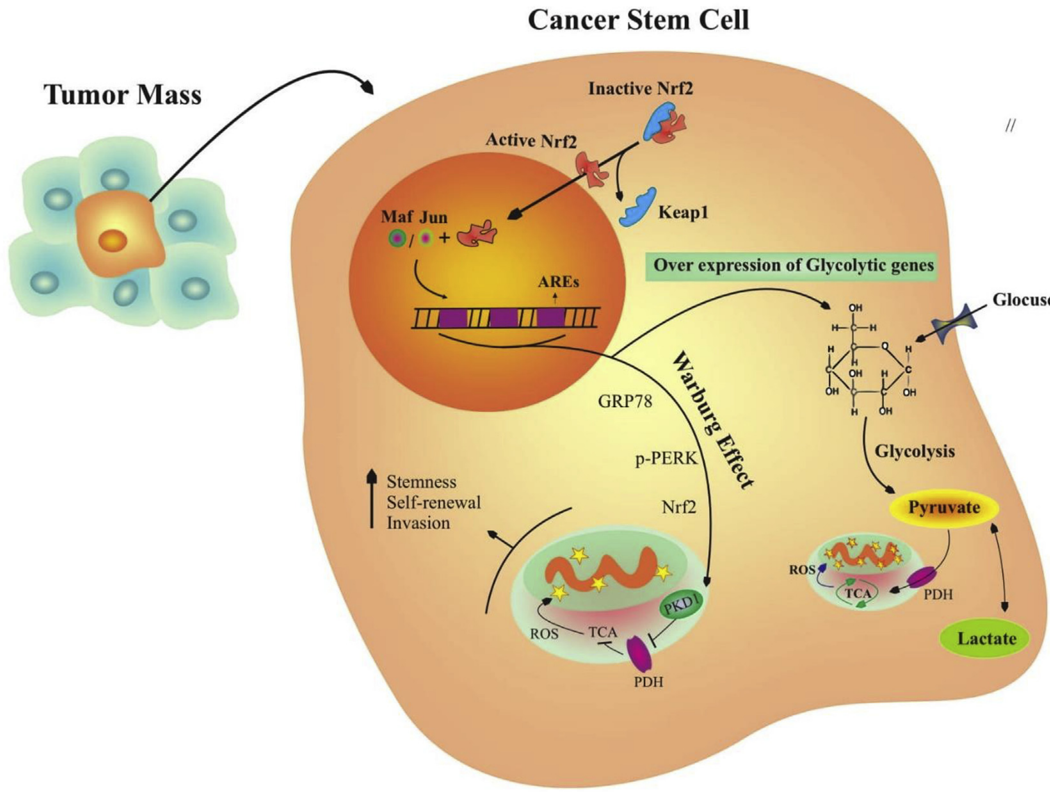

Fig. 1. Role of Nrf2 in establishment of Warburg effect through GRP78/p-PERK/NRF2 signaling pathway to maintain stemness, self-renewal ability and invasiveness for cancer stem cells (CSCs). Nrf2 activates over transcription of glycolytic genes in CSCs which results in over-production of pyruvate. Pyruvate is able to transform to lactate to make an acidic pH for tumor environment, also pyruvate may be obtaining with mitochondria by Pyruvate dehydrogenase complex (PDH) to enter tricarboxylic acid cycle (TCA). Mitochondria produces abundant amount of reactive oxygen species (ROS) during TCA which may induce CSCs damage. Therefore, CSCs utilize GRP78/p-PERK/NRF2 signaling pathway to activate PKD1 to suppress PDH activity, hence low amount of pyruvate is entered to the TCA to lower amount of ROS which is produced by mitochondria to provide more stemness and self-renewal ability, and invasion for CSCs.

to non-CSCs. Low ROS in CSCs mainly promotes stemness and tumorigenicity of the cells in contrast to high ROS CSCs [19,44] and also decreased antioxidant activity in CSC mainly reduces the proliferation ability and resistance of cancerous cells due to accumulation of oxidative insults [45]. Nrf2 activation in CSCs stimulates glycolytic genes transcription and also prevents tricarboxylic acid (TCA) cycle through activating of pyruvate dehydrogenase kinase 1 (PDK1) to provoke Warburg effect (for minimal ROS production in mitochondria) through GRP78/p-PERK/NRF2 signaling pathway which finally results in stemness maintenance of CSCs by reducing mitochondrial derived ROS (Fig. 1), [46].

Mesenchymal stem cells (MSCs) as multipotent stem cells are able to differentiate into osteoblast, chondrocyte and adipocyte. MSCs are found in tumor microenvironment which stimulate cancer growth and development by increasing the metastatic capability of cancer cells through supporting their motility and invasiveness beside playing role in formation of a metastatic niches [47,48]. Nrf2-negative-MSCs represent reduced expression of stem cell markers and subsequently lose their ability for osteogenesis. On the other hand, upregulation of Nrf2 in MSCs under oxidative stress sustains CSCs stemness by inducing expression of stem cell markers, promotes osteoblast differentiation and inhibits apoptosis [49]. Studies on bone marrow derived MSCs is indicated that Nrf2 positively regulates mRNA and protein levels of NAD-dependent deacetylase sirtuin-1 (a deacetylase which regulates metabolic activity in response to stress condition and also is able to reverse cellular senescence in aged MSCs) by negative regulation under control of p53 [50].

Nrf2 extreme overexpression in human embryonic stem cells (hESCs) is considered as a reason for self-renewal ability and maintenance of hESCs pluripotency, interestingly Nrf2 level indicates significant decrease in concentration after hESCs differentiation into the certain linages. Nrf2 is recognized as upstream controller for proteasome which controls its activity in hESCs through POMP gene expression, intracellular Nrf2 level is mutually controlled by proteasome activity which is crucial for self-renewal and pluripotency in hESCs that established a feedback between Nrf2 and the proteasome to protect against unintended loss of proteasome activity [51].

like adult stem cells, CSCs also apply similar stemness signaling pathways which are often dysregulated [52]. There is no definite Nrf2 based DNA repair mechanism in CSCs but due to a study in mouse, it is suggested that Nrf2 is able to bind to all antioxidant response elements (ARE) (5′-TGACXXXGC-3′) of 53BP1 gene in promoter region to stimulate the expression of DNA damage recognition and repair elements [53]. A list of Nrf2 targeted genes with ARE sequences is represented in Table 1.

Several tumor suppressor genes including BRCA1 are reported to participate in regulation of Nrf2 expression. BRCA1-deficient mice models revealed a significant down regulation in Nrf2-mediated antioxidant response mainly because of disability of deficient BRCA1 in binding to promoter region of NRF2 followed by marked decrease in intracellular NRF2 mRNA expression level. Moreover, BRCA1 is able to directly interact with intracellular NRF2 to stabilize this molecule. This phenomenon which is not proceeded in BRCA1-deficient mice induces low Nrf2 protein instability [73].

Also, certain set of genes are introduced as direct targets for NRF2 which are involved in Wnt, Notch, and BMP pathways in mouse embryonic fibroblasts and human lymphoid cells that may play a pivotal role in stemness establishment for malignant behavior of cells [74,75]. Aldehyde dehydrogenase 1 family member A1 (ALDH1A1) which oxidizes endogenous and exogenous aldehydes, indicates an overexpressed

Table 1
List of genes regulated by Nrf2 in normal and cancer condition in human.

Category	Function	Gene(S)	Reference
Drug De-Toxication	Drug oxidation, reduction and hydrolysis	AKR1B1, AKR1C1, ALDH3A1, CBR1, EPHX1, PTGR1, NQO1, CYP2A5, 1C2	[54–57]
	Drug conjugation and nucleophilic trapping	MGST1, SULT1A1, UGT1A1, UGT2B7, 1A6, 1A9, 2B7, MGST1	[54,55,58–60]
	Drug transport	ABCB6, ABCC2, ABCC3, MRP2	[54,55,61]
Antioxidant activity	GSH-based activity	GCLC, GCLM, GGT1, GLRX, GLS, GPX2, GSR1, SLC7A11	[54]
	TXN-based activity	PRDX1, PRDX6, SRXN1, TXN1, TXNRD1	
	Anti ROS defense	Prx1, GPx2, Prx6	[62–65]
	Redox balance	NQO1, HMOX1, TrxR, cGS, GCLc, GCLm, Gpx, GR, HO-1	[55,66]
	Regeneration of oxidized molecules	TrxR1	[67]
Metabolism	Carbohydrate and NADPH	G6PD, HDK1, ME1, PGD, TALDO1, TKT, UGDH	[54]
	Heme and iron	BLVRA, BLVRB, FECH, FTH1, FTHL12, FTHL17, FTL1, HMOX1	
	Transcription factors	MAFG, PPARG, PPARGC1B, RXRA	
	Ubiquitination	KEAP1	
	Metal-binding protein	MT1, FTL	[68,69]
Mitochondrial Signaling	Apoptosis and biogenesis	PARK7, NRF-1	[70,71]
Condition	**Function**	**Genes**	**References**
Cancer	Redox Balance	AKR1C3, FTH1, GCLC, GCLM, GSR, ME1, NQO1, PIR, PRDX1, SLC7A11, SRXN1, TXN, TXNRD1	[72]
	Response to Stress/Toxicity	AKR1C3, ASF1A, DNAJB4, EPHX1, FECH, GCLC, GCLM, GSR, GSTM3, MAFG, NQO1, PANX2, PRDX1, SLC7A11, SRXN1, TLK1, TXN, TXNRD1	
	–	ABCB6, ABCC3, ANXA10, KEAP1, NAMPT, NECAB2, SLC3A2, TKT, TMTC3, TRIM16L, ZNF746	

profile in CSCs which is considered as stemness marker. Upregulated ALDH1A1 provokes Nrf2 activation through p62-associated pathway in ALDH1-high CSC-like ovarian cancer cells which establishes chemoresistance and tumorigenicity [76]. ATRA is a cytotoxic chemotherapy drug which is able to repress ALDH1 activity. Treatment of CSC-like with high concentration of ALDH results in blocking of ALDH which subsequently suppresses ALDH-mediated Nrf2 activity in CSCs that decreases tumor growth [77]. Ovarian clear cell carcinomas represents stronger chemoresistance compared to epithelial ovarian cancer subtypes which is due to stemness feature of the cancer with regard to overexpression of ALDH1 and consequent connection to upregulation of Nrf2 [78,79].

Nrf2 signals are reported to increase the proliferation of U251 and U87 glioblastoma cell lines [80]. Nrf-2 upregulation is obsereved in cytosol and nucleus of glioma CSCs in comparison to glioma non-CSCs. MiR-153 in glioma represses self-renewal capability and drives cells into the apoptosis, but miR-153 downregulation in glioma CSCs causes overexpression of NRF2 (as a target gene) which promotes stemness in the CSCs [81]. Targeting of Nrf2 expression in glioma stem-like cells inhibits self-renewal ability [82].

6. Nrf2 mediated chemoresistance and anti-Nrf2 therapy in CSCs

CSCs are key players in tumor recurrence, they exhibit resistance to conventional anticancer therapies by induction of ROS scavenging molecules, drug transporters, and enhanced DNA repair capacity [83,84]. NRF2 is capable to induce chemoresistance in sphere-cultured of breast and colon cancer cells through upregulation of drug efflux transporters [77,85]. NRF2 level is reported to be associated with CD44-p62 signaling pathway in CD44+-high breast CSC-like cells, which modulates clinical outcome of the patients. This observation confirms participation of NRF2 in CSC-like properties improvement of stress resistance-related characteristics of CSCs [41].

Mammosphere culture of breast cancer cell lines produces CSCs. Recently it has been demonstrated that Nrf2 overexpression in mammospheres stimulates downstream target genes of Nrf2 including NQO1 and GCLM to establish chemoresistance of mammosphere to taxol, on the other hand, brusatol inactivates Nrf2 and confers CSCs with higher ROS content which are sensitive to taxol treatment [86].

Various conditions are able to cause oxidative stress against cells such as hypoxia, nutrient deficiency, radioactive injury, immune system reactions and drug-derived cytotoxicity [87–89]. The cellular anti-oxidant system continuously preserves redox hemostasis, Nrf2 as a basic redox-sensitive factor is able to stimulate cyto-protective responses against oxidative damage, inflammation, and programmed cell death by transcriptional induction of a great number of self-defense genes cooperating with phase II specific de-toxication and anti-oxidant stress enzymes [90,91]. Application of RNA interference technology against Nrf2 in glioma CSCs (in vivo and in vitro) decreased cloning efficiency of the cells through downregulated levels of pluripotency-associated transcription factors including BMI-1, Sox2 and cyclin E which resulted in inhibition of tumorigenicity and self-renewal capacity (Nrf2 knock down arrest cells in G2–M phase) [82]. CSCs frequently escape cancer treatments; it is reported that NRF2 become stable by TGF-β transcriptionally activated p21 which protects TGF-β-activated squamous cell carcinoma stem cells from cisplatin treatment through production of glutathione. Therefore, Nrf2 knockdown by shRNA restores cisplatin efficiency [78]. Overexpression of miR-153 in glioma CSCs restricts expression of NRF2 which leads to chemotherapy sensitivity that may result in apoptosis. The 153/Nrf-2/GPx1 signaling axis is the reported pathway to induce chemotherapy sensitivity [81].

Overexpression of Nrf2 in cervical CSCs is described to upregulate ABCG2 drug transporter, Bcl-2 and Bmi-1 expression causing tumor progression and resistance to therapies [92]. Disulfiram/Copper treatment on Leukemia stem cells ($CD34^+/CD38^+$) prevents proliferation, suppresses colony formation and induces apoptosis in vivo and in vitro through stress-related ROS-C-jun NH2-terminal kinase pathway by inactivation of pro-survival Nrf2 and nuclear factor-κB network [93].

Nrf2-Keap1 interaction in ovarian stem cell-like cells is considered to be responsible for platinum resistance. Platinum-based neoadjuvant chemotherapy on ovarian cancer patients resulted in decreased redox profile due to elevated expression of keap1 in cellular nucleus which blocks Nrf2 activity against cytotoxic therapy [94].

Oncogenic activity of Nrf2 (by overexpression) in different cancers is due to mutated NFE2L2 and keap1 genes. Moreover, epigenetic mechanisms and interruption of numerous proteins in binding of Keap1 and Nrf2 take role in carcinogenicity of Nrf2. Small interfering RNA molecules (siRNAs) against overexpressed Nrf2 in prostate, lung, and endometrial cancers boosted significant outcome in cancer suppressing. Keap1 overexpression and Nrf2 specific miRNAs delivery are further approaches in silencing of upregulated Nrf2 to develop better outcome for traditional therapies [95–97].

It has been recently reported that Hinokitiol, a natural bioactive compound of aromatic tropolone, attenuates expression of Nrf2 in glioma CSCs to suppress stem cell hallmarks which results in decreased self-renewal ability, migration, invasiveness and colony formation [98]. MCF-7-derived CSCs with a CD44high/CD24low profile are able to form mammospheres and demonstrate elevated expression of Nrf2. *Castanea crenata* leaf extract is also a compound which effectively reduces Nrf2 level in cytoplasm by inhibiting translocation from nucleus. Combination therapy of *Castanea crenata* leaf extract with paclitaxel dramatically increases cell death [99].

7 Conclusion

CSCs are small but significant cell population in tumor mass with effective role in tumor development and chemoresistance. CSCs show low ROS content in contrast to surrounding tumoral cells due to unique antioxidant mechanism that declines oxidative insults to inhibit fundamental damages which may suspend cells to loose stemness and force them toward apoptosis. Nrf2 as the main regulatory factor for ROS level, regulates antioxidant profile in the cells through targeting numerous set of genes and pathways including Wnt, Notch, and BMP. Nrf2 overexpression is essential for CSCs to maintains stemness as the turning point of cancer invasion, progression, and chemoresistance. Nrf2 concentration is raised at a constant rate in cancer cell lines and cancer biopsies (lung, breast, esophagus, endometrial, and prostate tumors).

Several molecular mechanisms are recognized to be involved in Nrf2 activation during cancer which are generalizable to CSCs including somatic mutations of Nrf2/Keap1, epigenetic silencing of the Keap1 expression, Nrf2/Keap1 disruptors, abnormal accumulation of proteins which compete Nrf2 for binding of Keap1, stress signaling, Nrf2 mRNA processing, hormonal activation and oncogene-mediated overexpression of Nrf2 [19,100].

Self-renewal ability is the direct result of stemness which protects cells against exposure to chemo- and radio-therapies. Traditional therapies target cellular metabolism and force malignant cells into the apoptosis, but over expression of Nrf2 overcomes internal stress condition through various pathways including autophagy. Therefore, redox status of malignant cells is a critical point in cancer therapies. A line of evidence has introduced NRF2 pathway as a driver of cancer progression, cancer dissemination, and cancer chemoresistance to therapies. Nrf2 regulates the expression pattern of proteins which are known to control cell growth, proliferation and the characteristics which are shared by oncogenes. However, considering of an oncogenic role for Nrf2 still is a debate because Nrf2 transient expression in cells is a key factor to overcome chemical carcinogenesis [101]. However, Nrf2 activators are considered as anti-cancer agents but over-expression of Nrf2 is reported to induce chemoresistance in tumor cells [102]. Novel approaches target tumors with traditional drugs in combination with anti-Nrf2 compounds to maximize the oxidative insults to force cell death. As a result, anti- Nrf2 therapies in cancers can be considered as a promising approach to overcome cancer.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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