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Redox control in cancer development and progression

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ABSTRACT

Cancer is the leading cause of death worldwide after cardiovascular diseases. This has been the case for the last few decades despite there being an increase in the number of cancer treatments. One reason for the apparent lack of drug effectiveness might be, at least in part, due to unspecificity for tumors; which often leads to substantial side effects. One way to improve the treatment of cancer is to increase the specificity of the treatment in accordance with the concept of individualized medicine. This will help to prevent further progression of an existing cancer or even to reduce the tumor burden. Alternatively it would be much more attractive and efficient to prevent the development of cancer in the first place. Therefore, it is important to understand the risk factors and the mechanisms of carcinogenesis in detail. One such risk factor, often associated with tumorigenesis and tumor progression, is an increased abundance of reactive oxygen species (ROS) arising from an imbalance of ROS-producing and -eliminating components. A surplus of ROS can induce oxidative damage of macromolecules including proteins, lipids and DNA. In contrast, ROS are essential for an adequate signal transduction and are known to regulate crucial cellular processes like cellular quiescence, differentiation and even apoptosis. Therefore, regulated ROS-formation at physiological levels can inhibit tumor formation and progression. With this review we provide an overview on the current knowledge of redox control in cancer development and progression.

Introduction

According to the World Health Organization (WHO), cancer burden and cancer-related death will rise by 70% within the next two decades (World Health Organization). Cancer is a hyper-proliferative and complex disease which arises from a multistep process called carcinogenesis in which the initiation phase is followed by a promotion and a progression phase (Berenblum and Shubik, 1947). The initial step is induced by an accumulation of unrepaired genomic mutations or epigenetic modifications such as DNA methylation or histone acetylation (Franco et al., 2008). Mutations, which initiate cancer, can develop spontaneously through replication defects (W. H. Freeman, 2000) or chemical and physical carcinogens, which are able to facilitate the production of reactive oxygen species (ROS). An uncontrolled increase of ROS formation can induce damage of macromolecules including DNA, proteins and lipids resulting in genomic instability and changes in cell growth. ROS can modulate cell cycle progression by influencing the activity of proteins such as cyclin-dependent kinase inhibitor p21 (Barnouin et al., 2002) or the serine/threonine protein kinase *ataxia telangiectasis mutated* (ATM) (He et al., 2011). ATM, in turn, is essential for DNA repair and influences cellular signaling important for proliferation and apoptosis such as the Akt (Halaby et al., 2008) or p53 pathway (Cheng and Chen, 2010).

Despite the obvious influence of ROS on cancer development and progression, treatment of cancer patients with antioxidants failed to improve and, in some cases, even impaired the outcome of the disease (DeNicola et al., 2011). Additionally, it is extremely important to distinguish between progression of an existing tumor and the formation of a new tumor when discussing the role of ROS in cancer. In fact, it appears that ROS play a dual role: increased ROS-levels can result in DNA damage and thereby lead to malignant transformation, whereas physiological levels seem to be essential for the prevention of cancer formation.

With this review we aim to provide an overview on how ROS influence cancer development and progression.

Sources of reactive oxygen species and anti-oxidative systems

Quantitatively, mitochondria generate the highest level of ROS (Holmström and Finkel, 2014). In the course of ATP generation by these organelles, superoxide anions ($\bullet O_2^-$) are produced as a byproduct, depending on the electron load and efficacy of the individual complexes of the respiratory chain. Besides mitochondria, many enzymes exist that produce ROS. Those are, namely, xanthine oxidase, cytochrome P450

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monooxygenases, cyclooxygenase and NADPH oxidases (Nox). Among them the family of NADPH oxidase is the only one having ROS formation as its sole function. The family of Nox enzymes consists of 7 members, Nox1-Nox5 and Duox1/2. Those 7 members; all of which produce ROS at distinct sites in the cell and are specialized to produce certain kinds of ROS. While Nox1-3 and 5 produce $\bullet O_2^-$, Nox4 directly forms hydrogen peroxide (H_2O_2) as well as the Duoxes (Deken et al., 2014; Schröder, 2010). This mixed bunch of ROS producing enzymes implies that ROS, depending on their species and site of formation, fulfill useful tasks, such as serving as second messengers.

Besides a more or less controlled physiological ROS formation, exogenous stimuli contribute to an increased ROS production in stress conditions and in the course of host defense. For example; UV radiation increases the amount of mitochondria derived $\bullet O_2^-$ (Yamamori et al., 2012) and pattern recognition patterns on pathogens induce Nox2 derived $\bullet O_2^-$ production and the oxidative burst in phagocytic cells (Torres et al., 2006).

ROS themselves are a group of oxygen derivatives, produced by the partial reduction of oxygen (Ray et al., 2012). Depending on their site of production and surrounding environment, the produced ROS can interact with each other and various other molecules (Fig. 1). Some ROS e.g. H_2O_2, are relatively stable and can diffuse within and between cells (Bienert et al., 2006). Additionally a transport via aquaporins has been described for H_2O_2 (Hara-Chikuma et al., 2015). Other reaction products such as $\bullet O_2^-$ or hydroxyl radicals (•OH) hold one unpaired electron, which limits their diffusion across cell membranes. These free radicals are relatively unstable and highly reactive, resulting in their potential harmful characteristics. One of the best characterized reactions of $\bullet O_2^-$ is the reaction with nitric oxide (•NO) derived from NO-Synthases (NOS). The subsequently formed peroxynitrite ($ONOO^-$) oxidizes tetrahydrobiopterin, the cofactor of endothelial nitric oxide synthase. Consequently, NOS is uncoupled which favors the production of $\bullet O_2^-$ by this enzyme (Harrison et al., 2010). In the Haber-Weiss reaction, catalyzed by free transition metal ions, the H_2O_2 and $\bullet O_2^-$ are reduced to •OH which has the highest oxidative potential (Manea, 2010).

The potential harm induced by ROS is prevented by their tightly controlled and highly efficient degradation. $\bullet O_2^-$ is processed into H_2O_2 either spontaneously or enzymatically catalyzed by superoxide dismutase (SODs: soluble Copper/Zinc-SOD (SOD1), mitochondrial Manganese-SOD (SOD2) and extracellular Copper/Zinc-SOD (SOD3)). H_2O_2 is further decomposed by catalase or glutathione peroxidase (GPX) that oxidizes glutathione (GSH) which is reduced back by glutathione reductase under NADPH consumption (Brigelius-Flohé and Maiorino, 2013). Peroxiredoxins (Prx) reduce H_2O_2 to water using NADPH, thereby becoming oxidized themselves (Rhee et al., 2012). Thioredoxins (TRX) facilitate the reduction of oxidized Prx (Fig. 1). In addition to the enzymatic systems, there exist non-enzymatic compounds (so called anti-oxidants) such as α-Tocopherol, ascorbate and lipoic acid that undergo oxidation when reacting with the substrate.

Regulation of gene expression in cancer

Normal somatic cells strongly differ with regards to their metabolic demand, motility and proliferative capacity amongst many other cellular functions. Cancer cells can boost their anti-apoptotic mechanisms to evade cell death by activating a specialized gene expression profile. Accordingly, those cancer gene profiles differ from the ones of the originating or precursor cells. The following section will highlight some redox-sensitive mechanisms related to gene expression.

Redox-sensitive transcription factors in cancer

One important transcription factor in cancer is hypoxia-inducible-factor-1α (Hif-1α). Hif1α is constantly produced and immediately degraded by the proteasome. Elevated levels of ROS in prostate and ovarian cancer cells maintain Hif-1α and the expression of its major downstream target vascular endothelial growth factor (VEGF) (Xia et al., 2007). Although it remains uncertain how ROS regulate Hif1α activity, Nox4 is a potential candidate for keeping Hif1α abundance stable (Zhang et al., 2010). An increase in the Hif1α/VEGF axis enables more efficient angiogenesis in an existing tumor, such as a fibro sarcoma (Helfinger et al., 2016).

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA, cytokine production and cell survival. NF-κB is a transcription factor which becomes activated upon dissociation from its inhibitor IκB, which is then degraded through the proteasome. Prevention of NF-κB activation by the proteasome inhibitor bortezomib induces apoptosis in gastric cancer cells and simultaneously induces ROS generation (Nakata et al., 2011). Activation of NF-κB in turn can be facilitated in a redox dependent manner via pyruvate dehydrogenase kinase 1 (PDK1). By that mechanism epithelial growth factor receptor (EGFR) facilitates proproliferative effects, which forces the formation of pancreatic precancerous lesions in a KRas mouse model (Liou et al., 2016). Nox4 is described to contribute to NF-κB activation in melanoma cells, thus combating apoptosis and promoting cancer development (Fried and Arbiser, 2008). In addition to cell survival/proliferation, invasion can also be affected by NF-κB. Bonner et al. demonstrated that Nox1-derived ROS contribute to cancer cell invasion by increasing NF-κB translocation into the nucleus and subsequent expression of the matrix metalloprotease-9 (MMP-9) (Bonner and Arbiser, 2012).

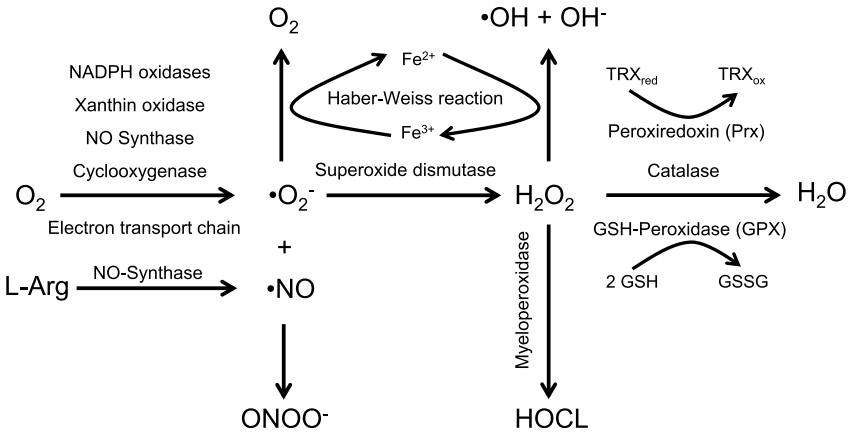

Fig. 1. Sources of reactive oxygen species and their conversion.
The figure shows endogenous and exogenous sources of various reactive oxygen species and their possible interaction partners or conversion. Additionally antioxidant systems and the Haber Weiss reaction are introduced. Details of the figure are listed and explained in the text.

ROS also influence the activation and synthesis of activator protein 1 (AP-1), another complex transcription factor that regulates proliferation, apoptosis and invasion. AP-1 is activated via JNK and MAP kinases including ERK1/2 and p38 (Chang and Karin, 2001). H_2O_2 induces AP-1 activity in a JNK/MAPK-dependent manner resulting in MMP-7 upregulation and metastasis in human colon cancer cells (Ho et al., 2011). Activated AP-1 is further responsible for increased cell proliferation due to its enhanced expression of growth-stimulatory genes including cyclin D1 and its simultaneously suppression of the cell cycle inhibitor p21 (Klaunig et al., 2010).

Redox regulation of p53 transcription factor represents a major regulatory mechanism for cell survival and apoptosis (Kim et al., 2011). ROS are capable of directly inactivating p53 by oxidation of cysteines in the DNA-binding domain (Méplan et al., 2000). Although these data appear to be explicit, others found conflicting data. For example, excessive formation of mitochondrial ROS, induced by chemotherapeutic agents, has been claimed to promote apoptosis in a p53-dependent manner (Chen et al., 2007; Hwang et al., 2001). ROS formation induced by ionizing radiation in radiotherapy of head and neck squamous cell carcinoma (HNSCC) lead to activation of p53 and subsequently an increased transcription of $p21^{cip1/waf1}$. Ultimately, senescence of the cancer cells is induced, thereby improving the survival of patients (Fitzgerald et al., 2015). Furthermore, high nuclear ROS levels contributed to a p53-dependent DNA repair which in turn diminished further malignant transformation (Ueno et al., 1999). An interesting hypothesis predicts that constitutive oxidative stress favors a selection of cell clones deficient in p53 and resistant to apoptosis, resulting in the formation of a tumor (Storz, 2005). Whether or not activation of p53 in those studies is a direct consequence of a redox modification of p53 or simply a consequence of general cell stress remains a point of discussion. When p53 is mutated or lost, as observed in more than 50% of human cancers, ROS accumulate and induce a pro-tumorigenic phenotype and cellular transformation (Levine and Oren, 2009). This effect, may be explained by the fact, that p53 increases the expression of antioxidant genes such as GPX1, catalase and SOD2, thereby suppressing ROS accumulation (Kruiswijk et al., 2015). Furthermore, the ability of p53 to maintain mitochondrial integrity and health, limits ROS generation and tumor development (Wang et al., 2014). Others found that ROS may be induced by the absence of p53 in an NF-κB or Nox4 dependent manner (Boudreau et al., 2017; Komarova et al., 2005).

Nrf2 (erythroid-derived 2-like 2) is the major driver of redox sensitive gene expression. Its activity is regulated by the cytosolic inhibitor Keap1 which favors its proteasomal degradation. ROS oxidize KEAP1 at redox-sensitive cysteine residues, disrupting the association of KEAP1 and Nrf2 and thereby stabilizing Nrf2 (Fourquet et al., 2010). Translocation of Nrf2 into the nucleus induces the expression of genes associated with an anti-oxidative defense, including GPX, Prx, catalase and phase II detoxification enzymes. Through this mechanism Nrf2 prevents cancer initiation by counteracting oxidative stress and exerting cyto-protective effects (Kumar et al., 2014). As a result of maintaining ROS balance Nrf2 prevents ROS-mediated activation of apoptosis-inducing JNK/p38 signaling cascades and thereby positively regulates tumor cell proliferation and tumorigenicity (Satoh et al., 2013). Moreover, suppression of Nrf2 inhibits tumor progression and enhances the response to chemo- or radiotherapy in a ROS-dependent manner (Singh et al., 2008; Tao et al., 2014). Oncogenes such as KRas, Braf and Myc increase the expression of Nrf2 activity, which increases the expression of the oxidative defense program and thereby reduces the intracellular ROS content. Nevertheless, the cells overexpressing these oncogenes are cancer cells, indicating a pro-tumorigenic effect of Nrf2 (DeNicola et al., 2011). In contrast, the tumor suppressor BRCA1 (breast cancer 1, early-onset) promotes the stability of Nrf2 and its anti-oxidative signaling in normal mouse primary mammary epithelial cells (Gorrini et al., 2013). These data indicate a dual role of Nrf2. It is stabilized in somatic cells to maintain their survival and normal function, while its over-activation in a tumor cell results in uncontrolled proliferation and survival.

Redox control of epigenetic modifications

Apart from transcription factor activation, changes in the expression of oncogenes or tumor suppressor genes are achieved by epigenetic alterations. Those epigenetic modifications include methylation or acetylation in the promoter regions of several genes. This is facilitated by acetyl- and methyltransferases as well as their counterparts, acetylases and demethylases respectively. In order to reduce complexity, this paragraph only scratches the tip of the iceberg focusing on methylation as an example of cancer related epigenetic modification. The interested reader is referred to specialized reviews of excellent quality for further reading.

Activation of protein kinase C (PKC) by the phorbol ester TPA can increase Nox2 activity and subsequent ROS formation in breast cancer MCF7 cells. Those ROS may increase histone H3 acetylation of the slug promoter region and induction of slug expression. Slug and snail are key transcription factors in the epithelial-mesenchymal transition (EMT) and their expression favors cell proliferation and migration (Kamiya et al., 2016). In line with this finding of a ROS induced EMT and migration it has been shown, that H_2O_2 downregulates the expression of the adhesion molecule E-cadherin in hepatocellular carcinoma cells. This is a consequence of a hypermethylation of the E-cadherin promotor, mediated by a snail-dependent recruitment of histone deacetylase 1 (HDAC1) and DNA methyltransferase 1 (DNMT1) (Lim et al., 2008). Additionally, metal compounds including nickel induce an E-cadherin promoter hypermethylation accompanied by an increase in ROS formation (Wu et al., 2012). ROS increase the expression of DNMT1 and HDAC1. In the human colorectal cancer cell line SNU-407 DNMT1 binds to HDAC1 which increases the binding of HDAC1 to the promotor of the tumor suppressor RUNX3 (runt related transcription factor 3). Consequently, the promotor is hypermethylated and expression of RUNX3 mRNA and protein is reduced (Kang et al., 2012). How ROS facilitate the upregulation of DNMTs or HDACs is illusive. However, in a model of long-term exposure of human bronchial epithelial cells (BEAS-2B) to fine particulate matter (PM2.5) an increase in ROS formation activates Akt which forces DNMT3B expression (Zhou et al., 2016).

DNA oxidation itself may also contribute to alterations in histone methylation. 8-hydroxy-2′-deoxyguanosine (8-OHdG) induces a switch in methylation from an active to a more suppressive state. This in turn leads to abnormal methylation of tumor suppressor genes resulting in their inactivation in human hepatocarcinogenesis (Nishida et al., 2013). Mono, di, and tri methylations of histones have very distinct distributions and functions. As an example H3K9me1 is enriched at the transcriptional start site of active genes while H3K9me2/3 were both found more often at silenced genes (Barski et al., 2007). Demethylation of H3K9me2 by LSD1 (histone lysine-specific demethylase 1) is an oxidative process that results in the production of H_2O_2, enabling the oxidation of nearby deoxyguanidine (dG) nucleobases. One mechanism preventing this effect is facilitated by base excision repair enzyme (BER) such as 8-oxo-guanine–DNA glycosylase 1 (OGG1) that can remove the 8-OHdG (Li et al., 2013).

Besides hypermethylation of histones DNA oxidation often results in DNA hypomethylation. Two pathways can be distinguished: 8-OHdG, can induce DNA hypomethylation by inhibiting DNA methylation at nearby cytosine bases, while 5-hydroxymethylcytosine (5hmC), may achieve active DNA demethylation processes (Wu and Ni, 2015). 5hmC is formed by a reaction mediated by the Tet family of enzymes (Ten-eleven translocation methylcytosine dioxygenase) (Ito et al., 2011). Global DNA hypomethylation is considered to induce genomic activation of oncogenes (Feinberg and Tycko, 2004) whereas promoter CpG island hypermethylation causes tumor suppressor gene silencing (Esteller, 2007). Both seem to occur as early events in carcinogenesis

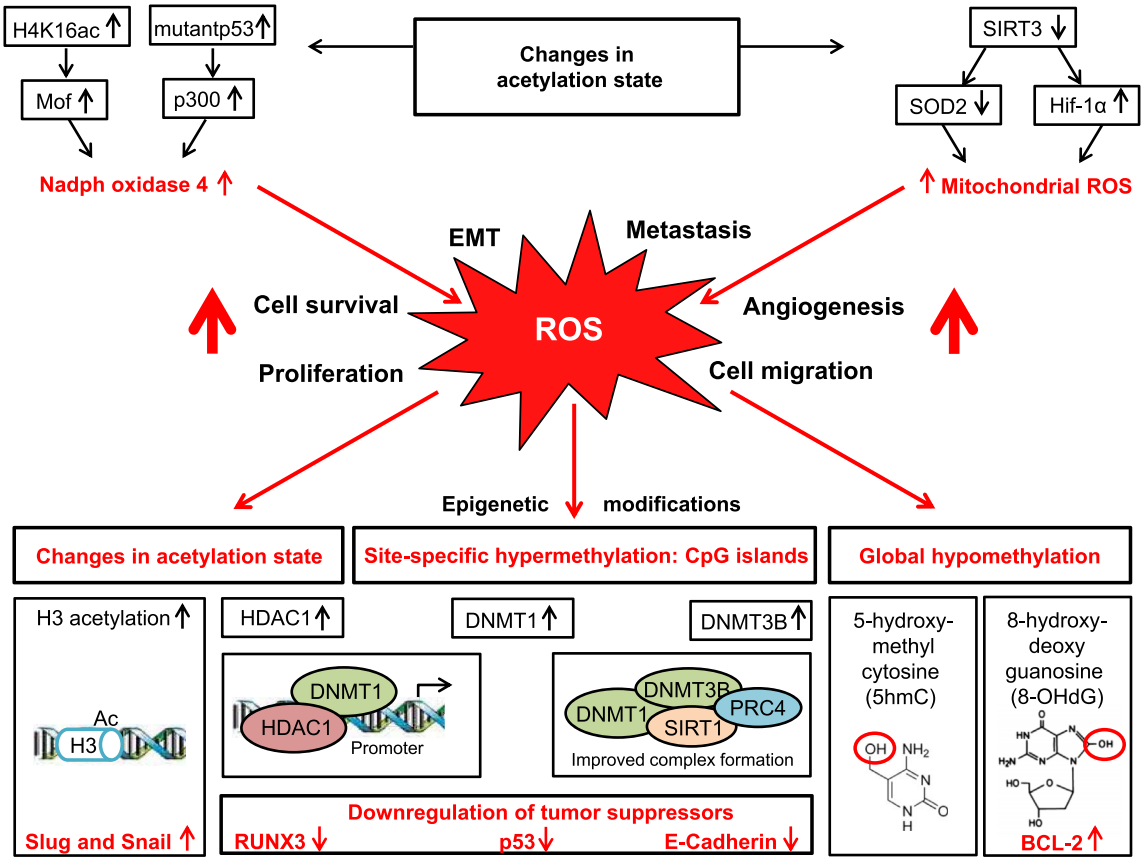

Fig. 2. Epigenetic modifications and their relation to ROS.
ROS can influence various epigenetic modifications thereby regulating tumor suppressor genes or oncogenes. ROS induce aberrant histone hypermethylation by increasing the expression or recruitment and complex formation of DNA methyltransferase DNMT1 and histone deacetylase 1 HDAC1 with different proteins. As a result, several genes usually inhibiting tumorigenesis are downregulated. The DNA oxidation structure, 8-OHdG, promotes global DNA hypomethylation by inhibiting DNA methylation at nearby cytosine bases. Another oxidation structure, 5hmC causes DNA hypomethylation through the regulation of DNA demethylation processes. Likewise epigenetic alterations influence ROS accumulation by influencing the expression of various genes including histone acetyltransferase Mof or the deacetylase Sirt3, causing accumulation of ROS.

leading to malignant transformation and are in addition, implicated in the progression of various cancers. (Fig. 2).

Likewise, epigenetic alterations can influence ROS accumulation. The study of Boudreau et al. mentioned in the paragraph above shows intriguing results in support of this. TGF-β/SMAD3 induced Nox4 promotor activity in human lung and breast epithelial cells which is mediated by overexpression of p300, a transcriptional co-regulator and histone acetyltransferase. The subsequent histone acetylation within the Nox4 promoter is enhanced by overexpression of a mut-p53 (R175H or R280K) (Boudreau et al., 2017). Another study revealed acetylation at the activating histone mark H4K16ac in the Nox4 gene leading to increased expression of Nox4 and senescence in lung fibroblasts. Silencing of the histone acetyltransferase Mof, specifically acetylating H4K16, downregulates Nox4 expression and reduces senescence (Sanders et al., 2015). On the side of oxidative defense, the mitochondrial deacetylase sirtuin3 (SIRT3) deacetylates and reduces the activity of SOD2 (Tao et al., 2010). Other studies showed that SIRT3 overexpression suppresses the activity of Hif-1α in mouse embryonic fibroblasts and tumor formation in a xenograft model (Bell et al., 2011).

Epigenetic modifications and their influence on tumorigenesis and cancer progression is a highly active field of research. We already learned a lot and new techniques will further increase our knowledge, hopefully leading to the development of innovative and highly efficient therapies in the future.

ROS induced signaling in tumor progression

Differentiation and cellular quiescence, as well as an adequate induction of apoptosis upon cellular damage, are the main components for the prevention of malignant deterioration of cells. Reactive oxygen species are able to modulate the activity of various proteins or intracellular signal transduction pathways regulating cell differentiation and proliferation. Redox sensitive components important for differentiation and proliferation include phosphatases and kinases (Duhé, 2013; Groitl and Jakob, 2014; Ostman et al., 2011; Surh et al., 2005). The idea is that ROS transiently modify the activity of phosphatases which will increase or decrease the prolongation of phosphorylation of e.g. MAPKinases. Alternatively, kinases may be oxidized which transiently induces a conformational change allowing an altered activity or binding of further molecules. These events will impact the subsequent outcome of cytokine or growth factor induced signal transduction. In the context of cancer, this means, that depending on their species, concentration and site of action ROS may be protective or detrimental for tumor progression. As pointed out above $\bullet O_2^-$ due to its aggressive nature will be rather detrimental and destroy macromolecules or even proteins while H_2O_2 appears to be prone to regulating protein activities in a transient manner as long as its abundance is in a physiological range. Overwhelming, ROS formation will always be detrimental and has nothing to do with modification of signal transduction. Consequently, the role of ROS has been discussed controversially in the context of cancer. Most studies claim a pro-tumorigenic role for ROS as they can induce oxidative stress but the number of studies showing a tumor-protective role of ROS has increased. This is particularly true for H_2O_2, as it fulfills the important task of a signaling molecule. Nevertheless, it appears that when it comes to ROS and cancer, everything is a matter of redox balance.

ROS signaling in promoting tumorigenicity of existing tumor cells

In an existing tumor there are several signaling pathways implicated in promoting cancer cell proliferation. Oxidation-induced inactivation of phosphatases is one aspect of how ROS regulate signaling pathways. By oxidizing cysteines in the active center ROS can transiently inhibit the phosphatase and tensin homolog (PTEN) and protein tyrosine phosphatase 1B (PTP1B) both of which are negative regulators of the pro-proliferative PI3K/Akt signaling (Lee et al., 2002; Salmeen et al., 2003). In fact, PTEN is a known tumor suppressor and is inactivated in numerous cancers including glioblastoma, melanoma, breast and prostate cancer (Wu et al., 2003). Its inactivation results in an increased formation of phosphatidylinositol (3, 4, 5) triphosphate by the PI3K. Consequently, Akt phosphorylation and subsequently cell proliferation increases. Oxidative inactivation of PTEN is a consequence of Nox1-derived ROS formation, as knockout of Nox1 attenuated its inactivation (Cui et al., 2011). The low molecular weight-protein tyrosine phosphatase (LMW-PTP) dephosphorylates the anti-apoptotic janus kinase JAK2. In pancreatic cancer cells this phosphatase can be oxidized by Nox4 derived ROS which leads to its inactivation and sustained JAK2 phosphorylation which eventually results in suppression of apoptosis (Lee et al., 2007). In these cells, an additional mode of action has been shown for ROS generated by Nox4. This NADPH oxidase transmits cell survival signals through the Akt-ASK1 (apoptosis signal-regulating kinase) – axis whereas depletion or inhibition of Nox4 results in apoptosis (Mochizuki et al., 2006). Nox4-induced Akt activation not only facilitates survival but also serves as a molecular switch which promotes an invasive phenotype in melanoma cells (Govindarajan et al., 2007). As well as facilitating proliferation, ROS mediated hyperactivation of the PI3K/Akt signaling is also implicated in apoptosis inhibition, promotion of tumor cell survival and resistance of tumor cells to chemotherapy.

ROS also oxidize and inactivate MAPK phosphatases, inducing the MAPK (p38, JNK, ERK1/2) pathway leading to tumor cell proliferation and cancer progression (Seth and Rudolph, 2006). A loss of the MAPK phosphatase MKP3 due to ROS-mediated proteasomal degradation leads to aberrant ERK1/2 activation and promotes tumorigenicity and chemoresistance of human ovarian cancer cells (Chan et al., 2008). Stimuli such as insulin-like growth factor-I and 17β-estradiol increase intracellular ROS formation in breast cancer cells. In these cells ROS facilitate the phosphorylation of ERK and JNK and thereby increase proliferation (Lin et al., 2007). An elevated ROS formation due to mitochondrial dysfunction also promotes cancer progression (Hu et al., 2012).

In addition to ROS- induced transient inhibition of phosphatases; ROS are capable to directly oxidize kinases, including the protein tyrosine kinase Src. Oxidation activates this kinase thereby enhancing invasion potential, serum- and anchorage-independent growth and tumor onset of NIH3T3 cells (Giannoni et al., 2005). Mitochondrial ROS also augment metastatic potential of tumor cells. In an intriguing study, Porporato et al. showed two different events: electron transport chain (ETC) overload and partial ETC inhibition as being responsible for an enhanced superoxide production. This superoxide anion production activated the protein tyrosine kinases Src and Pyk2; both contributing to cell migration and spontaneous tumor metastasis in murine and human tumor models (Porporato et al., 2014) (Fig. 3).

In summary ROS appear to induce numerous pathways leading to proliferation and survival of existing tumor cells.

Anti-tumorigenic ROS signaling

ROS not only favor tumor development but can also induce cancer cell death, cell cycle arrest and senescence. A study using melanoma cell lines and investigating tumor cell migration provides evidence, that ROS may prevent “amoeboid” invasion of melanoma cells and thereby metastasis formation in nude mice (Herraiz et al., 2016). Moreover, low levels of ROS are needed to prevent cancer initiation. Recently data indicating a protective role of ROS in tumor progression by existing tumor cells has accumulated. In human liver tumor cells a stable knockdown of Nox4 results in an elevated proliferative capacity of the cells as its absence increases nuclear β-catenin and cyclin D1 protein level. An effect that holds true *in vitro* as well as in an *in vivo* xenograft mouse model (Crosas-Molist et al., 2014). In a subsequent study from this group the protective role of Nox4 was strengthened. Loss of Nox4 leads to an increase in actomyosin and loss of E-cadherin, thereby promoting EMT and tumor aggressiveness (Crosas-Molist et al., 2017) (Fig. 5).

Many signaling pathways are described to, not only induce survival of established cancer cells in a ROS-dependent manner, but to simultaneously degrade malignant cells by apoptosis or autophagy. Brucein D, an apoptosis inducing agent, was shown to trigger the activation of Nox, thus generating superoxide. The increased amount of ROS induced apoptosis in pancreatic cancer cells by stimulating the p38 signaling cascade (Lau et al., 2010). The same holds true for immortalized MEFs and the human cancer cell lines DU145 and HT-29. In response to ROS-inducing oncogenes such as UV-light or cisplatin, apoptosis was initiated in a p38-dependent manner (Dolado et al., 2007). A potential mechanism for this phenomenon is the activation of ASK1. This kinase is associated with the reduced form of thioredoxin (TRX). Upon oxidation of TRX, ASK1 dissociates and is activated which in turn triggers the phosphorylation of p38 and JNK and augments the intrinsic pathway of apoptosis (Tobiume et al., 2001). Interestingly, TGFβ is a strong inducer of Nox4 expression and apoptosis. In fact NOX4 mediated increase in ROS formation following TGF-β stimulation induced apoptosis in endothelial cells (Yan et al., 2014). Further TGFβ-induced senescence is also mediated by Nox4 (Desai et al.). Although Nox4 induced apoptosis and senescence so far have been only demonstrated in healthy rather than malignant cells, it is likely, that this effect applies to cancer cells as well. Although Nox4 limits life span of cells, this may not hold true for whole organisms (Rezende et al., 2017).

Autophagy has been reported to reduce the efficacy of chemotherapy in various disease models. Inhibition of the EGF receptor by erlotinib increases Nox4 derived H_2O_2 formation and mediates autophagy in head and neck cancer cells (Sobhakumari et al., 2013). Whether or not the effect of erlotinib is due to a reduced suppression of Nox4 expression remains unclear in that study. However, when considering the growth inhibitory effect of an increased Nox4 expression it appears likely, that a reduced expression of Nox4 may contribute to an increase in proliferation in situations with overactive EGF signaling. However, whether or not autophagy is ROS sensitive per se, appears to be doubtless. ROS can influence autophagy, by inhibiting a negative regulator of autophagy: the serine/threonine kinase, mammalian target of rapamycin (mTOR). In response to increased levels of H_2O_2, ATM activates the TSC2 tumor suppressor by influencing the LKB1/AMPK metabolic pathway to repress mTOR activity (Alexander et al., 2010). Moreover in C6 glioma cells H_2O_2 inhibits mTOR activity via Bcl-2/E1B 19 kDa interacting protein 3 (BNIP3) (Byun et al., 2009). The reduced mTOR activity results in autophagy induction and cancer cell death.

Necroptosis is an additional ROS dependent process that reduces the survival of tumor cells. Mitochondrial ROS in particular induce necroptosis. These are induced by ceramides or RIP3-agonists and potentially occur due to an augmented energy metabolism (Ardestani et al., 2013; Zhang et al., 2009). Mitochondria are a major source of ROS production in Smac mimetic induced necroptosis as well (Rohde et al., 2017). Besides hyperpolarization and disruption of the mitochondrial membrane potential as described by Rhode et al., the activation of dynamin-related protein 1 (Drp1) appears to be a major step in TNFα-induced necroptosis. TNFα induces the assembly of the riboflavin kinase (RFK) with Nox1, facilitating Nox1 dependent ROS generation and mitochondrial fragmentation (Yazdanpanah et al., 2009). This confirms the theory of ROS induced ROS formation. Increased ROS levels, as observed in cancer cells, can either be achieved by elevated ROS production or diminished ROS scavenging. Details on this aspect

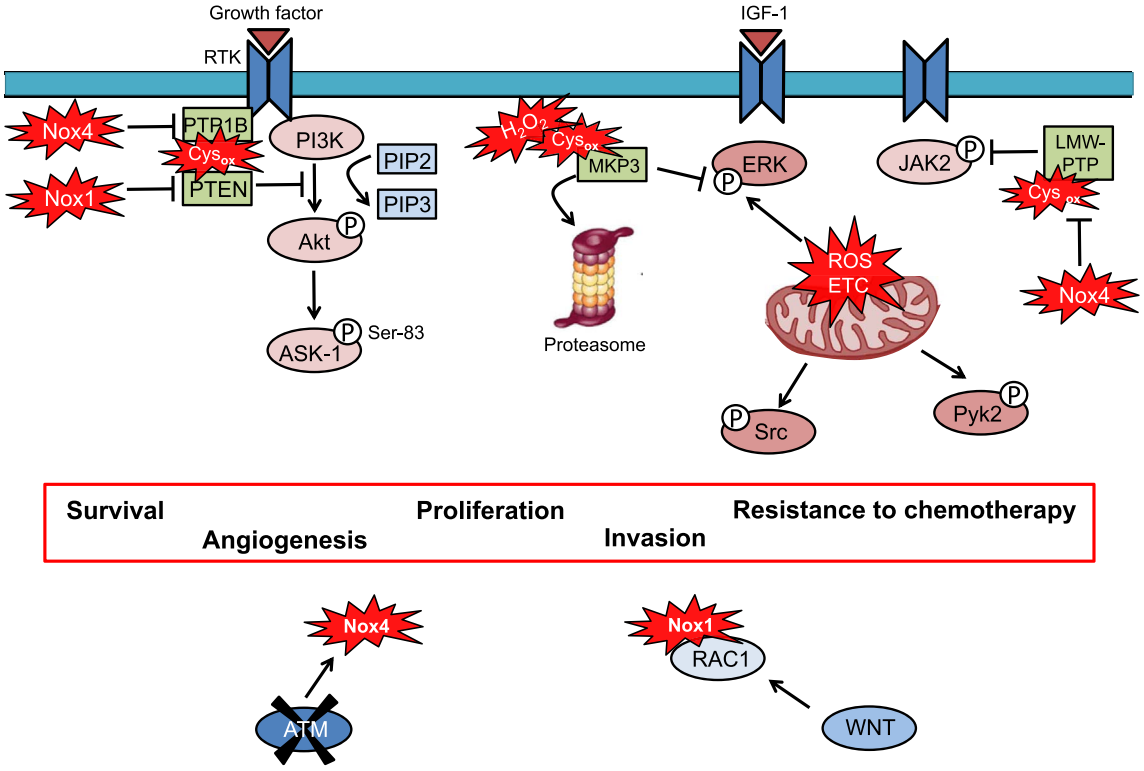

Fig. 3. Redox dependent pathways that favor carcinogenesis.
ROS regulate a number of signaling pathways that favor carcinogenesis including pro-proliferative and anti-apoptotic pathways. The oxidative inactivation of phosphatases like PTEN and PTPB1, promotes a sustained and prolonged activation of pro-proliferative pathways e.g. Akt. Oxidation of MKP3, a phosphatase regulating MAPK pathway, leads to aberrant ERK1/2 signaling and subsequently to chemotherapy resistance. Inactivation of the LMW-PTP by Nox4 facilitates downstream signaling of JAK2 thereby inhibiting apoptosis. Direct oxidation of kinases including Src and Pyk2 fuels migration and invasion.

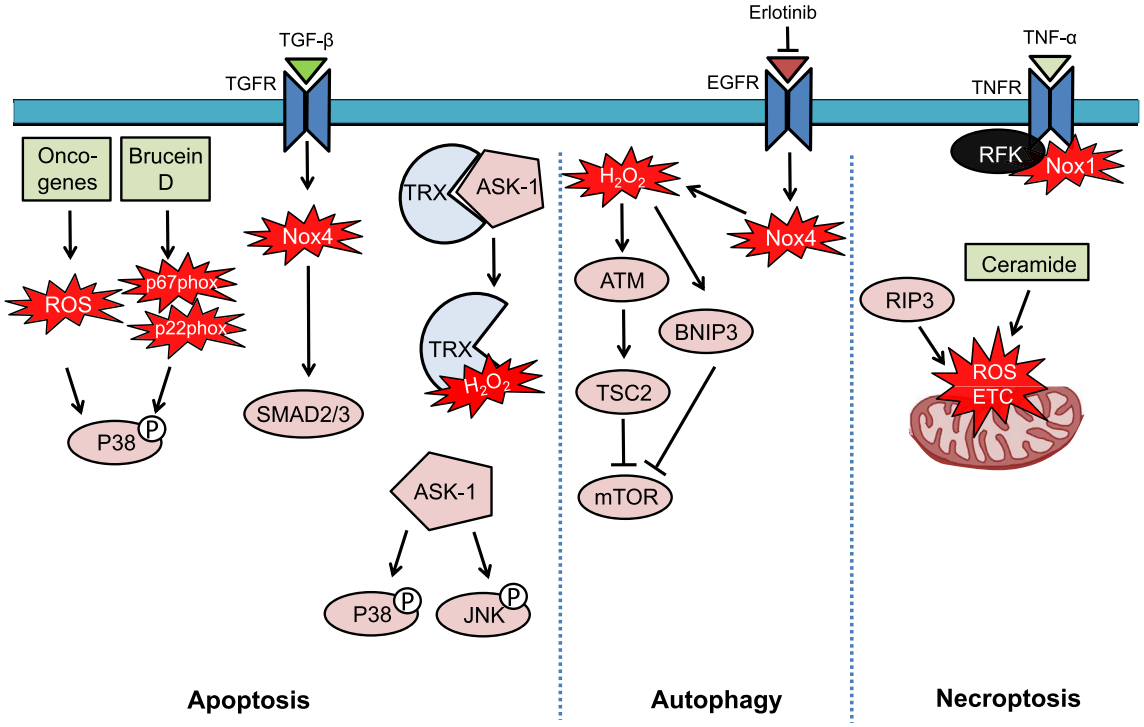

Fig. 4. Redox dependent pathways that inhibit carcinogenesis.
ROS, especially low levels of ROS are important to prevent cancer. They activate p38 in a pro-apoptotic manner causing cancer cell death. H_2O_2 induces oxidation of TRX which promotes its dissociation from ASK1. The kinase than is activated, induces phosphorylation of p38 and JNK and eventually apoptosis. Autophagy can be induced by H_2O_2 through inhibition the negative regulator of autophagy mTOR. Inhibition of the EGF receptor by erlotinib increases Nox4 which in turn activates autophagy in cancer cells. Ceramide and RIP3 lead to mitochondrial ROS generation followed by necroptosis induction. TNFα induces the assembly of RFK with Nox1 facilitating Nox1-dependent ROS production and necroptosis.

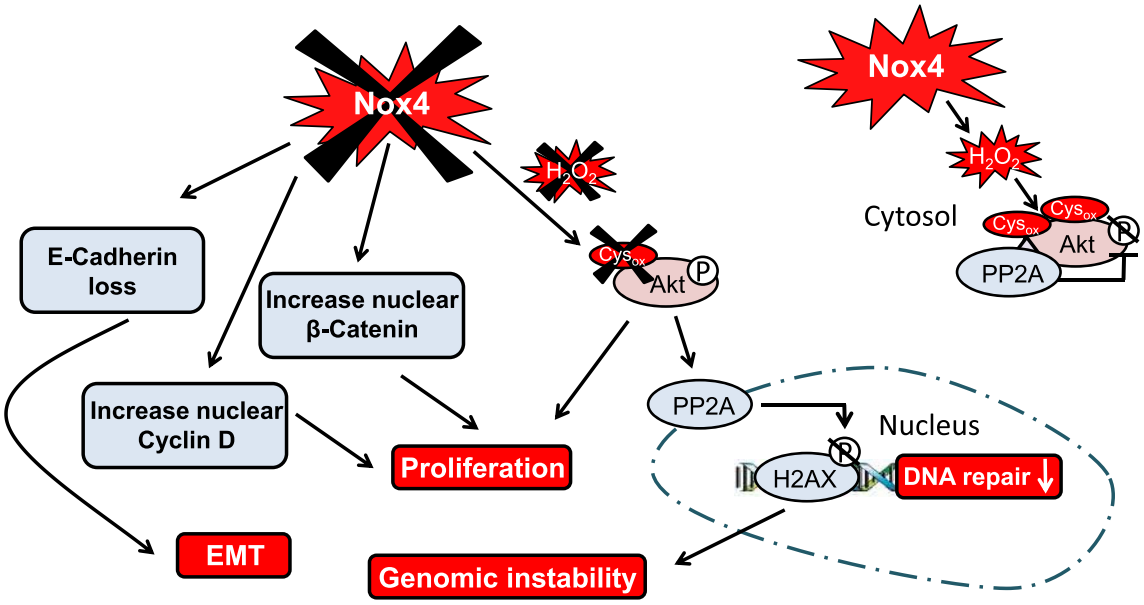

Fig. 5. Nox4 knockout promotes tumor development.
Loss of Nox4 results in an increased proliferation and favors EMT due to enhanced expression of cyclin D1 and nuclear β-catenin and loss of the tumor suppressor E-cadherin. Nox4 mediates the oxidation of the survival kinase Akt at two cysteines (Cys_{ox}) and strengthens its association with the phosphatase PP2A. Knockout of Nox4 results in dissociation of Akt and PP2A, as Akt oxidation is prevented. As a consequence phosphorylation of Akt is enhanced and PP2A translocates into the nucleus, where is prevents a proper DNA damage repair by dephosphorylation of γH2Ax. Consequently the incidence of mutation and proliferation is high and mice are more prone to cancer.

have been recently discussed in a review by Reczek et al. and are therefore not further evaluated in the present review (Reczek and Chandel, 2017). Some of the ROS mediated death pathways that may prevent cancer progression are summarized in Fig. 4.

ROS in tumorigenesis

Different to tumor progression the formation of development of a new tumor is a multistep process, which usually is interfered with at several levels to prevent tumorigenesis. One of the first steps in tumorigenesis, the formation of a new tumor from malignant transformed somatic cells, is DNA damage. Undoubtedly, high concentrations of ROS e.g. in the course of inflammation can lead to DNA damage, resulting in unrepaired nucleic acids and that leads to mutations. This is especially the case in proto-oncogenes and tumor suppressor genes whose mutations, if not repaired, can initiate cancer development (Du et al., 1994). Conversely, those mutated genes may promote ROS production such as in the case of activating mutations of KRas oncogene, which further cause DNA damage and malignant transformation of mouse lung epithelial cells (Maciag et al., 2004). ROS, produced from complex III of the respiratory chain, facilitate tumorigenesis in a KRas driven lung cancer cell model through activation of Erk/MAPK signaling. Total disruption of mitochondrial function reduced mitochondrial ROS formation and tumorigenesis (Weinberg et al., 2010).

Out of many ROS forming enzymes and systems, Nox4 has heightened attention. Nox4 expression is increased in many cancers and Nox4 is a stress inducible gene. Whether or not an increase in Nox4 expression is the cause or the consequence of cell stress and malignant transformation remains debated. Although Nox4 has been shown to be upregulated in the course of differentiation and has anti-inflammatory properties (Goettsch et al., 2013; Schröder et al., 2009; Schürmann et al., 2015), it has been attributed more to proliferation. Oncogene-dependent Nox4 and Rac1 upregulation accompanied by increased ROS are supposed to fuel hyperproliferation and DNA damage in Zebrafish. Interestingly in the same study the authors show, that DNA damage repair is activated by ROS and that ROS-induced senescence limits tumor progression (Ogrunc et al., 2014). Similar contrasting results show, that a permanent active mutant of HRas induces H_2O_2 production through Nox4 which subsequently facilitates DNA damage and cellular senescence - so to speak a tumorigenesis-promoting and -preventing event simultaneously (Weyemi et al., 2012). A follow-up study found that reduced activity of ATM in human fibroblasts results in an elevated expression of Nox4 and consequently an increased formation of H_2O_2 which induces DNA lesions (Weyemi et al., 2015). Unfortunately it has not been further identified, how ATM represses Nox4 expression and whether or not Nox4 is the only source of ROS targeted by that kinase. In fact mitochondria have been proposed to be the major source of ATM-induced ROS formation (Morita et al., 2014). This raises the question of whether a change in the source of ROS from mitochondria to Nox4 really matters so much. Thus, it appears necessary that further, more carefully carried out studies are needed, to analyze the role of Nox4 in malignant transformation and, importantly, to contribute mechanistic insights in the action of Nox4 at different stages of tumorigenesis. One of those studies has been provided by our group. We found that Nox4 maintains genomic stability and therefore has suppressive capacities at the stage of tumor initiation. Nox4 mediates oxidation of the survival kinase Akt, which prevents its association with the phosphatase PP2A. In the absence of Nox4 and less oxidation of Akt, PP2A is free to enter the nucleus, where it dephosphorylates γH2AX, an initiator of DNA repair. Consequently, the normal and frequently occurring DNA double strand breaks are not recognized by the endogenous DNA repair machinery. Eventually DNA damage sustains and induces malignant transformation of somatic cells. Those newly generated tumor cells are able to massively proliferate as Akt, due to its reduced interaction with the phosphatase, is more active and promotes proliferation. *In vivo*, Nox4 knock out mice are more prone to develop a tumor, when challenged with pro-inflammatory carcinogens (Helfinger et al., 2017).

A constant production of low levels of ROS, mainly by Nox4, prevents tumorigenesis, while mitochondrial ROS may facilitate tumorigenesis. Some of those aspects are summarized in (Fig. 5).

Antioxidants in cancer development and progression

For a long time antioxidants have been claimed to protect from cancer by inhibiting oxidative stress. Dietary supplementation with one

of the most widely used ROS scavengers N-acetyl- L –cysteine (NAC) can reduce tumor growth in a p53-deficient mouse model (Sablina et al., 2005). Furthermore, treatment with NAC has been correlated with a diminished proliferation of cancer cells by arresting glioma cells in the G1 phase (Martín et al., 2007). NAC in combination with Vitamin C prevented cancer onset in a xenograft MYC-dependent human B lymphoma model. This effect was linked to diminished Hif1α levels due to an increase in the activity of prolyl hydroxylase 2 and von Hippel-Lindau protein (Gao et al., 2007). Vitamin C itself induces apoptosis in various cancers and can enhance anticancer therapy (Abdel-Latif et al., 2005; Valenti et al., 2014). Overexpression of SOD1 and SOD2, significantly reduces tumor growth and augments survival of breast cancer cells (Weydert et al., 2006). In addition, SOD3 overexpression was in fact sufficient to decrease breast cancer metastasis *in vivo* (Teoh-Fitzgerald et al., 2014). This is only a small portion of studies in the plethora of data available, which demonstrate the efficacy of anti-oxidants in cancer treatment. Galadari et al. recently summarized the existing data on antioxidants used *in vitro* and *in vivo* and corresponding clinical trials (Galadari et al., 2017). Despite this promising data, the dogma of the exclusively positive effect of antioxidants in cancer treatment, is crumbling. Many studies demonstrate detrimental effects of dietary supplementation with anti-oxidants. Large-scale clinical studies have been published that show an enhanced incidence of cancer upon dietary supplementation with vitamin E or β-carotene (Lonn et al., 2005; Omenn et al., 1996). In circulating melanoma cells, interfering with their redox balance upon treatment with NAC enhanced the ability of the cells to metastasize, concluding that ROS interfere with the formation of metastatic tumors in melanoma models (Piskounova et al., 2015). Accordingly, in a mouse melanoma model treatment with NAC and the soluble vitamin E analogue Trolox increased the ability of cells to invade and migrate. While the number and size of primary tumors were unchanged, the number of lymph node metastases was doubled. Oxidized glutathione (GSSG), a marker of oxidative damage in cells, was reduced specifically in the metastatic melanoma cells after treatment with the antioxidants (Le Gal et al., 2015). It appears to be possible, that antioxidants interfere with the cells ability to recognize oxidative stress and thereby prevent the onset of cellular defense mechanisms. Accordingly, depletion of the GSH pool in cancer stem cells can increase ROS levels and thereby force oxidative stress-induced death (Dvorakova et al., 2000; Raj et al., 2011). In line with that, buthionine sulfoximine (BSO), an inhibitor of glutamate cysteine ligase, an enzyme required for GSH de-novo-synthesis, exhibits anti-tumorigenic activity by reducing the amount of GSH (Andringa et al., 2006; Griffith and Meister, 1979).

Interestingly a recent study showed that the antioxidant Vitamin C if used in high doses, acts as a pro-oxidant by depleting GSH. This in turn leads to accumulation of ROS and induces cell death of mutant KRas and BRaf colon cancer cells (Yun et al., 2015). This concentration dependent switch from an anti-oxidant to a pro-oxidant might partially explain the long lasting controversy. Others explain the failure of dietary antioxidant supplementation in clinical trials by an inefficient scavenging of ROS at the site of production (Chandel and Tuveson, 2014). Accordingly, site specific anti-oxidants might be more effective. Mitochondria appear to be especially good targets for site specific application of an antioxidant. As cancer cells ameliorate their mitochondrial ROS production to further fuel neoplastic transformation this is of high importance. Tumor cell migration and spontaneous tumor metastasis in different models could be blocked by the mitochondria-targeted superoxide scavenger MitoTEMPO (Abdel-Latif et al., 2005; Porporato et al., 2014). In a high-throughput screen of small molecules able to inhibit mitochondrial ROS production three compounds were found to specifically suppress complex III superoxide production without influencing the bioenergetic function of those organelles (Orr et al., 2015). Further studies will identify potential benefits from a treatment with site-specific anti-oxidants.

Taken together, cancer therapy using antioxidants must be considered as a double-edged sword being both beneficial and detrimental through inhibition of ROS-induced cancer cell death.

Concluding remarks

A stable redox homeostasis is of exceedingly high importance to keep a cell healthy and prevent its malignant transformation. An excessive ROS formation, as in inflammation, or a constant shortage of ROS, as with overwhelming antioxidant dietary supplementation or with dysfunctional ROS-producing enzymes, can both result in tumorigenesis. On the other hand, it might be possible to prevent cancer progression with localized alterations of the cellular redox balance. Since the goal of preventing or healing cancer has not yet been reached it is of the utmost importance to expand our knowledge on the role of ROS in cancer, with a differential focus on tumorigenesis and cancer progression.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.mam.2018.02.003.

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