Peroxiredoxins, gerontogenes linking aging to genome instability and cancer

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Age is the highest risk factor known for a large number of maladies, including cancers. However, it is unclear how aging mechanistically predisposes the organism to such diseases and which gene products are the primary targets of the aging process. Recent studies suggest that perox-iredoxins, antioxidant enzymes preventing tumor development, are targets of age-related deterioration and that bolstering their activity (e.g., by caloric restriction) extends cellular life span. This review focuses on how the perox-iredoxin functions (i.e., as peroxidases, signal transducers, and molecular chaperones) fit with contemporary theories of aging and whether peroxiredoxins could be targeted therapeutically in the treatment of age-associated cancers.

The life span of most organisms, from single-cell species to humans, is inherently restricted and involves genetic elements of regulation. The term "gerontogene" is used to signify such a genetic element, which influences an organism's life span by affecting the rate and/or onset of aging (Rattan 1995). This does not mean that geronto-genes are "programming" aging; the existence of such programming genes has been disputed on the basis of evolutionary arguments against the adaptive nature of aging (e.g., Medawar 1952; Hamilton 1966). Therefore, as these genetic entities were not originally selected as genes/alleles for or against aging, but are rather involved in aging as an emergent property (by-product), it has been suggested that they should be called "virtual geronto-genes" (Rattan 1995).

Operationally, gerontogenes are defined as genetic elements that can, when altered one way or the other, extend life span beyond what is normal for the specific species concerned. Such genetic alterations include increased gene dosage and partial or complete inactivation. The latter class is exemplified by the first gerontogene mutation identified, *age-1*, of the nematode *Caenorhab-ditis elegans* (Klass 1983; Friedman and Johnson 1988). Gerontogenes have subsequently been identified in many organisms, including yeast, flies, and mice (e.g., Guarente 2000; Jazwinski 2002; Fontana et al. 2010; Kenyon 2010), and potentially important genetic markers for slow aging have been found in humans (Suh et al. 2008). Elucidating the function of such genes is believed to enable decipher-ing the core of the aging process, answer to what extent the process is conserved, and pave the way for therapeutic interventions of age-related maladies, including cancers, neurodegeneration, and metabolic syndrome (Guarente 2011).

The identity of the virtual gerontogenes so far discovered in diverse taxa suggests, at least superficially, that a restricted set of signaling pathways controls the rate of aging. Specifically, aging is decelerated by mutations reducing signaling through nutrient-responsive pathways, including insulin/insulin-like growth factor, mTOR, and RAS–PKA signaling (Cohen and Dillin 2008; Kenyon 2010; Bartke 2011; McCormick et al. 2011). Such a re-duced activity in nutrient-responsive pathways results in the altered expression of a large number of genes, and it is presently not clear which of all of these genes are the most crucial targets responsible for life span extension. This is problematic, since hitting entire nutrient signal-ing pathways therapeutically has its obvious drawbacks and risks. The sirtuins, notably the paradigm *SIR2* in yeast, represent another class of gerontogenes—deletion of *SIR2* accelerates aging, whereas extra copies of the gene result in life span extension (Kaeberlein et al. 1999; Guarente 2000). The sirtuins are histone/protein deacet-ylases, and the role of Sir2 in regulating replicative longevity in yeast is linked, in part, to its role in stabilizing the genome, specifically by preventing recombination at the rDNA locus and the accumulation of extrachromo-somal rDNA circles (ERCs) (Sinclair and Guarente 1997). Similarly, specific sirtuins affect the stability of the aging genome also in mammalian cells (Mostoslavsky et al. 2006; Oberdoerffer et al. 2008). Sir2-dependent control of yeast aging appears interconnected with nutrient signaling, as reduced activity of TOR extends replicative life span, at least in part, by boosting Sir2 activity (Anderson et al. 2003; Medvedik et al. 2007; see also Steffen et al. 2008). Likewise, life span extension achieved by reducing the activity of the yeast mitochondrial translation control module (MTC) acts through Sir2 activation (Caballero et al. 2011).

Alongside the sirtuins, genes encoding the perox-iredoxins (Prxs) have recently emerged as a new class

of gerontogenes that link aging to genome stability and nutrient-responsive signaling. For example, a neuronal Prx, Jafrac1, in *Drosophila* acts as a downstream effector of the nutrient-responsive transcription factor FOXO in life span extension (Lee et al. 2009). Likewise, the major cytosolic Prx of budding yeast, Tsa1, and its repair enzyme, the sulfiredoxin (Srx) Srx1, are downstream targets for nutrient-responsive (RAS–PKA) signaling, and bolstering their activity extends life span (Molin et al. 2011). These results highlight new and intriguing potential inroads in therapeutic gerontology, and this review focuses on how the Prx functions (i.e., as peroxidases, signaling enzymes, and molecular chaperones) may affect genome stability and the rate of aging, how this fits with the free radical hypothesis of aging, and whether Prxs could be targeted therapeutically in the treatment of age-related cancers and/or chemotherapy resistance.

Prxs and their repair enzymes

Prxs act as hydrogen peroxide and organic hydroperoxide scavengers. They all use cysteine (Cys) as the primary site of oxidation and are divided into the 1-Cys and 2-Cys groups based on the number of conserved Cys residues participating in the redox reaction. The 2-Cys Prxs are further divided into the "typical" and "atypical" ones: The typical ones form homodimers through an intersubunit disulfide bond (Fig. 1), whereas the atypical ones form a monomer with an intramolecular disulfide bond during hydrogen peroxide catalysis (D'Autreaux and Toledano 2007). The yeast Prx most significantly contributing to peroxide resistance, genome stability, and antimutation is the typical 2-Cys Prx Tsa1 (Fourquet et al. 2008; Iraqui et al. 2009); the human functional homolog is Prdx1 (Iraqui et al. 2008).

Interestingly, eukaryotic Prxs are exquisitely sensitive to hyperoxidation and inactivation. Specifically, the active Cys-thiol is prone to become hyperoxidized to Cys-sulfinic acid (Fig. 1), which is specifically reduced by Srxs in organisms from yeast (Biteau et al. 2003) to humans (Woo et al. 2005). In the absence of Srxs, typical Prxs become "locked" in the hyperoxidized, peroxide scavenger-deficient form upon peroxide stress (Fig. 1). All the same, structural features that stabilize the hyperoxidized forms seem to have been selected for in the evolution of eukaryotic Prxs, suggesting that such hyperoxidation might provide a distinct and ostensibly advantageous function (Wood et al. 2003a). Specifically, the peroxide-sensitive 2-Cys Prxs have been suggested to act as "floodgates" such that their inactivation by sulfinylation allows peroxide levels to rise above a certain threshold needed for signal transduction (Wood et al. 2003a). In response to growth factor stimulation, it has been shown that localized inactivation of a target Prx in specific tissues may also involve phosphorylation that appears to coincide with sites of growth factor-dependent hydrogen peroxide production (Woo et al. 2010; Rhee et al. 2012). Other results in line with a beneficial role for hyperoxidation show that the sulfinylated forms of the
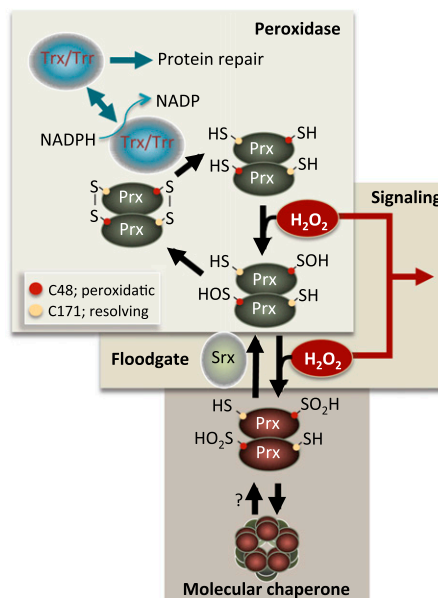

Figure 1. Overview of catalysis in typical 2-Cys Prx. Hydrogen peroxide (H_2O_2) is reduced by the peroxidatic Cys that is oxidized to a sulfenic acid intermediate (C48-SOH in yeast). The nascent R-SOH then condenses with the resolving Cys (C171-SH in yeast) of the other Prx molecule in the Prx dimer to produce a disulfide bond. This bond is subsequently reduced by Trx, thus completing the catalytic cycle. A proportion of Cys-SOH molecules can be further oxidized (hyperoxidation) to the sulfinic acid form (Cys-SOOH) in each catalytic cycle, which inactivates peroxidase activity (Wood et al. 2003b). Srxs reduce the sulfinylated forms of 2-Cys Prxs (Biteau et al. 2003; Woo et al. 2005), which allows Prx to re-enter the catalytic, peroxidatic cycle. The hyperoxidized form of Prx forms oligomers (Hall et al. 2011; Saccoccia et al. 2012) that act as molecular chaperones (i.e., inhibit protein aggregation in vitro) (Jang et al. 2004). The boxes denote three principal Prx activities that may affect genome stability and life span: (1) peroxidase activity reducing the levels of harmful peroxides, (2) hyperoxidation by the "floodgate reaction" allowing peroxide levels to reach local thresholds as a second messenger in signal transduction, and (3) hyperoxidation leading to Prx oligomer formation and molecular chaperone activity. (Trr) Trx reductase.

yeast Prx Tsa1 multimerize and gain a molecular chaperone activity (Fig. 1); i.e., multimer Tsa1 inhibits the aggregation of model protein substrates such as insulin in vitro (Jang et al. 2004; Lim et al. 2008). Recent structural analysis suggests that the hyperoxidized chaperone form of Prx is a double decamer; i.e., it consists of two "sandwiched" decamer rings (Saccoccia et al. 2012). Oxidative stress (peroxide) triggers the peroxidase-to-chaperone switch, which in yeast is guided by the Cys 48 residue on Tsa1. Therefore, it has been proposed that 2-Cys Prxs serve as redox sensors in the cell that, depending on the severity of oxidative insults, may act as a peroxidase, molecular chaperone, or both (Jang et al. 2004). In addition, it has recently been shown that hyperoxidation of Prxs may be beneficial upon severe peroxide stress also by an indirect effect. Specifically, Prx heterodimers engaged in the catalytic cycle upon low-level hydrogen peroxide

stress appear to be a main target for thioredoxin (Trx) (Fig. 1). However, the sulfinylated form of Prx is not a target for reduction by Trx (Fig. 1), and it was therefore proposed that more Trx becomes available for the reduction of other oxidatively damaged enzymes upon Prx hyperoxidation (Day et al. 2012).

Notably, some eukaryotes, including *C. elegans*, appear to lack Srxs and the means to reduce hyperoxidized Prxs. Possibly, sestrins might be able to reduce hyperoxidized Prx (Budanov et al. 2004) in organisms lacking Srxs, but the sestrins do not carry sulfinic acid reductase activity (Woo et al. 2009), and it is unclear whether hyperoxidation of Prx in organisms lacking Srxs is physiologically relevant (Olahova et al. 2008; Woo et al. 2009; Thamsen et al. 2011).

Links between aging, caloric restriction (CR), and Prx activity

Prx deficiency results in accelerated aging in yeast, worms, flies, and rodents (Neumann et al. 2003; Olahova et al. 2008; Lee et al. 2009; Timmermann et al. 2010). Moreover, the yeast and rat Prxs, Tsa1 and PrxII, are becoming increasingly hyperoxidized during aging in the absence of external peroxide stress (Musicco et al. 2009; Molin et al. 2011), indicating that Prx inactivation may be a common phenomenon in different aging organisms. Thus, like Sir2 (Dang et al. 2009), the activity of the major Prx of yeast is reduced during aging, indicating that the yeast genome may become destabilized, in part, because proteins involved in both silencing/chromatin organization (Sir2) (Dang et al. 2009) and anti-mutation (Tsa1) (Molin et al. 2011) are themselves inactivated or produced in limiting amounts in aging cells. This is consistent with the hypothesis of McMurray and Gottschling (2003, 2004), which suggests that accumulation of oxidatively damaged proteins in aging cells results in the loss of function of gene products critical for maintaining genome integrity and points out that determining the identity of these proteins and how they become damaged represents a new challenge for understanding the relationship between age, genomic instability, and cancer. In addition, age-associated genome instability (i.e., mitotic recombination in the yeast rRNA gene cluster) is the result also of Sir2-independent processes (Lindstrom et al. 2011). Furthermore, nuclear genome instability induced by age-associated mitochondrial dysfunctions has been linked to defects in iron–sulfur biogenesis that in turn were hypothesized to inactivate key DNA repair enzymes (Veatch et al. 2009).

With respect to the Prxs, it is not clear how aging affects their oxidation, but sulfinylation may be the result of endogenously elevated levels of hydrogen peroxide, as the levels of this oxidant have been shown to increase with the replicative age of yeast mother cells (Laun et al. 2001; Erjavec and Nystrom 2007) and with the chronological age of both rats and mice (Andres-Mateos et al. 2007; Asha Devi et al. 2011). In conjunction with this, old cells appear to have a diminished capacity for Srx-dependent reduction of Prxs, and providing yeast cells with

an extra copy of the *SRX1* gene counteracts age-related hyperoxidation of Tsa1 (Molin et al. 2011). Remarkably, an extra copy of *SRX1* also extends life span by 20% in a *TSA1*-dependent manner (Molin et al. 2011). This life span extension by *SRX1* merodiploidy is similar to that achieved by an extra copy of *SIR2* (Kaeberlein et al. 1999, 2004) and is effective also in the absence of Sir2 (Molin et al. 2011).

CR, a practice that prolongs life span in taxonomically diverse organisms (Fontana et al. 2010; Kenyon 2010; McCormick et al. 2011), counteracts sulfinylation of Tsa1 during aging in an Srx1-dependent manner (Molin et al. 2011). Specifically, a CR-induced reduction in RAS–PKA signaling bolsters Gcn2-dependent translation of the *SRX1* transcript (Fig. 2). Apart from counteracting Tsa1 sulfinylation, this boost in *SRX1* translation appears to be an imperative part of CR-dependent life span extension, as CR fails to efficiently extend life span in cells lacking either Tsa1 or Srx1 (Molin et al. 2011). Again, Tsa1/Srx1-dependent life span extension reached by CR works in both the presence and absence of *SIR2*, suggesting that Tsa1 and Sir2 act in parallel pathways of life span control.

In summary, data supporting a link between Prx activity and aging include the following: (1) Yeast, worms, flies, and rodents with diminished Prx activity age prematurely. (2) Aging causes hyperoxidation (sulfinylation) of Prxs, which diminishes their catalytic activity. (3) Counteracting Prx sulfinylation and bolstering Prx activ-
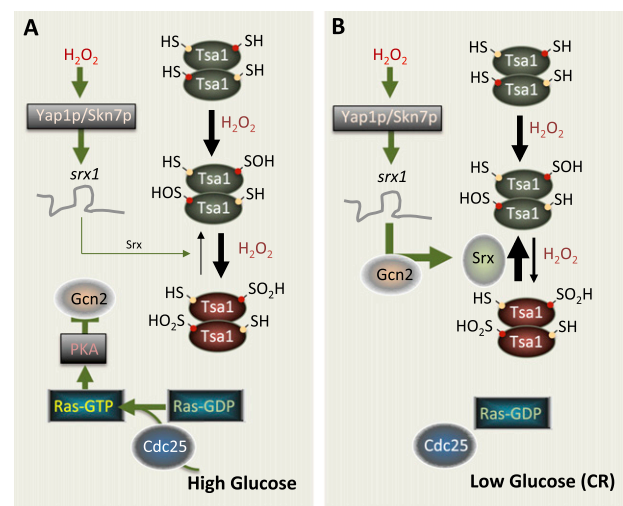

Figure 2. Schematic representation of how CR, through RAS–PKA signaling, sustains yeast Prx catalytic activity. (*A*) At a high concentration of glucose, leading to a high RAS–cAMP–PKA activity, hydrogen peroxide can activate Yap1/Skn7-dependent transcription of the *SRX1* mRNA, but its translation is inhibited by PKA. In the absence of Srx, a large portion of Tsa1 becomes hyperoxidized and inactivated. (*B*) During CR, Ras–PKA activity is reduced, and this relieves the translational inhibition of the *SRX1* mRNA in a Gcn2-dependent manner to provide more Srx1 protein and, as a consequence, more reduced peroxidase-active Tsa1. Conditional mutations in Cdc25 reduce Ras activity, create a phenocopy of CR, and extend life span in a Tsa1-dependent manner (Molin et al. 2011).

ity in yeast by elevating the levels of its repair enzyme, Srx1, extend life span. (4) CR, by elevating Prx activity through augmented Srx1-dependent repair, slows replicative aging.

Prxs and the free radical hypothesis of aging

The evolved version of Harman's (Harman 2003) free radical theory of aging proposes that organisms age because the constituents of cells and tissues accumulate damage over time caused by reactive oxygen (and/or nitrogen) species originating from endogenous metabolism, including, among many other possible activities, mitochondrial respiration. At first glance, it appears that the data concerning Prxs and aging fit this theory like a glove, as Prxs become "damaged" (catalytically inactivated as a peroxidase) during aging due to a modification caused by a reactive oxygen species (ROS), specifically hydrogen peroxide (or organic hydroperoxides), and that counteracting this "damage" by elevating the levels of the "repair" enzyme Srx1 prolongs life span (Molin et al. 2011). Moreover, as the Prxs themselves act as enzymatic antioxidants and protect the genome against oxidative modifications (see below), it is possible that peroxide-dependent inactivation of Prxs gives rise to a negative feedback loop with respect to the cell's capacity for ROS homeostasis.

On the other hand, it could be questioned whether the sulfinylation of typical 2-Cys Prxs by hydrogen peroxide should be regarded as damage per se. Rather, hydrogen peroxide could be considered an effector/signaling molecule triggering a switch in Prx functions—a reversible redox switch under control of Srxs (Wood et al. 2003a; D'Autreaux and Toledano 2007). This redox switch may be critical for modulating signaling through proliferation, checkpoint, and cell cycle regulatory pathways (see below), and such control could potentially be more important than peroxide scavenging in protecting the genome, suppressing tumorigenesis, and assuring longevity. Likewise, the chaperone functions of the sulfinylated Prxs could be critical in defending the cells against cytotoxic stress and affect the rate of aging. However, it should be noted that the Prxs are exquisitely suitable as scavengers of low concentrations of endogenously generated peroxides in protecting the genome (D'Autreaux and Toledano 2007; Fourquet et al. 2008; Hall et al. 2011), and it cannot be ruled out that this is the major reason for life span extension by increasing Prx function in aging cells (Molin et al. 2011). Nevertheless, the fact that Prxs and Srx act as gerontogenes does not on its own support the free radical hypothesis of aging, but deciphering the exact biochemical role of the Prxs in life span extension should resolve this issue.

Links between genome instability, cancer, and Prx activity

Before being recognized as gerontogenes, Prxs have received special attention in cancer research due to their association with signaling cascades, growth control, tumor suppression, and chemotherapy resistance (Neumann et al. 2003; Chen et al. 2006; Neumann and Fang 2007). To wit, deletion of yeast TSA1 causes a drastic loss of genome stability, gross chromosomal rearrangements (GCRs), and increased occurrence of base substitutions and frameshift mutations (Iraqui et al. 2008, 2009). In fact, Tsa1 is absolutely required for cell survival in the absence of functional, Rad51/Rad52-dependent, recombinational repair or Rad6-mediated post-replication repair (Huang and Kolodner 2005). In addition, mice lacking PrdxI display an increased risk of developing hemolytic anemia and acquire several malignant cancers prematurely during aging, and their fibroblasts contain increased levels of oxidatively damaged DNA (Neumann et al. 2003). However, it remains to be established whether Prxs act as tumor suppressors in organisms other than mice and in preventing tumors other than lymphoid tumors.

But how do Prxs protect the genome? One possibility is that the spontaneous genome instability and cell death associated with Prx1 deficiency is primarily linked to Prxs functioning as peroxide scavengers. In support of this view, Tsa1 deficiency combined with deficiencies in Ogg1, a glycosylase that removes 7,8-dihydro-8-oxo-2'-deoxyguanosine (8-oxo-dG; a major, mutagenic product of DNA oxidation) results in markedly elevated mutation rates (Huang and Kolodner 2005). Furthermore, the increased mutation rate in tsa1 cells is suppressed by anaerobiosis (Ragu et al. 2007). However, in contrast to Ogg1-deficient cells, where the mutation rate returns to wild-type levels in the absence of oxygen (Northam et al. 2010), a tsa1 mutant has a somewhat higher mutation rate than wild-type cells also in the absence of oxygen (Ragu et al. 2007).

Studies in which mutations in the yeast Prx gene TSA1 are combined with DNA repair or cell cycle checkpoint defects provide additional insights into possible causes of increased genomic damage and mutations in Prx-deficient cells. For example, the removal of mismatch repair (MMR) proteins Msh2 or Msh6 in a tsa1 mutant results in a more than additive elevation of base substitutions and frameshifts without increasing GCRs (Huang and Kolodner 2005). In contrast, combining a deletion in DUN1, encoding the protein kinase of the Mec1–Rad53–Dun1 cascade, with tsa1Δ causes a synergistic increase in the rate of GCR while actually suppressing base substitutions and frameshifts (Huang and Kolodner 2005; Tang et al. 2009). The Mec1–Rad53–Dun1 pathway is crucial for DNA damage-induced up-regulation of the ribonucleotide reductase (RNR), which in turn increases dNTP levels (Niida et al. 2010). Specifically, the Dun1-dependent elevation of RNR expression and dNTP levels in a tsa1Δ mutant as shown by Tang et al. (2009) probably leads to a more efficient translesion DNA synthesis (TLS) (Sabouri et al. 2008) that may serve as a response to deal with DNA damage triggered by the absence of Tsa1. However, the trade-off for this damage repair response is a TLS-dependent increase in mutation rates. Recently, RNR induction and expansion of dNTP pools were recorded in tsa1Δ and other genome instability mutants deficient in various seemingly unrelated processes (repli-

cation fork progression, recombinational repair, and sister chromatid cohesion) (Davidson et al. 2012; Poli et al. 2012). By analyzing these data, it appears as if a *tsa1Δ* mutant displays higher mutation rates than expected from the dNTP pools alone, suggesting that Tsa1 deficiency results in additional problems related to mutation protection. Recent results indicate that such additional problems may be related to *tsa1Δ* mutants failing to block replication fork progression upon DNA damage (exposure to the *RNP* inhibitor hydroxyurea) (Davidson et al. 2012).

Similar to Tsa1-deficient yeast, Prdx1-deficient mice contain higher levels of 8-oxo-dG (Neumann et al. 2003) and accumulate oxidatively modified DNA nucleosides in different tissues (Egler et al. 2005). However, no direct correlation could be established between the levels of DNA oxidation and tumor susceptibility (Egler et al. 2005), indicating that PrdxI may suppress tumorigenesis by mechanisms other than protecting the genome directly against oxidative attack; for example, by affecting cell cycle signaling. In line with this notion, PrdxI deficiency increases c-Myc activity (Egler et al. 2005) as well as Akt activity, the latter of which has been argued to result from the accumulation of the oxidatively inactivated PTEN phosphatase (Cao et al. 2009). Moreover, PrdxI inhibits c-Abl tyrosine kinase activity (Wen and Van Etten 1997), and overexpression of PrdxI inhibits c-Myc-mediated transformation of mouse embryonic fibroblasts (Mu et al. 2002). PrdxI has also been reported to negatively regulate Ask1 (apoptosis signal-regulating kinase 1) activation in response to hydrogen peroxide stress (Kim et al. 2008), a response that critically modulates chemically induced skin tumorigenesis in mice (Iriyama et al. 2009). The Ask1-mediated stress response was proposed to involve both tumor-suppressing p38/c-Jun N-terminal kinase-mediated apoptosis of initiated cells and tumor-promoting p38-mediated inflammation in later tumor stages (Iriyama et al. 2009).

Taken together, current evidence suggests that (1) loss of Prx increases a wide range of DNA damage, the repair of which involves diverse pathways and checkpoints; (2) genome instability in Prx-deficient cells is partly, but not entirely, due to an oxidation-dependent attack of DNA; (3) aberrant signaling through proliferation/cell cycle control pathways may contribute to genome instability and tumorigenesis in cells with aberrant Prx expression; and (4) the mutator phenotype of cells lacking Prxs is partially due to elevated dNTP pools and TLS and, possibly, defects in replication fork progression control. To what extent the chaperone function of sulfinylated Prxs contributes to genome stability (or chemotherapy resistance; see below) is an intriguing question that remains to be elucidated.

Links between chemotherapy resistance and Prx activity

Apart from the fact that Prxs act as tumor suppressors, Prxs have attracted attention in cancer research also due to the fact that their levels are drastically elevated in many cancer tissues and immortalized cell lines (Neumann and Fang 2007), which can lead to increased resistance to both radiotherapy and chemotherapy (e.g., cisplatin resistance) (Chung et al. 2001). Specifically, increased *PRX* expression has been reported in several studies of both lung cancer and breast cancer (Noh et al. 2001; Park et al. 2006). With respect to human lung cancer, differential *PRX* expression was reported for various tumor subtypes, including adenocarcinoma and high-grade squamous cell carcinoma, as well as advanced tumor stages (Chen et al. 2006). Interestingly, modified (presumably oxidized) PrdxI accumulates in human lung cancer samples (Park et al. 2006), indicating, perhaps, a role for the chaperone function of PrdxI in tumorigenesis (or elevated peroxide signaling). Furthermore, a recent study reported that increased Srx expression deregulates PrdxIV activity in lung cancers, and Srx and PrdxIV were found to be required for several key aspects of tumor growth and metastasis; e.g., anchorage-dependent colony formation, cell migration, and invasion (Wei et al. 2011). In a previous study, increased Srx expression was observed also in several types of skin cancers (Wei et al. 2008), indicating that deregulation of Prx activity may be involved in several types of human cancers.

Similar to Prxs, both Trx and Trx reductase (Trr) levels are increased in several human cancers (Berggren et al. 1996; Park et al. 2006), and overproduction of Trx in MCF-7 human breast cancer cells induced tumorigenesis in a manner dependent on the catalytic cysteines (Gallegos et al. 1996). A detailed description of the roles of the Trxs in tumorigenesis is beyond the scope of this review, but it should be noted that increased Trx levels contribute to many of the hallmarks of cancer, including increased proliferation, resistance to apoptosis, and increased angiogenesis (Powis and Kirkpatrick 2007). Moreover, an inhibitor, PX-12, of the catalytic cysteines of Trx is currently under clinical development as an anti-tumor agent, and in a phase I study, a decrease in circulating Trx-1 levels upon PX-12 administration was demonstrated to increase the survival of patients with advanced refractory solid tumors (Ramanathan et al. 2007). Like for Prx, an uncontrolled and elevated Trx activity in cancer tissues constitutes a recognizable clinical problem, as Trx overproduction renders tumor cells resistant to therapy.

Based on the problems associated with Prx overexpression in both chemotherapy and radiotherapy, it has been proposed that inactivation of Prx enzymes may be a promising approach to improve the treatment outcome of cancer patients (Chen et al. 2006). However, in view of the fact that a diminished Prx activity in noncancerous tissue cells results in the loss of genome maintenance, promotes tumor development, and accelerates aging, treatments aimed at reducing Prx levels could potentially be risky and even counterproductive.

Future perspectives

Does the dual role of Prxs in chemotherapy resistance and tumor suppression make them unsuitable targets for therapy? Perhaps not—as outlined here, the biochemical

functions of the Prxs are multifaceted, and it is possible that Prx activities associated with age-related tumor development are distinct from the ones providing resistance to chemotherapy/radiotherapy. Elevated Prx activity may protect a cancer cell against chemotherapy by means other than protecting its genome against oxidative attack; for example, by enhancing the cell's ability to deal with protein damage, such as stress-induced protein aggregation and proteotoxicity. In other words, it is possible that the established role of Prxs as anti-mutators/tumor suppressors on the one hand and protectors against chemotherapy on the other is provided by different, biochemical functions and forms of the Prxs, which could allow targeting one discrete function without blocking the others. For example, hyperoxidation of Prx may protect cancer cells against chemotherapy/radiotherapy in two ways: first, by directly converting Prx to a molecular chaperone (Jang et al. 2004), and second, by allowing more Trx to participate in the repair of other damaged proteins, as the hyperoxidized Prx is no longer a substrate for Trx (Day et al. 2012). In this context, it would be interesting to learn whether the formation of Prx double decamers can be targeted therapeutically—an exciting possibility worth pursuing.

In view of the clinically established problems related to aberrant and elevated Prx production in treating age-related cancers, approaching these possibilities and hypotheses experimentally may provide the means for future drug treatment improvements. Moreover, illuminating which Prx functions are critical for life span extension should give new and general insights into the aging process and its specific targets, a knowledge that in itself could guide future approaches in therapeutic gerontology.

Acknowledgments

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