**Abstract:** Peroxiredoxins (PRDXs) are members of a highly conserved peroxidase family and maintain intracellular reactive oxygen species (ROS) homeostasis. The family members are expressed in most organisms and involved in various biological processes, such as cellular protection against ROS, inflammation, carcinogenesis, atherosclerosis, heart diseases, and metabolism. In mammals, six PRDX members have been identified and are subdivided into three subfamilies: typical 2-Cys (PRDX1, PRDX2, PRDX3, and PRDX4), atypical 2-Cys (PRDX5), and 1-Cys (PRDX6) subfamilies. Knockout mouse models of PRDXs have been developed to investigate their in vivo roles. This review presents an overview of the knockout mouse models of PRDXs with emphases on the biological and physiological changes of these model mice.

**Keywords:** peroxiredoxin; peroxides; reactive oxygen species; knockout mouse; animal model

1. Introduction

The peroxiredoxin (PRDX) family has peroxidase activity to remove peroxides, including hydrogen peroxide (H$_2$O$_2$), organic hydroperoxides, and peroxynitrite [1,2]. PRDXs are widely distributed in almost all organisms and there are more than 3500 members in this protein family [3]. PRDXs are classified into three subfamilies (typical 2-Cys, atypical 2-Cys, and 1-Cys) based on the number and location of the active cysteine residues and the type of disulfide bonds produced during the catalytic reaction (Figure 1) [4–8]. Typical 2-Cys PRDXs function as a homodimer [7]. Peroxides oxidize the conserved peroxidatic cysteine (C$_P$) in typical 2-Cys PRDXs, and then the oxidized cysteine sulfenic acid residue in a subunit forms an intermolecular disulfide bond with the resolving cysteine (C$_R$) in the other subunit [7]. Finally, the intermolecular disulfide bond is reduced by the thioredoxin (Trx)/Trx reductase/NADPH system [7]. Atypical 2-Cys PRDXs remove peroxides using the same mechanism as 2-Cys PRDXs except that atypical 2-Cys PRDXs form an intramolecular disulfide bond between C$_P$ and C$_R$ in a PRDX molecule [9]. 1-Cys PRDXs have only a C$_P$ residue and the oxidized C$_P$ is reduced by glutathione (GSH) instead of Trx [10]. According to the PeroxiRedoxin classification indEX (PREX) database that classifies PRDXs based on structural information around active sites, PRDXs are also divided into six subfamilies: AhpC-Prx1, BCP-PrxQ, Tpx, Prx5, Prx6, and AhpE [11,12]. In mammals, there are six PRDX members (PRDX1–PRDX6) [5]. PRDX1–PRDX4 are members of the typical 2-Cys or AhpC-Prx1 subfamily [5,12]. PRDX5 is a member of the atypical 2-Cys or Prx5 subfamily, and PRDX6 is classified into the 1-Cys or Prx6 subfamily [5,12]. Mammalian PRDXs are widely distributed in cells and perform various biological functions. PRDX1 is present in the nucleus and cytosol; PRDX2 and PRDX 6 are in the cytosol; PRDX3 is in the mitochondria; PRDX4 is in the endoplasmic reticulum (ER) and the cytosol; and PRDX5 is in the cytosol, peroxisomes, and mitochondria [8,13].
Figure 1. Catalytic cycle of typical 2-Cys (a), atypical 2-Cys (b), and 1-Cys (c) peroxiredoxins (PRDXs). 

CP, peroxidatic cysteine; CR, resolving cysteine; GSH, glutathione; ROOH, peroxide; Trx, thioredoxin.

As genetically modified mouse (GEM) models, knockout mice are useful to investigate the roles of a gene. In the case of mouse Prdx genes, several knockout mouse strains targeting each Prdx gene have been generated by independent research groups [14]. These knockout mice provide useful information that is hard to obtain from other experiments. The present review summarizes the properties of Prdx-knockout mouse models and focuses on the biological and physiological changes of these model mouse strains.

2. PRDX1

2.1. Genetics and Knockout Mouse Strains

PRDX1 is a ubiquitously expressed nuclear and cytosolic peroxidase protein and is a member of the typical 2-Cys PRDX subfamily [7,13]. PRDX1 is involved in tumor suppression [15–18], inflammation [13,19–26], apoptosis [19,27,28], atherosclerosis [13,21], and molecular chaperoning [29,30]. According to the mouse Ensembl database, the Prdx1 gene is located on mouse chromosome 4 and there are five alternative forms of Prdx1 protein-coding transcripts [31]. Prdx1-knockout mouse strains have been generated by the homologous recombination [15,32] or gene trap [17,33] approaches. No Prdx1-knockout mouse strain with conditional potential has been reported, although the International Mouse Phenotyping Consortium (IMPC) has embryonic stem (ES) cell clones that possess the reporter and conditional allele [34].
2.2. Cancer

Neumann et al. have generated the first Prdx1-knockout mice (Prdx1−/−) [15]. The knockout mouse strain targets exon 3 of the Prdx1 gene by the insertion of a transposon containing a PGK-neomycin-resistant (neoR) cassette, which disrupts all protein-coding transcripts [15]. The knockout mice are viable and fertile but show severe hemolytic anemia and several malignant cancers, including lymphomas, sarcomas, and carcinomas, which cause a shortened life span [15]. Using the same knockout mice, Neumann’s group indicated that PRDX1 is involved in Pten-mediated tumor suppression in Ras-induced breast cancer [16] and inhibition of fibroblast transition into cancer-associated fibroblasts (CAFs) [18]. The tumor suppressor function of PRDX1 was also demonstrated in another study using a different Prdx1-knockout mouse strain, which was generated using the Lexicon gene trap ES cell clone, which has a gene trap vector in intron 3 of the Prdx1 gene [17]. Elevated nuclear ROS on primary tissues isolated from the Prdx1−/− leads to increased DNA damage and tumor susceptibility [17].

2.3. Erythrocytes

Severe hemolytic anemia with defects in blood parameters, which is observed in Neumann’s Prdx1-knockout mice, is not observed in other Prdx1-knockout mouse models [32,33], although Prdx1 deficiency aggravates hemolytic anemia symptoms in Prdx2-knockout mice [32]. These knockout mouse strains have been generated by replacing whole exons of the Prdx1 gene with a neoR cassette [32] or using the gene trap clone [33].

2.4. Inflammation

In different inflammation disease models, Prdx1−/− show conflicting results. PRDX1 enhances cerebral ischemia–reperfusion (I/R) injuries by activation of inflammation and apoptosis [19], and it initiates inflammation in the ozone-exposed lung [20]. Prdx1 deficiency, however, aggravates pulmonary inflammation and fibrosis in the bleomycin-treated model [26]. Atherosclerosis and chronic inflammation model mice (Prdx1−/−;ApoE−/−) show increased formation of atherosclerotic plaque compared with Prdx1+/+;ApoE−/− mice [13,21]. Prdx1-deficient macrophages present impaired lipophagic flux and cholesterol homeostasis [13]. Lipopolysaccharide (LPS)-induced lung injury, lethal shock, and neuroinflammation are increased in Prdx1−/− [22–24]. PRDX1 is a negative regulator of Th2-type allergic asthma that is induced by ovalbumin [25]. Inflammatory stimuli produce the intramolecular disulfide bond in HMGB1, which is mediated by PRDX1 or PRDX2 [35]. The formation of the disulfide bond is sufficient for HMGB1 secretion and secreted HMGB1 signals danger to surrounding cells. HMGB1 secretion induced by LPS is attenuated in macrophages isolated from Prdx1- or Prdx2-knockout mice [35].

2.5. Others

PRDX1 interacts with Gde2 and reduces the formation of an intramolecular disulfide bond between the N- and C-terminal regions of Gde2, which induces neuronal differentiation [36]. Prdx1 deficiency attenuates cisplatin-induced nephrotoxicity [37]. Studies using Prdx1-knockout mouse models also show that PRDX1 is involved in maintenance of stemness of mouse embryonic stem cells by suppression of ROS/JNK-induced neurogenesis [38], modulation of cellular senescence in mouse embryonic fibroblasts (MEFs) [39], host defenses against Mycobacterium tuberculosis and Staphylococcus aureus [40,41], and maintenance of progesterone production in the corpus luteum through regulating the unfolded protein response [42].
3. PRDX2

3.1. Genetics and Knockout Mouse Strains

PRDX2 is a cytosolic typical 2-Cys PRDX and has a similar structure to that of PRDX1 [7]. Mouse PRDX1 and PRDX2 proteins share 89% sequence similarity and 74% sequence identity and perform overlapping and distinct biological functions [31]. The Prdx2 gene is on mouse chromosome 8 and there are five alternative forms of Prdx2 protein-coding transcripts [31]. The first Prdx2-knockout mice (Prdx2−/−) have been generated by replacing the genomic DNA encoding exons 1-5 with a neoR cassette. They are viable and fertile [43] and most studies have used the same Prdx2-knockout mouse model. ES cell clones possessing the reporter and conditional allele of the Prdx2 gene have been produced [34], but a Prdx2-knockout mouse strain with conditional potential has not been reported.

3.2. Erythrocytes

Typical phenotypes of Prdx2−/− are hemolytic anemia, splenomegaly, Heinz body formation, and morphologically abnormal red blood cells [43]. PRDX2 is expressed in all cell types and is the third most abundant protein in erythrocytes [44]. Three PRDX isoforms (PRDX1, PRDX2, and PRDX6) are expressed in mature erythrocytes and PRDX2 is the most abundant protein among them [45]. The role of PRDX2 in protecting erythrocytes against oxidative stress has been verified by several studies using the same Prdx2-knockout mouse model [46–55]. PRDX2 has roles to protect erythrocytes from ROS-mediated DNA damage during erythropoiesis [48] and to protect hemoglobin from oxidative stress [49,50]. The decameric structure of PRDX2 binds to hemoglobin to stabilize and protect the protein [49]. Studies using Prdx2−/− show that PRDX2 is involved in the homeostasis of iron and membrane proteins of erythrocytes, as well as cellular senescence of erythrocytes and skin cells [51,53,56]. Erythrocytes lose PRDX2 protein gradually during the life span of erythrocytes [54]. PRDX2 is hyperoxidized by H2O2 and the hyperoxidized PRDX2 is degraded by the 20S proteasome [54].

3.3. Blood Vessels

PRDX2 is also involved in the homeostasis of blood vessels [57–59]. The redox-sensitive transcription factor Nrf2 activates PRDX2 expression to protect vascular smooth muscle cells from oxidative vascular injury [57]. In vascular endothelial cells, VEGFR2 no longer responds to VEGF stimulation by the oxidative-stress-induced formation of a cysteine disulfide bond in the C-terminal region of VEGFR2 [58]. PRDX2, not PRDX1, inhibits the formation of the intramolecular disulfide bond in VEGFR2 [58]. Furthermore, tumor angiogenesis is suppressed in Prdx2−/− [58]. The antioxidant activity of PRDX2 needs negative regulation of collagen-stimulated platelet activation and platelet-dependent thrombosis [60]. Among 2-Cys Prdxs, Prdx2 deficiency exacerbates the neointimal hyperplasia induced by the balloon injury of the carotid arteries [59].

3.4. Immune Responses

ROS are harmful byproducts but are also essential for immune responses [61] and their scavenger, PRDX2, inhibits immune cell responsiveness [62,63]. Increased exposure to ROS by Prdx2 deficiency activates the proliferation of T lymphocytes and the differentiation of dendritic cells [62,64]. Like Prdx1−/−, Prdx2−/− are sensitive to LPS-induced inflammatory responses, including lethal shock [65]. LPS activates inflammatory responses which are mediated by NADPH-oxidase-derived ROS generation in Prdx2-deficient macrophages [65]. Prdx2 deficiency increases immune cell accumulation in atherosclerotic lesions, which exacerbates atherosclerosis in ApoE−/− mice [66]. Hypoxia-induced oxidative stress in the lung of Prdx2−/− causes an amplified inflammatory response, vascular dysfunction, and autophagy activation, which lead to the development of pulmonary arterial hypertension [67]. Prdx2 deficiency ameliorates dextran sulfate sodium (DSS)-induced colitis by enhancing the development of Foxp3+ regulatory T cells [68].
3.5. Cancer

In the Apc+/Min colorectal cancer model, the depletion of Prdx2 inactivates the formation of intestinal adenomatous polyposis through Axin/β-catenin signaling [69,70]. Increased intracellular H₂O₂ level by the Apc mutation leads to the direct binding of PRDX2 to a poly(ADP-ribose) polymerase (PARP) tankyrase. This binding protects the tankyrase from its oxidative inactivation, and thus induces PARP-dependent Axin degradation [69,70].

3.6. Bone

Prdx2−/− have higher levels of bone mass than those of wild-type mice because PRDX2 is a negative regulator of BMP2-induced osteoblast differentiation [45]. PRDX2 also functions as a negative regulator of LPS-induced osteoclastogenesis and bone loss, which are induced by ROS-mediated JNK and STAT3 activation [71].

3.7. Others

PRDX2 is important for homeostasis of other tissues. PRDX2 protects hippocampal neurons from age-dependent mitochondrial decay [72] and maintains the stemness of mouse embryonic stem cells [38]. Oxidation of protein tyrosine phosphatases by ROS in Prdx2−/− fed a high-fat diet causes reduced body weight and increased glucose clearance [73]. PRDX2 controls corpus luteum regression that is induced by prostaglandin F2α-mediated ROS and protects against age-related ovarian failure [74,75].

4. Prdx3

4.1. Genetics and Knockout Mouse Strains

PRDX3 is a member of typical 2-Cys PRDXs and is mainly localized in mitochondria due to a mitochondrial targeting sequence at the N-terminal region. The Prdx3 gene is localized on mouse chromosome 19 and there is a Prdx2 protein-coding transcript [31]. Two knockout mouse lines have been analyzed to study the in vivo function of PRDX3. The first knockout mouse line was produced in 2007 using an ES cell clone generated by the gene trap approach [76]. In this ES clone, the VICTR20 gene trap vector [77] is inserted in intron 1 of the Prdx3 gene [76]. The second knockout mouse line was generated by the homologous recombination approach [78]. The genomic DNA region possessing exons 1-4 of the Prdx3 gene is replaced with the neoR cassette in the knockout mouse line [78]. ES cell clones possessing the reporter and conditional allele of the Prdx3 gene have been produced [34], but no Prdx3-knockout mouse strain with conditional potential has been reported.

4.2. Muscles

PRDX3 is important to protect mitochondria against oxidative stress. Prdx3 deficiency leads to reduced mitochondrial DNA content and ATP production and impaired mitochondrial fusion [79,80]. Mitochondrial homeostasis is necessary for the proper function of skeletal muscles. PRDX3 has roles in the prolonged contraction of skeletal muscles and physical strength [79,80].

4.3. Metabolism

PRDX3 is involved in metabolic homeostasis. Prdx3−/− show increased fat mass by adipocyte hypertrophy, impaired mitochondrial enzymes, and adipokine dysregulation, resulting in impaired glucose tolerance and insulin resistance [78].
4.4. Others

PRDX3 protects the lungs from LPS-induced damages, such as 8-hydroxy-2′-deoxyguanosine (8-OHdG) formation and protein carbonylation [76]. PRDX3 also protects macrophages and the liver against LPS-induced oxidative stress and pyrazole-induced oxidative damage, respectively [81,82]. Increased oxidative stress in Prdx3−/− shows placental defects, including focal necrosis and hyaline degeneration in trophoblast giant cells and vessel degeneration [83,84]. PRDX3 also has a protective role in UV-induced apoptosis of epidermal keratinocytes [85].

5. Prdx4

5.1. Genetics and Knockout Mouse Strains

PRDX4 is a member of typical 2-Cys PRDXs. Prdx4 is on the X chromosome and produces two forms of alternative transcripts [31]. Each of them uses a different exon 1 (exon 1A and exon 1B) [86]. All tissues, including the testis, express Prdx4 mRNAs transcribed from exon 1B, which encodes the cleavable N-terminal signal sequence, whereas the testis produces a testis-specific form of Prdx4 mRNAs transcribed from exon 1A [86]. PRDX4 is predominantly present in the ER and secreted to extracellular space [87,88]. A Prdx4-knockout mouse strain has been widely used to study in vivo functions of PRDX4 [89]. Originally, the knockout mouse line was generated with conditional potential by insertion of two loxP sequences flanking exon 1B of the Prdx4 gene [89]. However, most studies have used Prdx4-null mice, in which exon 1B is deleted. The testis-specific form of PRDX4 is not deleted in this knockout mouse strain [86].

5.2. Phenotypes

Prdx4-knockout male mice (Prdx4−/y) are fertile but show testicular atrophy [89]. Spermatogenic cells in Prdx4−/y are susceptible to cell death by oxidative stress [89]. In a DSS-induced colitis model, Prdx4−/y show loss of body weight and shortening of colon length, which may be caused by ER stress and oxidative damage in colonic epithelial cells [90]. Prdx4−/y show a higher incidence of hepatocellular carcinoma in the diethylnitrosamine injection model compared with that of wild-type mice [91]. Triple deletion of ER thiol oxidases, Ero1l and Ero1lb, and Prdx4 causes interfered procollagen maturation and thus forms defective connective tissues in the extracellular matrix [92]. Prdx4 and superoxide dismutase 1 (Sod1) double-knockout mice (Prdx4−/y;Sod−/−) show more severe liver phenotypes, such as aggravated liver steatosis and liver failure, at a relatively young age compared with those of wild-type, Prdx4−/y, and Sod−/− [93].

6. Prdx5

6.1. Genetics and Knockout Mouse Strains

PRDX5 is a unique member of the atypical 2-Cys subfamily in mammals and is ubiquitously expressed in tissues [5,12]. PRDX5 is present in the cytosol, peroxisomes, and mitochondria [8]. The Prdx5 gene is located on mouse chromosome 19 and there are four alternative forms of Prdx5 protein-coding transcripts [31]. A Prdx5-knockout mouse line has been generated by the homologous recombination approach [94]. Another Prdx5-knockout mouse line that is generated by the gene trap approach is commercially available [95]. In this knockout line, a gene trap vector is inserted in the 5′UTR region of the Prdx5 gene. ES cell clones possessing the reporter and conditional allele of the Prdx5 gene have been produced [34], but a Prdx5-knockout mouse strain with conditional potential has not been reported.

6.2. Metabolism

Prdx5 deficiency leads to increased susceptibility to high-fat-diet-induced obesity, and thus Prdx5-knockout mice fed a high-fat diet show several metabolic abnormalities, including increased
body weight, adipocyte hypertrophy, fat accumulation in the liver, hepatic steatosis, and an increased triglyceride level in the serum [94,96].

7. Prdx6

7.1. Genetics and Knockout Mouse Strains

In mammals, PRDX6 is a unique member of the 1-Cys subfamily [5,12]. The Prdx6 gene is located on mouse chromosome 1 and produces two forms of alternatively spliced protein-coding transcripts [31]. PRDX6 is widely expressed in tissues and localized in the cytosol [8,97]. Two Prdx6-knockout mouse lines have been generated [97,98]. Exons 1 and 2 of the Prdx6 gene are replaced by a LacZ reporter and a neoR cassette in the first knockout mouse line [97], and a part of exon 3 is replaced by a neoR cassette in the second line [98]. Both knockout mouse lines are viable, fertile, and display no gross morphological defects [97,98]. IMPC produced a Prdx6-conditional knockout mouse line [34], although the mouse line has not been used for detailed phenotyping.

7.2. Tissue Protection

The protective roles of PRDX6 in the lung have been analyzed with Prdx6−/−. Administration of paraquat, an herbicide that produces damaging ROS within cells, causes tissue damage, decreased survival rate, and increased oxidation of lipids and proteins in the lungs of Prdx6−/− [97,99]. Exposure to 100% oxygen leads to similar defects in the lungs of Prdx6−/− [100]. Comparison between glutathione peroxidase 1 (Gpx1)-knockout mice and Prdx6−/− reveals that PRDX6 is the major enzyme for the reduction of phospholipid hydroperoxides in the lung [101]. In addition to the glutathione-dependent peroxidase activity, PRDX6 also has phospholipaseA2 (PLA2) and lysophospholipid:acyltransferase activities [102,103]. The deficiency of PLA2 activity alters phospholipid metabolism in the lungs of Prdx6−/− [102]. The lung and pulmonary microvascular endothelial cells (PMVECs) isolated from Prdx6−/− show increased sensitivity to peroxidative stress induced by exposure to 100% oxygen or tert-butyl hydroperoxide (t-BOOH) treatment [104,105]. These defects are partially rescued by the expression of mutant PRDX6 with either peroxidase activity alone or PLA2 activity alone [104,105]. However, coexpression of these mutant forms of PRDX6 rescues Prdx6-null PMVECs treated with t-BOOH as well as the expression of wild-type PRDX6 [104]. The glutathione-dependent peroxidase activity of PRDX6 can reduce both short-chain hydroperoxides such as H2O2 and phospholipid hydroperoxides [106]. The repair of peroxidized cell membranes of the lung or PMVECs is mostly dependent on the phospholipid hydroperoxidase activity rather than peroxidase activity toward H2O2 [106]. Protective effects of PRDX6 in the lung have been revealed using other lung injury models, including exposure to H2O2, LPS, or chronic cigarette smoke and cecal ligation and puncture (CLP)-induced acute lung injury [107–110]. Interestingly, the treatment of angiotensin II or phorbol ester increases the generation of superoxide and H2O2 in wild-type PMVECs but not in Prdx6-deficient PMVECs [111,112]. The authors explain that the PLA2 activity of PRDX6 is necessary for the activation of NADPH oxidase type 2 (NOX2), which produces superoxide [111,112]. PRDX6 also has protective roles in other tissues. PRDX6 protects the kidney from metabolic acidosis by contributing to the maintenance of anion exchanger 1 [113] and blood vessels in wounded skin [114].

7.3. Prion Disease

In ME7-infected prion disease models, Prdx6 deficiency worsens prion-related neuropathology [115]. These defects are caused by Prdx6 deficiency in astrocytes because PRDX6 is predominantly expressed in astrocytes rather than neurons in the brain [115].

7.4. Inflammation and Metabolism

Oxidative stress contributes to the pathogenesis of various inflammatory and metabolic diseases. Hepatic I/R injury causes a significant increase of PRDX6 expression and PRDX6 transfer from the
cytoplasm to the mitochondria [116]. Prdx6 deficiency in the I/R model increases the mitochondrial generation of H₂O₂ and mitochondrial dysfunction, thus leading to severe hepatocellular damage [116]. In Prdx6−/−, ethanol-induced lipid accumulation and peroxidation are observed in the liver [117]. An intensive study shows that Prdx6−/− develop insulin resistance, diabetic dyslipidemia, impaired insulin signaling, morphological changes in the pancreas and liver, and increased pro-inflammatory responses, suggesting that Prdx6 deficiency is a key mediator of hyperglycemia in type 2 diabetes [118]. A study suggests that PRDX6 is involved in the biosynthesis of fatty acid esters of hydroxy fatty acids that are lipid mediators with potent antidiabetic and anti-inflammatory activities [119]. In acute and chronic DSS-induced colitis models, however, Prdx6 deficiency attenuates the development of colitis [120]. The authors explain that Prdx6 deficiency is compensated by the upregulation of other PRDXs (PRDX3 and PRDX4) and antioxidant enzymes (Nrf2, Gss, and Gclm). A study tested the relationship between PRDX6 and atherosclerosis using Prdx6−/− with three different genetic backgrounds: atherosclerosis-resistant 129/SvJ (129), atherosclerosis-susceptible B6, and mixed B6;129 [121]. The effects of Prdx6 deficiency in atherosclerosis are minor and background dependent.

7.5. Aging

Prdx6−/− show age-related phenotypes [122–124]. Prdx6 deficiency decreases the fertility of male Prdx6−/− in an age-dependent manner [122]. PRDX6 protects spermatozoa against the oxidative stress that causes protein oxidation, lipid peroxidation, and DNA oxidation and fragmentation [122,123]. Lens epithelial cells (LECs) isolated from Prdx6−/− display elevated ROS expression and ER-stress-associated phenotypes [124,125]. Human LECs derived from aged men show a decreased level of PRDX6 and ER-stress-associated phenotypes [124]. LECs of Prdx6−/− are also more vulnerable to UV irradiation than those of wild-type mice [126].

7.6. Cancer

Prdx6 deficiency enhances susceptibility to tumorigenesis in the human-papillomavirus-8-induced skin cancer model [127]. The anti-tumorigenic effect of PRDX6 is achieved by the reduction of oxidative stress rather than altered proliferation, apoptosis, or the inflammatory response in keratinocytes [127].

8. Conclusions

PRDXs are typical peroxidases for the removal of cellular peroxides [1,2]. To investigate the biological roles of PRDXs, numerous approaches have been performed using the cell culture system. Although these experiments have provided valuable insights into PRDX biology, the approaches are not sufficient to reveal physiological functions in the human body. Knockout mouse models offer more reliable data to understand the in vivo functions of PRDXs (Table 1). More than one knockout mouse model of each PRDX has been generated and analyzed intensively. These knockout mouse models show that each PRDX functions essentially as a similar peroxidase and also performs specific functions depending on organs or intracellular organelles. In the past, the generation of knockout mouse models was time-consuming and labor-intensive work. However, recently developed gene-editing techniques using the CRISPR/Cas9 system have dramatically reduced these efforts [128]. Now, we can easily obtain GEM models that are more precisely modified than the previous complete knockout mouse models. Future studies using these new models, as well as complete knockout mouse models, will help us better understand the physiological roles of PRDXs and provide possible therapeutic targets for drugs against diseases, such as cancer and inflammatory and metabolic diseases.
Table 1. Knockout mouse models of Prdxs.

| Gene   | Models                                                                 | Phenotypes                          | Challenges ¹ | Affected Organs/Cells                      |
|--------|------------------------------------------------------------------------|-------------------------------------|--------------|-------------------------------------------|
|        | **KO1 [15]**                                                           |                                     |              |                                           |
|        | (Homologous recombination, Insertion, exon 3) ²                        | Tumorigenesis ¹⁵,¹⁶,¹⁸               | None         | Various                                   |
|        |                                                                       | Hemolytic anemia ¹⁵                 | None         | Red blood cells (RBCs)                    |
|        |                                                                       | Atherosclerosis ²¹                  | Normal diet, ApoE⁻/⁻ | Aorta                                    |
|        |                                                                       | Neuronal defects ³⁶                 | None         | Embryonic neurons                         |
|        | **KO2 [32]**                                                           |                                     |              |                                           |
|        | (Homologous recombination, Replacement, exons 1–6)                    | Pro-inflammation ²³                 | Lipopolysaccharide (LPS) | Liver                                    |
|        |                                                                       | Defective RBC clearance ³²          | None         | Macrophages                               |
|        |                                                                       | Cellular senescence ³⁹              | None         | Mouse embryonic fibroblasts (MEFs)        |
|        |                                                                       | Defective host defense ⁴¹          | *Staphylococcus aureus* | Liver, lung                              |
|        | **KO3 [17]**                                                           |                                     |              |                                           |
|        | (Gene Trap, Insertion, Intron 3)                                       | Tumorigenesis ¹⁷                   | None         | Brain, liver, spleen, MEFs                |
|        | **Prdx1**                                                              | Anti-inflammation ²⁰               | Ozone        | Lung                                      |
|        | **KO4 [33]**                                                           | Pro-inflammation ²⁶                 | Bleomycin    | Lung                                      |
|        | (Gene Trap, Insertion, Intron 3)                                       | Fibrosis ²⁶                        | Bleomycin    | Lung                                      |
|        |                                                                       | Asthma ²⁵                         | Cisplatin    | Lung                                      |
|        |                                                                       | Defective host defense ⁴⁰          | *Mycobacterium tuberculosis*     | Lung                                      |
|        |                                                                       | Kidney defects ³⁷                  | Ovalbumin    | Kidney                                    |
|        |                                                                       | Pro-apoptosis ²⁸                   | UVA          | MEFs                                      |
|        | **Uncertain**                                                          | Anti-inflammation ¹⁹               | Ischemia–reperfusion (I/R) injury | Brain                                    |
|        |                                                                       | Pro-inflammation ²⁴                 | LPS          | Microglia                                 |
|        |                                                                       | Anti-apoptosis ¹⁹                  | I/R injury   | Brain                                    |
|        |                                                                       | Pro-apoptosis ⁴²                   | Tunicamycin  | Corpus luteum                             |
|        |                                                                       | Atherosclerosis ¹³                 | Normal or high-fat diet, ApoE⁻/⁻ | Aorta                                    |
|        |                                                                       | Lung defects ²²                   | LPS          | Lung, macrophages                         |
|        |                                                                       | Loss of stemness ³⁸               | Differentiation medium | Embryonic stem (ES) cells |
|        |                                                                       | Reduced progesterone ⁴²            | Tunicamycin  | Corpus luteum                             |
|        |                                                                       | Defective HMGB1 secretion ³⁵       | LPS          | Macrophages                               |
Table 1. Cont.

| Gene | Models | Phenotypes | Challenges | Affected Organs/Cells |
|------|--------|------------|------------|-----------------------|
| Prdx2 KO1 [43] (Homologous recombination, Replacement, exons 1–5) | | | | |
| Hemolytic anemia [32,43,46–55] | None | RBCs, spleen, bone marrow (BM) |
| Defective iron homeostasis [53] | Carbonyl-iron, LPS | RBCs, liver, BM |
| Blood vessel defects [58,59] | None | Endothelial cells |
| Platelet defects [60] | Collagen | Platelet |
| Pro-inflammation [62–65] | None | Spleen, BM, thymus |
| Anti-inflammation [68] | Dextran sulfate sodium (DSS) | Colon |
| Atherosclerosis [66] | Atherogenic cholate-containing diet, ApoE−/− | Aorta |
| Anti-tumorigenesis [69,70] | Apc+/Min | Intestine, colon |
| Metabolic defects [73] | High-fat diet | MEFs, serum, muscle |
| Ovary defects [74,75] | None, PGF2α, 4-vinylcyclohexene dioxide | Ovary |
| Bone defects [45,71] | LPS | Bone |
| Neuronal defects [72] | None | Neurons |
| Pulmonary hypertension [67] | Hypoxia | Lung |
| Cellular senescence [56] | None | MEFs |
| Loss of stemness [38] | Differentiation medium | ES cells |
| Defective HMGB1 secretion [35] | LPS | Macrophages |
| Uncertain | Blood vessel defects [57] | FeCl3 | Carotid arteries |
| Gene     | Models                        | Phenotypes             | Challenges | Affected Organs/Cells |
|----------|-------------------------------|------------------------|------------|-----------------------|
|          |                               | Pro-apoptosis [85]     | UVB        | Keratinocytes         |
|          |                               | Muscle defects [79]    | None       | Muscle                |
|          |                               | Liver defects [82]     | Pyrazole   | Liver                 |
|          |                               | Metabolic defects [78] | None       | Fat, adipocytes       |
|          | KO1 [78]                      |                        |            |                       |
|          | (Homologous recombination,    |                        |            |                       |
|          | Replacement, exons 1–4)       |                        |            |                       |
| Prdx3    | KO2 [76]                      | Pro-apoptosis [80]     | None       | Brain                 |
|          | (Gene Trap, Insertion, Intron 1) | Muscle defects [80]    | None       | Muscle                |
|          |                               | Lung defects [76]      | LPS        | Lung                  |
|          |                               | Macrophage defects [81]| LPS        | Macrophages           |
|          |                               | Placental defects [83,84]| None     | Placenta              |
| Prdx4    | KO1 [89]                      | Tumorigenesis [91]     | Diethylnitrosamine | Liver               |
|          | (Homologous recombination,    | Colon defects [90]     | Dextran sulfate sodium | Colon              |
|          | Cre-loxP deletion, exon 1)    | Liver defects [93]     | Sod1<sup>−/−</sup> | Liver              |
|          |                               | Defective connective tissues [92]|<sup>1</sup>Ero1l<sup>−/−</sup>, Ero1bl<sup>−/−</sup>| Connective tissues |
| Prdx5    | KO1 [94]                      | Metabolic defects [94,96]| High-fat diet | Fat, liver            |
|          | (Homologous recombination,    |                        |            |                       |
|          | Replacement, not specified)   |                        |            |                       |
| Gene Models | Phenotypes | Challenges \(^1\) | Affected Organs/Cells |
|-------------|------------|----------------|----------------------|
| Prdx6 KO1 [97] (Homologous recombination, Replacement, exons 1 and 2) | Tissue defects [97] | Paraquat | Lung, kidney, liver, macrophages |
| &nbsp; | Anti-inflammation [120] | DSS | Colon |
| &nbsp; | Tumorogenesis [127] | Human papillomavirus 8 | Skin |
| &nbsp; | Atherosclerosis (mild) [121] | Atherogenic high fat diet | Aorta, plasma |
| &nbsp; | Metabolic defects [118] | None | Various |
| &nbsp; | Lens defects [124,125] | None, hypoxia, CoCl\(_2\), tunicamycin, H\(_2\)O\(_2\) | Lens epithelial cells (LECs) |
| &nbsp; | Lar defects and pro-apoptosis [126] | UVB | LECs |
| &nbsp; | Liver defects [117] | Ethanol | Liver |
| &nbsp; | Prion disease [115] | ME7 | Brain |
| &nbsp; | Vascular defects [114] | UV | Skin, blood vessels |

| Prdx6 KO2 [98] (Homologous recombination, Replacement, exon 3) | Lung defects [99–101,107–110] | Paraquat | Lung |
| &nbsp; | &nbsp; | Hyperoxia | Lung |
| &nbsp; | &nbsp; | Hyperoxia, tert-butylhydroperoxide (t-BOOH), Paraquat | Lung, pulmonary microvascular endothelial cells (PMVECs) |
| &nbsp; | &nbsp; | H\(_2\)O\(_2\) | Type II alveolar epithelial cells |
| &nbsp; | &nbsp; | Cigarette smoke | Lung |
| &nbsp; | &nbsp; | Cecal ligation and puncture | Lung |
| &nbsp; | &nbsp; | LPS | Lung |
| &nbsp; | Lung defects (phospholipid metabolism) [102] | None | Lung |
| &nbsp; | PMVEC defects [104] | t-BOOH | PMVECs |
| &nbsp; | Lung and PMVEC defects [105,106] | t-BOOH, hyperoxia | PMVECs, lung |
| &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| &nbsp; | Attenuated production of superoxide and H\(_2\)O\(_2\) [111,112] | Angiotensin II, Phorbol ester | Lung, PMVECs, alveolar macrophages |
| &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| &nbsp; | Defective spermatogenesis [122,123] | Aging, t-BOOH | Sperm |
| &nbsp; | Liver defects [116] | I/R injury | Liver |
| &nbsp; | Kidney defects [113] | NH\(_4\)Cl | Kidney |

\(^1\) Most phenotypes are induced by various challenges. \(^2\) Methods to generate knockout mouse models.
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