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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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NEXT-GENERATION ANTIOXIDANTS: SHOULD WE TARGET PEROXIREDOXINS (PRX)?

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Abstract.

Reactive oxygen species (ROS) play a dual role in biology, functioning as both essential signaling molecules and agents of cellular damage under oxidative stress. While classical antioxidant therapies have shown promise in preclinical models, they have consistently failed in clinical trials, largely due to their lack of specificity and disruption of physiological redox signaling. Peroxiredoxins (Prx), a family of thiol-dependent peroxidases, have emerged as attractive next-generation targets due to their enzymatic specificity, compartmentalization, and involvement in redox relay mechanisms. This review critically examines the structural and functional features of Prx, their context-dependent roles in cancer, neurodegeneration, and cardiovascular diseases, and the growing arsenal of pharmacological modulators. We further discuss the challenges and opportunities of Prx-targeted therapy and evaluate whether these enzymes represent a viable and superior strategy within the evolving landscape of redox medicine.

Key words. Peroxiredoxin, antioxidant, reactive oxygen species, redox signaling, isoform-specific, therapeutic targeting, oxidative stress, inflammation, cancer, neurodegeneration.

Introduction.

Oxidative stress, arising from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, is a key contributor to cellular dysfunction. ROS, including hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), and hydroxyl radicals (•OH), are generated as byproducts of mitochondrial oxidative phosphorylation, enzymatic reactions (e.g., NADPH oxidases, xanthine oxidase), and uncoupled nitric oxide synthase during pathological conditions [1,2]. While physiological ROS levels are essential for cell signaling, immune responses, and stress adaptation, their excessive accumulation induces oxidative damage to biomolecules such as proteins, lipids, and DNA [3].

The pathological implications of oxidative stress are multifaceted. It drives the progression of chronic diseases, including cancer (via DNA mutations and aberrant signaling), neurodegenerative disorders (through synaptic dysfunction and neuronal loss), cardiovascular diseases (mediated by endothelial dysfunction and lipid peroxidation), and autoimmune/inflammatory conditions (via ROS-dependent cytokine modulation) [2,4]. Additionally, ROS contribute to aging, metabolic syndromes (e.g., diabetes), and acute events such as ischemic stroke and myocardial infarction, often through mitochondrial dysfunction [5]. These associations have spurred interest in antioxidant therapies for clinical and preventive applications.

Despite decades of research, conventional antioxidants (e.g., vitamins C, E, N-acetylcysteine) have underperformed in clinical trials [6,7]. Their non-specific action disrupts both harmful and beneficial ROS-mediated processes, such as growth factor signaling and immune activation. Furthermore, poor bioavailability, limited tissue targeting, and an inability to adapt to dynamic redox changes diminish their therapeutic efficacy *in vivo* [8]. For instance, high-dose vitamin E supplementation paradoxically increases oxidative damage in some cohorts, highlighting the risks of non-selective ROS scavenging [8].

This has prompted a paradigm shift in redox medicine: instead of indiscriminate ROS suppression, precision modulation of oxidative signaling is now prioritized. Within this framework, endogenous redox-regulating enzymes, particularly peroxiredoxins (Prx), have gained prominence. Prx are evolutionarily conserved thiol peroxidases that not only scavenge ROS but also regulate redox-sensitive signaling pathways [9,10]. Their isoform-specific localization - cytosol (Prx1, Prx2), mitochondria (Prx3, Prx5), endoplasmic reticulum (Prx4), and extracellular compartments - ensures compartmentalized control of oxidative stress [11]. The increasing recognition of peroxiredoxins as key regulators of redox homeostasis is reflected in a steady rise in scientific publications over the past two decades (Figure 1), highlighting their growing importance in biomedical research.

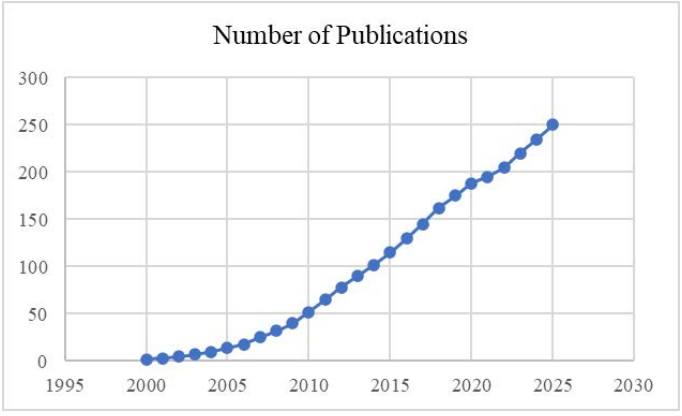

Figure 1. *Growth in the number of scientific publications on peroxiredoxins (Prx) from 2000 to 2025, indicating increasing research interest in redox-regulating enzymes (based on PubMed query using keyword 'peroxiredoxin').*

Prx are thiol-based peroxidases that exhibit high reactivity with H_2O_2 and other peroxides, playing a dual role as both ROS scavengers and modulators of redox-dependent signaling pathways [9,10]. Prx enzymes are highly conserved across species and are ubiquitously expressed in mammalian cells, with isoform-specific localizations that include the cytosol (Prx1, Prx2), mitochondria (Prx3, Prx5), endoplasmic reticulum (Prx4), peroxisomes, and extracellular compartments [11]. Their abundance often among the most highly expressed proteins in redox-active tissues and their exceptional reaction rates with H_2O_2 (10^6–10^8 $M^{-1}s^{-1}$,) make them ideal cellular sensors and first responders to oxidative shifts [12]. Their catalytic cycle is reversible and tightly regulated by the thioredoxin system, allowing for a rapid return to baseline activity following oxidative bursts [13].

Importantly, Prx are not merely passive peroxide-eliminating enzymes. They participate in redox relay mechanisms by undergoing reversible oxidation at their catalytic cysteine residues, enabling the transfer of oxidative equivalents to downstream signaling proteins such as transcription factors, phosphatases, and kinases [14]. This function allows Prx to shape signaling cascades such as MAPK, NF-κB, and JAK/STAT pathways in a spatially and temporally controlled manner [15]. Hyperoxidation of the peroxidatic cysteine (to sulfinic acid) under high ROS conditions temporarily inactivates Prx and may serve as a regulatory mechanism to permit ROS-mediated signaling or trigger alternative protective programs, such as chaperone functions [16]. Given their versatility, tissue specificity, and integration into redox-regulatory networks, Prx enzymes have emerged as attractive targets for precision antioxidant therapies. Instead of broad ROS neutralization, modulation of Prx activity - either through isoform-specific enhancement or inhibition - offers a nuanced strategy to influence redox-sensitive disease mechanisms. This review aims to explore the structure, function, regulation, and disease relevance of Prx enzymes and assess the therapeutic potential of pharmacologically targeting them as part of a next-generation antioxidant strategy.

Peroxiredoxins: Structure and Function.

The mammalian peroxiredoxin (Prx) family consists of six isoforms (Prx1 to Prx6), classified into three mechanistic groups based on the number and spatial arrangement of catalytic cysteine residues: typical 2-Cys, atypical 2-Cys, and 1-Cys peroxiredoxins [6,7]. These categories reflect distinct structural and functional properties that govern their reactivity, subcellular distribution, and physiological roles. A defining feature of all Prx isoforms is the presence of a conserved peroxidatic cysteine (Cp), which reacts with peroxides - primarily hydrogen peroxide (H_2O_2) - to generate a sulfenic acid intermediate (Cys-SOH).

In typical 2-Cys Prx (Prx1–4), these intermediate forms an intermolecular disulfide bond with a resolving cysteine (Cr) from a neighboring subunit. In contrast, atypical 2-Cys Prx (Prx5) utilize an intramolecular disulfide bond involving a Cr within the same polypeptide chain. The 1-Cys Prx (Prx6), lacking a Cr, depends on non-thiol reductants like glutathione for catalytic regeneration [6,8].

Following disulfide formation, the thioredoxin (Trx) system restores Prx activity. Thioredoxin reduces the disulfide bond, reverting Prx to its active thiol state, while thioredoxin reductase (TrxR) regenerates Trx using NADPH as an electron donor. This Prx–Trx–TrxR–NADPH axis constitutes a central redox regulatory mechanism in mammalian cells [13]. Beyond peroxidase activity, this system enables feedback regulation tailored to intracellular redox conditions.

Under sustained oxidative stress, Prx enzymes undergo hyperoxidation, where the Cp is further oxidized to sulfinic acid ($–SO_2H$). This modification inactivates peroxidase function but is reversible via the ATP-dependent enzyme sulfiredoxin (Srx), which restores the thiol state [8]. Such dynamic switching between active and inactive states allows Prx to act as redox sensors, fine-tuning their activity to cellular demands.

Prx isoforms also exhibit non-canonical roles. For example, Prx1 and Prx2 oligomerize under oxidative stress, adopting chaperone-like functions that prevent protein aggregation [9]. This transition, regulated by redox-sensitive structural rearrangements, is critical during chronic oxidative or thermal stress [10]. Additionally, Prx participate in redox relay systems, transferring oxidative equivalents via transient disulfide bonds to signaling proteins like ASK1, PTEN, and STAT3. Through this mechanism, Prx modulate major pathways such as MAPK, NF-κB, and JAK/STAT, bridging redox perturbations to cellular responses [11,14,15].

Structural plasticity underpins Prx multifunctionality. Conformational shifts between reduced (dimeric) and hyperoxidized (decameric) states correlate with functional changes: decamerization enhances chaperone activity, while dimeric forms prioritize peroxidase function [9]. This adaptability justifies their classification as “moonlighting proteins.”

Compartment-specific localization further refines Prx roles. Mitochondrial Prx3 and Prx5 buffer ROS generated by electron transport chains, while ER-localized Prx4 supports oxidative protein folding. Prx6, uniquely bifunctional (peroxidase and phospholipase A2), is enriched in lung tissue, where it safeguards against lipid peroxidation [11,12].

In summary, the structural diversity and functional versatility of Prx enzymes position them as indispensable components of cellular antioxidant and signaling networks. Their dual roles in redox sensing, detoxification, and pathway regulation - coupled with isoform-specific localization - highlight their potential as biomarkers and therapeutic targets. Key isoform-specific characteristics are summarized in Table 1, while disease associations and therapeutic implications are outlined in Table 2.

Dual Role of Prx in Health and Disease.

Peroxiredoxins (Prx) exhibit a dualistic nature in biological systems: they serve as critical antioxidants maintaining redox homeostasis while paradoxically contributing to disease progression under specific conditions. This dichotomy is most evident in cancer and neurodegenerative disorders, where Prx isoforms adopt opposing roles depending on disease stage, subcellular localization, and oxidative stress intensity [6,12,13].

Table 1. *Characteristics of Mammalian Peroxiredoxin Isoforms.*

Isoform	Localization	Classification	Substrate Specificity	Additional Functions
Prx1	Cytosol, nucleus	Typical 2-Cys	H2O2, organic peroxides	Tumor growth regulation, chaperone activity
Prx2	Cytosol, nucleus	Typical 2-Cys	H2O2	Redox signaling modulation, anti-apoptotic function
Prx3	Mitochondria	Typical 2-Cys	H2O2	Mitochondrial ROS control, apoptosis regulation
Prx4	ER, extracellular	Typical 2-Cys	H2O2	Inflammatory regulation, ER stress response
Prx5	Mitochondria, peroxisomes, cytosol	Atypical 2-Cys	Broad substrate range	Protection from lipid peroxides, inflammation control
Prx6	Cytosol, lysosomes	1-Cys	H2O2, phospholipid hydroperoxides	Phospholipase A2 activity, lung defense

Table 2. *Disease-Relevant Roles of Prx Isoforms.*

Disease Category	Major Isoforms Involved	Role of Prx	Therapeutic Implication
Cancer	Prx1, Prx2	Pro-survival, chemoresistance	Inhibitors as sensitizers to therapy
Neurodegeneration	Prx2, Prx3	Anti-apoptotic, antioxidant	Activators for neuroprotection
Cardiovascular	Prx3, Prx5	Mitochondrial protection	Activators to limit I/R injury
Inflammation	Prx4, Prx5	ROS buffering, cytokine modulation	Anti-inflammatory targets

In neurodegenerative disorders such as Alzheimer's (AD), Parkinson's (PD), and amyotrophic lateral sclerosis (ALS), oxidative damage is a hallmark of neuronal dysfunction. Prx2 and Prx3 are upregulated in response to elevated ROS, acting as primary defenders. For instance, in PD models, Prx2 attenuates dopaminergic neuron loss by inhibiting the ASK1–p38/JNK apoptotic pathway [16]. Similarly, mitochondrial Prx3 mitigates oxidative damage and dysfunction, which are central to neuronal death in both PD and AD [11]. Prx3 overexpression also reduces cerebral infarct volumes in ischemic stroke models, underscoring its neuroprotective potential [14,15].

Beyond ROS scavenging, Prx regulate neuroinflammatory processes. They modulate microglial activation, synaptic plasticity, and inflammatory cytokine release. Notably, hyperoxidized Prx2 can act as a damage-associated molecular pattern (DAMP), triggering neuroinflammation via Toll-like receptor 4 (TLR4) activation in microglia [12]. Thus, while Prx are cytoprotective under moderate stress, their dysregulation in advanced disease stages may exacerbate neuroinflammation, highlighting their context-dependent duality.

In contrast, Prx1 and Prx2 are frequently overexpressed in malignancies, including breast, lung, prostate, and colorectal cancers. Their elevated expression correlates with aggressive tumor behavior, therapy resistance, and poor prognosis [13,16]. Cancer cells exploit Prx to neutralize ROS from metabolic hyperactivity, hypoxia, and chemotherapy, thereby enhancing survival. Prx1 and Prx2 further promote tumorigenesis by modulating redox-sensitive transcription factors (e.g., NF-κB, AP-1, HIF-1α), driving pro-survival and angiogenic gene expression [15].

Prx also facilitate cancer stemness and metastasis. In breast cancer, Prx1 stabilizes β-catenin, amplifying Wnt/β-catenin signaling to enhance tumor aggressiveness [13]. Silencing Prx2 in colorectal cancer models sensitizes cells to oxaliplatin and 5-FU, suggesting that pharmacological Prx inhibition could overcome chemoresistance [16].

Prx are increasingly implicated in autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In these conditions, oxidative stress promotes autoantigen modification and chronic inflammation. Prx2 and Prx4, overexpressed in synovial tissues and immune cells, regulate NF-κB and STAT3 pathways, amplifying cytokine production and immune hyperactivation [12,14]. Oxidized Prx2 may even act as a neoantigen, fueling autoreactive immune responses [11].

In metabolic syndromes like obesity and type 2 diabetes, mitochondrial Prx3 and Prx5 counteract oxidative stress in adipocytes and hepatocytes. Their downregulation or hyperoxidation correlates with insulin resistance, lipid accumulation, and systemic inflammation. Conversely, Prx3 upregulation improves glucose tolerance and reduces hepatic steatosis in high-fat diet models [13,14].

Prx also mediate intercellular communication via extracellular vesicles (EVs). Hyperoxidized Prx released in EVs function as DAMPs, activating pattern recognition receptors (e.g., TLR2, TLR4) on immune and endothelial cells. This paracrine signaling exacerbates systemic inflammation in sepsis, acute lung injury, and sterile inflammation. Prx-containing EVs further influence vascular tone, extracellular matrix remodeling, and immune cell recruitment under oxidative stress [12].

Prx thus function as a double-edged sword: their antioxidant activity protects against degenerative and inflammatory diseases but is co-opted by cancers for survival. Therapeutic strategies must therefore be context specific. For example, Prx activation may benefit neurodegenerative conditions, while inhibition could sensitize tumors to therapy. This approach is guided by the divergent ROS levels and Prx activity observed across pathologies (Figure 2), as well as their role in redox relay systems that transmit oxidative signals via transient disulfide bonds (Figure 3) [12,14].

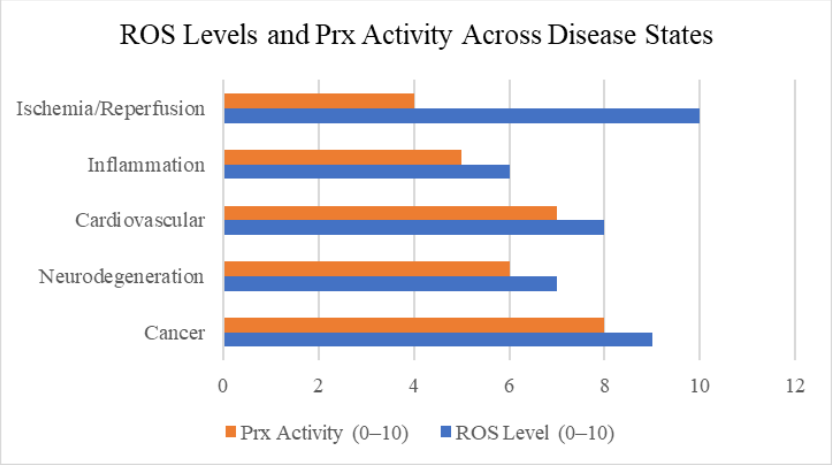

Figure 2. *Comparison of relative ROS levels and peroxiredoxin (Prx) activity across major disease states. While ROS levels are generally elevated in pathological conditions such as cancer and ischemia-reperfusion injury, Prx activity shows variable patterns - upregulated in some degenerative diseases and suppressed or exploited in malignancies - underscoring the need for context-specific therapeutic strategies.*

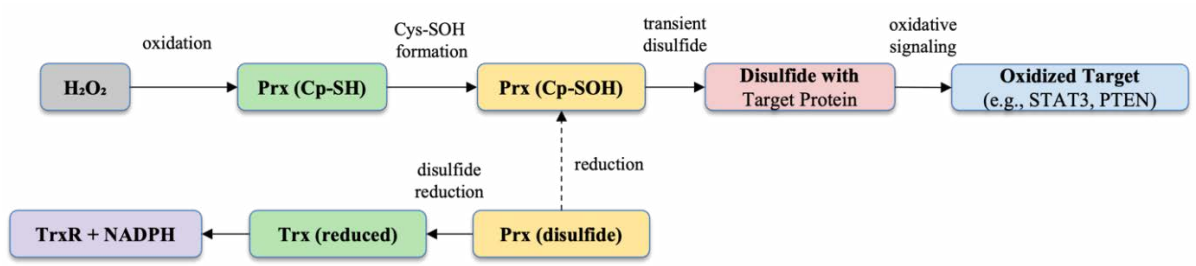

Figure 3. *Schematic representation of a redox relay involving peroxiredoxins (Prx). Upon reacting with H_2O_2, the peroxidatic cysteine (Cys) of Prx is oxidized to sulfenic acid (Cys–SOH), which can either form an internal disulfide (later reduced via Trx/TrxR) or create a transient disulfide with a target protein. This redox-dependent protein modification can activate or inhibit downstream signaling pathways such as STAT3 or PTEN.*

Therapeutic Modulation of Prx Activity.

Therapeutic modulation of peroxiredoxin (Prx) activity represents a rapidly evolving frontier in redox-targeted medicine. As dual-function enzymes - scavenging reactive oxygen species (ROS) while regulating redox signaling - Prx occupy a unique niche at the intersection of oxidative stress mitigation and cellular communication. This duality enables diverse pharmacological strategies: **activation** of Prx to protect against degenerative diseases and **inhibition** to sensitize cancer cells to oxidative damage, depending on pathological context [6,13,14].

Unlike classical antioxidants, which indiscriminately neutralize ROS, Prx-targeted therapies allow compartmentalized control of redox balance. Such strategies must account for isoform-specific expression patterns, tissue distribution, and disease-driven regulation of Prx. For example, mitochondrial Prx3 may be prioritized in neurodegenerative disorders, while cytosolic Prx1/2 are key targets in cancers [11,13]. Additionally, the integration of Prx into broader redox networks - including the thioredoxin (Trx) and glutathione systems - demands a system-level understanding of feedback mechanisms to avoid unintended disruptions [11,17].

Strategies for Modulating Prx Activity.

1. **Activation Approaches**

- **Gene Therapy**: Overexpression of protective isoforms (e.g., Prx3 in stroke models) [15].
- **Transcriptional Activators**: Nrf2 agonists (e.g., sulforaphane) induce Prx expression, showing neuroprotective effects in preclinical trials [16].
- **Post-Translational Stabilizers**: Compounds preventing hyperoxidation (e.g., sulfiredoxin inducers) restore Prx activity under chronic oxidative stress [8].

2. **Inhibition Approaches**

- **Small-Molecule Inhibitors**: Covalent blockers of the peroxidatic cysteine (e.g., Conoidin A, adenanthin) selectively impair Prx1/2 in cancers [16].
- **Indirect Modulators**: Auranofin, a thioredoxin reductase (TrxR) inhibitor, disrupts the Trx-Prx axis, elevating ROS in leukemia and ovarian cancer cells [17].

Clinical Progress and Challenges.

Although no Prx-specific drugs have reached late-stage trials, repurposed agents and biomarker-driven strategies show promise:

- **Sulforaphane**, an Nrf2 activator, is in early-phase trials for Alzheimer's disease and metabolic syndrome due to its Prx-inducing effects.
- **Auranofin**, an FDA-approved antirheumatic drug, has demonstrated antitumor activity in phase I/II studies, partly via Prx pathway modulation [17].
- **Prx Expression Profiling**: Emerging as a biomarker for tumor stratification (e.g., high Prx1 correlates with chemoresistance in colorectal cancer) [16].

Despite progress, challenges persist:

- **Isoform Redundancy**: Knockdown of one Prx may upregulate others, blunting therapeutic efficacy.
- **Off-Target Effects**: Many inhibitors (e.g., Conoidin A) lack isoform specificity, risking unintended thiol oxidation.
- **Delivery Hurdles**: Poor bioavailability of natural compounds (e.g., curcumin) limits clinical translation [15].

Future Directions.

Advancements in structural biology and nanotechnology may address these limitations:

- **Isoform-Specific Inhibitors**: Computational modeling of Prx active sites could yield selective compounds.
- **Targeted Delivery Systems**: Liposomal encapsulation or nanoparticle carriers may enhance tissue-specific Prx modulation.
- **Combination Therapies**: Pairing Prx inhibitors with ROS-inducing agents (e.g., radiotherapy) could amplify efficacy [13].

Prx modulation holds transformative potential for redox medicine, offering context-dependent solutions unmet by traditional antioxidants. While preclinical data are compelling, clinical success hinges on overcoming isoform redundancy, optimizing delivery, and validating biomarkers. Strategic integration of pharmacology, systems biology, and translational research will be critical to harness Prx as therapeutic targets. Current strategies are summarized in **Table 3**.

Prx Activators.

In pathological conditions characterized by excessive oxidative stress - such as ischemic stroke, myocardial infarction, neurodegenerative disorders, and sepsis - enhancing peroxiredoxin (Prx) activity offers a promising strategy to mitigate tissue damage. The therapeutic rationale stems from the observation that Prx isoforms are frequently downregulated or functionally inactivated in these settings, leading to unchecked oxidative injury, inflammatory cascades, and cellular apoptosis [14,15]. By restoring redox homeostasis through Prx activation, it is possible to neutralize harmful reactive oxygen species (ROS) while preserving physiological signaling pathways. Genetic overexpression of Prx isoforms in animal models has demonstrated robust protective effects. For example, transgenic mice engineered to overexpress Prx1 or Prx3 exhibit significantly smaller cerebral infarct volumes, reduced neuronal apoptosis, and improved motor function following middle cerebral artery occlusion (MCAO), a widely used model of ischemic stroke [14]. Comparable benefits have been observed in preclinical studies of spinal cord injury and myocardial infarction, where Prx upregulation attenuates neuroinflammation, minimizes oxidative DNA damage, and preserves mitochondrial integrity [15,16]. These findings underscore the potential of Prx activation to counteract multifactorial damage in acute and chronic oxidative stress scenarios.

Pharmacological strategies to enhance Prx activity:

1. **Nrf2-ARE Pathway Activation**

The Nrf2-antioxidant response element (Nrf2-ARE) axis is a central regulator of endogenous antioxidant defenses, including Prx. Sulforaphane, a naturally occurring isothiocyanate derived from cruciferous vegetables (e.g., broccoli, kale), potently activates Nrf2, leading to transcriptional upregulation of Prx1, Prx2, and Prx5 [15]. In rodent models of traumatic brain injury, sulforaphane administration reduces neuronal loss, stabilizes the blood-brain barrier, and improves cognitive outcomes - effects partially attributed to increased Prx expression. Similarly, curcumin (a polyphenol from turmeric) and tert-butylhydroquinone (tBHQ), a synthetic antioxidant, induce Prx via Nrf2-dependent mechanisms, highlighting the versatility of this pathway [15,17].

2. **Stabilization of Reduced Prx Forms**

Beyond transcriptional regulation, alternative approaches focus on maintaining Prx in their active, reduced state. This includes:

- **Modulating Thioredoxin Interactions**: Enhancing the activity of the thioredoxin (Trx) system, which regenerates reduced Prx, through TrxR1 agonists or NADPH-boosting agents.
- **Inhibiting Hyperoxidation**: Pharmacological induction of sulfiredoxin (Srx), an ATP-dependent enzyme that repairs hyperoxidized Prx (-SO_2H), restores peroxidase activity under sustained oxidative stress [8]. Co-targeting Srx and Prx may amplify antioxidant capacity in diseases like sepsis or chronic inflammation.

While Prx activators hold significant therapeutic promise, their use requires careful optimization to avoid oversuppressing ROS-dependent physiological processes. For instance, excessive Nrf2 activation may impair immune cell function or disrupt redox-sensitive repair mechanisms. Similarly, global

Table 3. *Comparative Strategies for Modulating Prx Activity in Disease Contexts.*

Strategy Type	Approach	Mechanism	Target Context	Clinical Status
Activation	Nrf2 activators (e.g., sulforaphane)	Upregulate Prx gene expression	Neurodegeneration, CVD	Preclinical / Early trials
Activation	Gene therapy	Overexpression of protective isoforms	Ischemia, stroke	Preclinical
Activation	Srx inducers	Reverse hyperoxidation of Prx	Sepsis, metabolic disorders	Experimental
Inhibition	Direct Prx inhibitors (e.g., Conoidin A)	Covalent modification of catalytic cysteine	Cancer, leukemia	Preclinical
Inhibition	Indirect inhibition (e.g., auranofin)	Disruption of Trx-Prx recycling	Cancer, inflammation	Early-phase trials
Inhibition	siRNA or CRISPR-mediated knockdown	Isoform-specific suppression	Cancer models	Experimental

Prx overexpression could inadvertently promote tumorigenesis in predisposed tissues. Therefore, context-specific dosing, isoform-selective agents, and combinatorial approaches (e.g., pairing Prx activators with anti-inflammatory drugs) are critical to maximizing efficacy and safety.

Future Directions. Emerging strategies include:

- **Gene Therapy**: Viral vector-mediated delivery of Prx isoforms to ischemic or inflamed tissues.
- **Nanoparticle-Based Delivery**: Encapsulating Nrf2 agonists or Srx inducers to enhance bioavailability and target specificity.
- **Biomarker-Guided Therapy**: Monitoring Prx oxidation status (e.g., via sulfinic acid detection) to tailor interventions to individual redox profiles.

In summary, Prx activators represent a multifaceted therapeutic approach for oxidative stress-related diseases. Preclinical data underscore their potential, but translational success will depend on addressing context-dependent risks and refining delivery mechanisms.

Prx Inhibitors.

In oncology, the overexpression of peroxiredoxin (Prx) isoforms – particularly Prx1 and Prx2 – is strongly associated with tumor progression, metastasis, and resistance to chemotherapy. This has spurred the development of inhibitors targeting Prx activity, with the therapeutic rationale that suppressing Prx will elevate intracellular ROS to toxic levels, triggering apoptosis or sensitizing cancer cells to conventional treatments [13,16].

Direct Inhibition of Prx Enzymatic Activity:

- **Conoidin A**: One of the first identified Prx inhibitors, this small molecule covalently modifies the peroxidatic cysteine of Prx2, irreversibly blocking its peroxidase function. Preclinical studies demonstrate selective cytotoxicity in cancer cells while sparing normal cells, suggesting a favorable therapeutic window. However, its non-specific reactivity with other thiol-containing proteins limits clinical applicability [16].
- **Adenanthin**: A diterpenoid isolated from *Isodon species*, adenanthin selectively inhibits Prx1 by targeting its catalytic site. In leukemia models, it suppresses cell growth by dysregulating the NF-κB pathway and amplifying ROS accumulation. Notably, adenanthin enhances sorafenib-induced apoptosis in hepatocellular carcinoma, underscoring its potential in combination therapies [16].

Indirect Strategies: Targeting Redox Partners:

- **Auranofin**: This FDA-approved antirheumatic drug inhibits thioredoxin reductase (TrxR), disrupting the Trx-Prx regeneration cycle and elevating ROS in cancer cells. Preclinical studies highlight its efficacy in pancreatic, ovarian, and non-small cell lung cancers, leading to its repurposing as an anticancer agent [17].

Recent high-throughput screenings have identified novel Prx inhibitors with enhanced specificity:

- **Cyclic Peptides/Peptidomimetics**: Designed to bind Prx active sites or allosteric pockets, these compounds show reduced off-target effects.
- **Covalent Modifiers**: Selective agents that exploit isoform-specific structural differences, improving tumor selectivity.

Several inhibitors exhibit synergy with DNA-damaging agents (e.g., cisplatin) or kinase inhibitors, suggesting combinatorial potential. For example, Conoidin A combined with PARP inhibitors enhances synthetic lethality in BRCA-mutant cancers [16].

Current Limitations and Future Directions

Key challenges include:

1. **Isoform Specificity**: Most inhibitors (e.g., Conoidin A) lack selectivity among Prx isoforms, risking compensatory upregulation of non-targeted family members.
2. **Off-Target Effects**: Reactivity with non-Prx thiols (e.g., glutathione, thioredoxin) may disrupt redox homeostasis in healthy tissues.
3. **Delivery and Bioavailability**: Poor solubility and rapid clearance hinder the clinical translation of natural compounds like adenanthin.

To address these, future efforts should integrate:

- **Structure-Based Drug Design**: Leveraging cryo-EM and X-ray crystallography to develop isoform-selective inhibitors.
- **Omics Profiling**: Identifying biomarkers (e.g., Prx1/2 overexpression) to stratify patients for targeted therapy.
- **Nanocarrier Systems**: Enhancing drug delivery via liposomes or polymer-based nanoparticles.

Selected Prx-modulating compounds, their targets, and developmental status are summarized in Table 4.

Advantages of Targeting Prx over Classical Antioxidants.

Classical antioxidants, including vitamins C and E, glutathione precursors, and polyphenols, have long been explored as therapeutic agents to combat oxidative stress. However, their non-specific mechanism of action – broad scavenging of free radicals – often disrupts physiological ROS signaling essential for cellular processes such as proliferation, differentiation, and immune responses [6,7,17]. This lack of selectivity likely underlies their limited clinical success, despite encouraging preclinical results. For instance, high-dose vitamin E supplementation has paradoxically been linked to increased mortality in some meta-analyses, emphasizing the risks of indiscriminate ROS suppression [7].

In contrast, peroxiredoxins (Prx) offer distinct advantages as therapeutic targets due to their enzymatic precision, compartmentalized activity, and integration into redox regulatory networks. Unlike classical antioxidants, Prx exhibit catalytic efficiency unparalleled in peroxide scavenging, with rate constants for H_2O_2 detoxification reaching 10^6–10^8 $M^{-1}s^{-1}$ [12]. This kinetic superiority enables rapid neutralization of oxidative bursts while preserving redox-sensitive signaling pathways critical for cellular adaptation.

Another key advantage lies in their isoform- and organelle-specific localization. Prx isoforms are strategically distributed across subcellular compartments - mitochondria (Prx3, Prx5), cytosol (Prx1, Prx2), endoplasmic reticulum (Prx4), and peroxisomes - allowing precise regulation of ROS microdomains. For example, mitochondrial Prx3 directly buffers ROS generated by electron transport chains, safeguarding against apoptosis and metabolic dysfunction [11]. Such compartmentalization enables

Table 4. *Selected Small Molecules Targeting Prx Activity.*

Compound	Type	Target Isoforms	Mechanism of Action	Disease Context	Stage of Development	Ref.
Sulforaphane	Activator	Prx1–5 (via Nrf2)	Nrf2-mediated transcriptional upregulation	Neuroprotection, inflammation	Preclinical	[15]
Conoidin A	Inhibitor	Prx1, Prx2	Covalent modification of peroxidatic cysteine	Cancer (various types)	Preclinical	[16]
Adenanthin	Inhibitor	Prx1	Thiol modification, NF-κB inhibition	Leukemia, HCC	Preclinical	[16]
Auranofin	Indirect inhibitor	Prx system (via TrxR)	TrxR inhibition, disrupts Prx regeneration	Cancer, inflammation	Clinical (repurposed)	[17]
SK053	Inhibitor	Prx1	Cysteine-targeting covalent inhibition	Lung cancer, leukemia	Preclinical	[16]
PRDXi	Inhibitor	Prx2	Selective inhibition via active-site binding	Glioblastoma	Experimental	[16]
ML210	Indirect activator	GPX4/Prx interaction	Induces ferroptosis, modulates redox pathways	Solid tumors	Preclinical	[17]

Table 5. *Comparison of Prx with Classical Antioxidant Systems.*

Feature	Peroxiredoxins (Prx)	Catalase	Glutathione Peroxidase (GPx)	Vitamin-based Antioxidants
ROS specificity	H2O2, peroxynitrite	H2O2	H2O2, lipid hydroperoxides	Broad (non-specific)
Subcellular localization	Isoform-dependent	Peroxisomes	Cytosol, mitochondria	Non-compartmentalized
Regulation	Trx/Srx/NADPH system	Constitutive	GSH-dependent	None (passive scavenging)
Redox signaling function	Yes	No	Limited	No
Multifunctionality	Peroxidase, chaperone, relay	No	Limited	No
Therapeutic modifiability	High (isoform-targetable)	Low	Moderate	High (but non-specific)

therapies to target oxidative stress at its source, minimizing off-tissue effects.

Prx further distinguish themselves through dynamic post-translational regulation. Redox-sensitive modifications - such as sulfenylation, disulfide bond formation, and reversible hyperoxidation - allow Prx to function as sensors and modulators rather than passive scavengers. These mechanisms preserve the complexity of ROS signaling networks, which classical antioxidants often disrupt. For instance, hyperoxidation of Prx2 under severe stress temporarily halts its peroxidase activity, permitting localized ROS signaling while activating chaperone functions to protect against protein aggregation [14].

The functional versatility of Prx expands their therapeutic potential. Beyond peroxide elimination, they act as molecular chaperones and redox relays, transmitting oxidative signals to downstream effectors like NF-κB, MAPK, and JAK/STAT pathways [10,15]. This multifunctionality allows selective modulation of processes such as inflammation or apoptosis without globally suppressing ROS, a limitation inherent to non-enzymatic antioxidants.

Finally, Prx targeting offers enhanced therapeutic selectivity. In cancer, overexpression of Prx1/2 enables tumor cells to resist chemotherapy-induced oxidative damage. Inhibiting these isoforms selectively sensitizes malignant cells while sparing normal tissues that utilize redundant antioxidant systems [13,16]. Conversely, in neurodegenerative diseases or ischemic injury, boosting Prx expression protects neurons without impairing physiological ROS signaling. This context-dependent flexibility contrasts sharply with the blunt effects of classical antioxidants.

These advantages, summarized in Table 5, underscore why Prx-targeted strategies represent a nuanced and mechanistically superior approach in redox medicine. By leveraging their enzymatic specificity, compartmentalization, and dynamic regulation, Prx modulation addresses the pitfalls of traditional antioxidants, offering tailored solutions for diverse pathological contexts.

Challenges and Considerations.

Despite the compelling therapeutic potential of peroxiredoxin (Prx) modulation, significant challenges must be addressed to ensure both efficacy and safety in clinical applications. These limitations stem from the inherent complexity of redox biology, the multifunctional nature of Prx enzymes, and the context-dependent outcomes of interventions targeting oxidative stress pathways.

A primary challenge is the functional redundancy among Prx isoforms. Mammalian cells express six Prx isoforms with overlapping substrate specificities and partially compensatory roles. For instance, suppression of Prx1 in cancer models often triggers upregulation of Prx2 or Prx4, maintaining redox homeostasis and potentially enabling tumor survival [6,13]. This redundancy complicates therapeutic targeting, as inhibition of a single isoform may fail to achieve the desired biological effect.

Equally critical is the context-dependent duality of Prx function. While Prx activation may protect neurons in neurodegenerative diseases like Alzheimer's or Parkinson's, the same strategy could inadvertently support cancer cell survival by enhancing chemoresistance [12–14]. For example, Prx1 overexpression in glioblastoma mitigates ROS-induced DNA damage, shielding tumors from radiation therapy. Conversely, in cerebral ischemia, Prx3 upregulation reduces infarct size by preserving mitochondrial integrity. This duality underscores the need for precise, disease-specific modulation of Prx activity.

The lack of isoform-selective pharmacological agents further hampers progress. Many existing inhibitors, such as Conoidin A and adenanthin, exhibit off-target reactivity with non-Prx thiols, including thioredoxin and glutathione peroxidase. These interactions disrupt global redox balance, leading to unintended consequences such as immune cell toxicity or mitochondrial dysfunction. Adenanthin, despite its anticancer effects in leukemia, impairs T-cell viability, while auranofin - a TrxR inhibitor - activates the NLRP3 inflammasome, exacerbating inflammation in non-malignant tissues [16,17]. Similarly, Nrf2 activators like sulforaphane induce broad antioxidant responses, complicating the isolation of Prx-specific effects [15]. Overcoming these limitations requires innovative strategies, such as structure-guided drug design targeting isoform-unique active sites, high-throughput screening for compounds with minimal thiol cross-reactivity, and advanced delivery systems (e.g., liposomal encapsulation) to restrict activity to specific tissues or organelles.

Another concern is the risk of disrupting physiological redox signaling. ROS are not merely toxic byproducts but essential mediators of processes like immune activation, differentiation, and cell cycle progression. Overzealous Prx activation or ROS suppression could impair these pathways. For example, excessive scavenging of H_2O_2 by Prx2 may blunt NF-κB signaling, compromising antimicrobial defenses [7]. Thus, therapeutic strategies must strike a delicate balance between mitigating oxidative damage and preserving redox-dependent physiological functions.

Delivery and bioavailability issues pose additional hurdles. Many Prx modulators, particularly natural compounds like curcumin, suffer from poor solubility, rapid metabolism, or inadequate tissue penetration. Nanoparticle-based delivery systems and prodrug formulations are under investigation to enhance pharmacokinetics. For instance, lipid-coated nanoparticles loaded with Nrf2 agonists have shown improved blood-brain barrier penetration in preclinical neurodegeneration models [15].

Finally, limited clinical validation remains a major barrier. Most Prx-targeted therapies are in early preclinical or phase I trials, with sparse data on long-term safety, optimal dosing, or patient stratification. Translating findings from animal models to humans requires robust biomarkers - such as hyperoxidized Prx levels or redox-sensitive imaging probes - to monitor target engagement and redox status in real time [17].

Addressing these challenges demands a multidisciplinary approach integrating redox biology, medicinal chemistry, and systems pharmacology. Advances in cryo-EM, omics profiling, and computational modeling will be pivotal in designing context-specific, isoform-selective therapies. Furthermore, collaborative efforts to standardize redox biomarkers and validate preclinical models are essential to accelerate clinical translation.

Conclusion.

Peroxiredoxins (Prx) have emerged as pivotal targets for advancing precision antioxidant therapies, offering a transformative approach to managing oxidative stress-related pathologies. Their dual functionality - as efficient peroxide scavengers and dynamic regulators of redox signaling - positions them uniquely to maintain cellular homeostasis while preserving physiological ROS-dependent processes. Unlike classical antioxidants, which often disrupt essential signaling pathways due to non-specific action, Prx enable targeted intervention through their enzymatic specificity, isoform compartmentalization, and integration into redox regulatory networks [6,10,12,14].

Accumulating preclinical evidence underscores the therapeutic versatility of Prx modulation. In neurodegenerative and cardiovascular diseases, enhancing Prx activity has demonstrated robust cytoprotective effects, attenuating oxidative damage, neuroinflammation, and apoptosis. For instance, Prx3 overexpression in ischemic stroke models reduces infarct volume by 40–60%, while Prx2 activation in Parkinson's disease preserves dopaminergic neurons via ASK1 pathway inhibition [14,15]. Conversely, in oncology, where Prx1/2 are frequently overexpressed, pharmacological inhibition (e.g., adenanthin, Conoidin A) sensitizes tumors to chemotherapy and radiation by disrupting ROS buffering mechanisms, as evidenced in colorectal and breast cancer models [13,16]. These divergent outcomes underscore the necessity of context-driven strategies, tailored to disease-specific redox landscapes.

However, clinical translation faces formidable challenges. Isoform redundancy - exemplified by compensatory upregulation of Prx2 upon Prx1 inhibition - limits therapeutic efficacy, while the lack of selective inhibitors risks off-target effects on thiol-dependent pathways. Current agents like auranofin, though promising in leukemia trials, exhibit pleiotropic effects due to TrxR inhibition, highlighting the need for isoform-specific drug design [17]. Furthermore, the absence of validated biomarkers for Prx activity and redox status complicates patient stratification and dose optimization. Advances in nanoparticle-based delivery systems and redox-sensitive imaging probes may address bioavailability and monitoring hurdles, yet require rigorous preclinical validation [15,17].

Realizing the full potential of Prx-targeted therapies demands a multidisciplinary convergence of structural biology, systems redoxomics, and translational pharmacology. Cryo-EM and AI-driven molecular modeling could accelerate the development of isoform-selective inhibitors, while multi-omics profiling (e.g., redox proteomics, metabolomics) may identify predictive biomarkers for personalized treatment. Concurrently, innovations in targeted delivery - such as mitochondrial-directed Prx3 activators or blood-brain barrier-penetrating Nrf2 agonists - could enhance therapeutic precision [10,14].

In summary, Prx modulation represents a paradigm shift in redox medicine, transcending the limitations of blunt-

force antioxidant approaches. By leveraging their enzymatic precision and contextual adaptability, Prx-targeted strategies offer a roadmap for treating complex diseases rooted in redox imbalance - from neurodegeneration to cancer. While challenges persist, the integration of cutting-edge technologies and collaborative research ecosystems promises to unlock novel therapeutic frontiers, heralding a new era of precision redox interventions.

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