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Commentary

Redox-based cancer therapeutics: A critical commentary on selective hydrogen peroxide amplification

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Central Argument

Selective generation of hydrogen peroxide (H_2O_2) in malignant cells is a mechanistically well-supported but clinically unproven strategy in oncology. We argue that further progress in this field depends less on the identification of additional, nonspecific H_2O_2-generating compounds than on five interlocking requirements: (i) biomarker-guided patient selection, (ii) standardized measurement of intratumoral redox change, (iii) tumor-selective delivery or activation, (iv) rational combination therapy, and (v) pharmacodynamic confirmation of target engagement. We develop this position through a critical reading of the review by Ali and Fatima (2024) [1], identifying where the evidence assembled there supports tumor-selective prooxidant therapy and where important uncertainties remain unresolved.

The Redox Vulnerability Hypothesis: Support and Its Limits

Cancer cells are frequently reported to maintain elevated baseline H_2O_2 relative to normal cells, a state attributed to metabolic reprogramming and altered antioxidant adaptation [2–4]. Hileman *et al*. [5] and Schumacker [6] proposed that this elevated baseline positions malignant cells closer to a cytotoxic threshold, providing a conceptual rationale for prooxidant therapy. This observation, however, describes a tendency reported across particular cell lines and experimental systems rather than a uniform property of all tumors.

Redox status varies substantially across cancer types, molecular subtypes, disease stage, metabolic state, tumor microenvironment, and treatment history, and some tumor subpopulations are comparatively redox-resistant rather than redox-vulnerable. Recent work on cancer stem cells illustrates this heterogeneity directly: these subpopulations can maintain relatively low steady-state reactive oxygen species alongside enhanced mitochondrial adaptability and Nrf2-dependent antioxidant signaling, properties associated with survival under oxidative challenge and with therapy resistance [7]. Because cancer stem cells are frequently implicated in relapse, a therapeutic strategy that assumes uniform proximity to a cytotoxic H_2O_2 threshold risks leaving the most clinically consequential subpopulation comparatively unaffected. Normal tissue stem cells share some of these adaptive metabolic features, which further narrow the therapeutic window that the selectivity hypothesis presumes. We therefore regard redox vulnerability as a context-dependent, testable property rather than a general characteristic of malignancy, and one that should be established in a given tumor before a prooxidant strategy is pursued.

Mechanisms of H_2O_2 Elevation: Direct and Indirect Strategies

The reviewed article organizes H_2O_2-generating agents into direct mechanisms (autoxidation, redox cycling, and metal-ion interactions) and indirect mechanisms (inhibition of antioxidant

enzymes). Among direct mechanisms, the structure-activity relationships described for polyphenols are informative for medicinal chemistry: ortho-dihydroxyl and ortho-trihydroxyl (pyrogallol-type) configurations facilitate electron transfer and are associated with greater H_2O_2-generating capacity than catechol-type structures [8–11]. Quinone-containing compounds generate H_2O_2 through redox cycling initiated by one-electron reduction via NADPH-cytochrome P450 reductase (POR) or two-electron reduction via NAD(P)H:quinone oxidoreductase 1 (NQO1) [12]. β-Lapachone is the most clinically developed compound acting through this mechanism, and its derivative ARQ 761 has undergone early clinical testing. These mechanistic descriptions are useful starting points for compound design, but, as discussed below, mechanistic clarity at the bench has not yet translated into predictable tumor selectivity in patients.

Measurement of H_2O_2: An Unresolved Methodological Problem

A recurring difficulty in this literature is that reported H_2O_2 concentrations are not directly comparable across studies. For a single compound, epigallocatechin gallate (EGCG), reported values range from approximately 1.5 μM [13] to 20 μM [14] depending on cell line and detection method, a roughly ten-fold spread that is difficult to attribute to biology alone. Several sources of this variability warrant explicit discussion: extracellular versus intracellular measurement; direct versus indirect detection chemistry; the specificity of a given probe for H_2O_2 as opposed to reactive oxygen species generally; cell-free, medium-based oxidation of test compounds that is independent of cellular metabolism; the influence of serum components, dissolved oxygen, pH, and trace metal ions on probe behavior; subcellular compartmentalization of H_2O_2 production; whether a study reports absolute concentration or relative fluorescence; and the timing of measurement relative to compound exposure. Commonly used fluorescent probes (e.g., $DCFH_2$-DA) are frequently treated as specific H_2O_2 reporters in this literature, but they respond to a broader range of oxidants and should not be interpreted as direct, quantitative measures of intracellular H_2O_2 without additional validation.

Some recent tools address parts of this problem. Genetically encoded ratiometric sensors of the HyPer family, including the ultrasensitive HyPer7 variant, allow real-time, compartment-specific, quantitative estimation of intracellular H_2O_2 and largely avoid the confound of cell-free, medium-based oxidation [15]. Community guidelines for measuring reactive oxygen species and oxidative damage have also been published to standardize reporting and reduce method-dependent artifacts across laboratories [16]. Wider adoption of genetically encoded, compartment-resolved sensors, together with adherence to such reporting guidelines, would materially improve comparability across the compound classes surveyed in the reviewed article; at present, this standardization has not been applied consistently across the field.

Antioxidant Enzyme Targets are Mechanistically Distinct

Superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase are sometimes discussed together as antioxidant enzymes whose inhibition would be expected to raise H_2O_2. This grouping elides an important mechanistic distinction. Catalase and GPx directly remove H_2O_2; inhibiting either enzyme is mechanistically expected to increase H_2O_2 accumulation. SOD, in contrast, converts superoxide into H_2O_2 as part of its catalytic cycle; inhibiting SOD would be expected to increase superoxide but does not, by itself, increase H_2O_2, and may reduce it. Strategies aimed at indirect H_2O_2 elevation through antioxidant enzyme inhibition should therefore be evaluated separately according to which enzyme is targeted, rather than as a single mechanistic class.

Clinical Translation: A More Precise Accounting

The reviewed article notes that several H_2O_2-generating agents advanced to early-phase clinical testing without progressing further. ARQ 761, a β-lapachone analog developed to exploit NQO1-mediated bioactivation, was evaluated in a phase 1 dose-escalation study that established a maximum tolerated dose, identified dose-limiting toxicities, and reported pharmacodynamic evidence of NQO1 pathway engagement together with modest single-agent antitumor activity [17]. MB12066, another β-lapachone derivative, was assessed in independent single- and multiple-ascending-dose phase 1 studies focused on pharmacokinetics and tolerability rather than efficacy [18]. Of the roughly 2,000 anthracycline analogs synthesized historically, only a small number reached clinical use, largely because of dose-limiting cardiotoxicity linked to redox cycling of the quinone moiety rather than to lack of anticancer activity [19].

These outcomes should not be read as evidence that H_2O_2-mediated cytotoxicity is not achievable in patients; each case involved specific pharmacokinetic, toxicity, or trial-design limitations rather than a demonstrated failure of the underlying redox mechanism. A more accurate summary is that, to our knowledge, no anticancer therapy has been approved specifically on the basis of biomarker-guided, tumor-selective H_2O_2 amplification as its principal mechanism of action. This is distinct from the broader observation that several approved cytotoxic agents, including anthracyclines and arsenic trioxide, generate reactive oxygen species as part of their pharmacological effect without having been developed or approved as biomarker-selected prooxidant therapies.

Toward Translation: Biomarkers, Delivery, and Combinations

Biomarkers for patient selection

Because redox status varies across tumors, biomarker-guided patient selection is likely a precondition for consistent clinical benefit rather than an optional refinement. Candidate biomarkers relevant to this class of therapy include NQO1 expression and enzymatic activity, catalase and GPx activity, glutathione availability, NRF2 pathway activation, KEAP1 alterations, mitochondrial redox status, iron availability, tumor hypoxia, baseline oxidative damage, and evidence of prior antioxidant adaptation. NQO1 has the most direct clinical precedent, given its role in β-lapachone bioactivation and its elevated expression in several solid tumor types [20], but it has not yet been used prospectively to select patients in a controlled trial of an NQO1-activated prooxidant.

Nanoparticle delivery: Promise and translational barriers

Metal peroxide nanoparticles (CaO_2, MgO_2, ZnO_2) offer a route to tumor-localized H_2O_2 generation, exploiting the acidic and hypoxic tumor microenvironment for selective activation [21–24]. This approach addresses some pharmacokinetic limitations of small-molecule prooxidants, but its translational path faces separate

barriers, including manufacturing reproducibility, batch-to-batch variability, particle stability, biodistribution and clearance, off-target accumulation, long-term toxicity, immunogenicity, manufacturing scale-up, regulatory complexity, and systematic differences between preclinical animal models and human tumors. These barriers are common to nanomedicine generally and are not specific to redox-active particles, but they should temper expectations about the near-term clinical timeline for this approach.

Rational combinations

Combination strategies may address selectivity and potency limitations that single agents have not overcome. Pairing H_2O_2-generating prooxidants with H_2O_2-activated prodrugs has been proposed to enhance efficacy while lowering the required dose of each component [25]. The combination of ascorbic acid and menadione, which induces a distinct form of cell death termed autoschizis, illustrates the potential of mechanistically paired agents [26]. Combinations with immunotherapy or conventional chemotherapy have also been proposed on the grounds that redox stress can modulate antitumor immune signaling [27], though clinical evidence specific to this pairing remains limited.

Conclusion: Conditions for Clinical Translation

Established: cancer cells in many experimental systems maintain elevated baseline H_2O_2 relative to normal cells, and multiple chemical strategies exist to raise H_2O_2 further, some with demonstrated tumor-selective cytotoxicity *in vitro*. Not yet established: that this vulnerability is uniform across tumor types and subpopulations, that it can be reliably measured and confirmed in patients before and during treatment, or that it can be exploited with a therapeutic index sufficient for regulatory approval.

Closing this gap will require, in our view, biomarker-defined patient selection, tumor-localized activation or delivery, standardized and validated redox measurement, pharmacodynamic confirmation of target engagement in treated patients, mechanism-based combination design, early and systematic toxicity monitoring, and confirmation that clinically achievable drug exposures are sufficient to reach cytotoxic H_2O_2 thresholds in tumor tissue. The review by Ali and Fatima (2024) [1] provides a useful catalog of the chemical means available to raise H_2O_2 in cancer cells; the central task that remains is determining, prospectively and in defined patient populations, when and in whom that chemistry translates into clinical benefit.

Author Contributions

A.A. and K.F. contributed to the conception and design of the review, performed the literature search, drafted and critically revised the commentary.

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Conflict of Interest

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