Received: 29 July 2018 | Accepted: 8 August 2018

DOI: 10.1002/jcb.27594

PROSPECTS

WILEY Journal of Cellular Biochemistry

Disruption of the redox balance with either oxidative or anti-oxidative overloading as a promising target for cancer therapy

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Abstract

Oxidative stress acts as a double-edged sword by being both a promoter and a suppressor of cancer. Moderate oxidative stress is beneficial for cancer cell proliferative and invasiveness features, while overexposure of the cells to oxidative insults could induce cancer cell apoptosis and reduce hypoxia along with modulating the immune system for regression of tumor. Cancer cells and cancer stem cells have highly efficient redox systems that make them resistant to oxidative insults. The redox disruptive approach is an area of current research and key for oxidative targeted cancer therapies. This disruption is applicable by using either oxidative or anti-oxidative overloading strategies, specifically on cancer cells without influencing normal cells or tissues around tumor. The activity of tumor suppressor cells within tumor microenvironment is needed to be maintained in patients receiving such approaches.

KEYWORDS

cancer, oxidative stress, reactive oxygen species (ROS), redox

1 | INTRODUCTION

Oxidative stress and related signaling pose a great challenge for anticancer therapies. This is due to its dichotomous role of being both pro- and anti-tumor. Reactive oxygen species (ROS) are byproducts of cellular metabolism, which play cardinal roles for promotion of tumorigenesis and also for directing responses from cancer cells to anti-tumor therapy.[1] Modulation of ROS is a common outcome of most radio- and chemotherapeutic drugs used for the treatment of cancer.[2]

ROS can be both inhibitors and activators of cancer-promoting mediators.[3,4] Bulk cancer cells and cancer stem cells (CSCs) are highly sensitive to any alterations in their intracellular redox state.[5] This sensitivity is dependent, to a great extent, on the ROS concentration. A high ROS concentration could be therapeutic via induction of apoptotic-related mediators. By contrast, activation of

anti-oxidative enzymes after reduction of intracellular ROS levels could be a promoter of cancer cell proliferation.[1] ROS concentration in cancer cells is modified through mitophagy-related processes in which a huge increase in ROS concentration formed in the early phase mitophagy is counteracted and modified in the late phase through noticeable attenuation of ROS production.[6] CSCs maintain ROS levels to low amounts, which is mainly due to the expression of ROS scavenging molecules and their efficient DNA repair systems, thereby promoting resistance to oxidative targeted therapies.[2] Actually, the controlled release of ROS to the TME provides an immune escape mechanism for cancer cells in attaining their proliferative and invasive features.[7]

Interestingly, activation of both oxidative and antioxidative machineries is therapeutic; both of these induce cancer cell apoptosis. The antioxidative system would do such a work through activation of endoplasmic reticulum stress.[8] This is a virtue for cancer targeted therapies by overloading cancer cells with either system in favor of cancer retardation.

In this review, we intended to focus on how oxidative stress could take two opposite schemes in cancer, and how to push these two diverse destinations for cancer-targeted therapies. The general subjects in this regard have not been discussed (like oxidative stress as a general subject, sources of ROS within the cell, and anti-oxidative enzymes), as they have been clearly illustrated by other researchers and by us.[9] With an ever-growing rise in the knowledge about oxidative stress and the related plethora of fates, we hope to design more specific therapeutic approaches for cancer. The PubMed database was searched for relevant articles in this context. The criteria for article selection were based on the quality of journals and the novelty of subjects presented by the relevant articles. About 150 papers were scanned for this review by searching the key words "oxidative stress" and "cancer;" among them, about 30 papers met the criteria for further discussion.

2 | EVIDENCE FOR ANTI-TUMOR ACTIVITY OF OXIDATIVE STRESS

Macrophages are considered as one of the leading cells in the immune system and represent up to 50% of infiltrated cells to the stroma of tumor.[10] These cells have key interactions with other cells of tumor stroma for the hampering or promotion of cancer.[11] A cardinal characteristic for macrophages is their plasticity and their potential to tailor responses depending on signals received from stroma of tumors.[12] Generally, macrophages are classified into two extremes: M1 and M2 cells.[10] M1 cells are classically activated cells that have a proinflammatory phenotype with antitumor activity, while M2 cells are alternatively activated cells that have immunosuppressive features for progression of cancer.[12] Increase in ROS levels in antitumor M1 phenotype of macrophages not only increases their number through activation of the NF-κB-mediated pathway,[10] but also induces tumoricidal activity in cells.[13]

Regulatory T cells (Tregs) are another immune cells that are frequently found in the tumor TME.[14] An increase in the number for Tregs in the TME indicates immunosuppression in the milieu, which is essential for cancer cells to escape from the immune system posing as a main obstacle for cancer therapy.[15] Tregs are attributed to monocyte differentiation toward M2 phenotype,[15] which, in turn, are responsible for the recruitment of Tregs to the TME for exerting tumor progressive roles.[16] The protumor Tregs are highly sensitive to oxidative conditions, in which an increase in the production of ROS would cause a decrease in the number of these tumor promoting cells.[17] Moreover, over release of ROS to the cytosol of cancer cells could induce membrane permeability transition pores for releasing cytochrome c and further activation of apoptotic-related caspase cascades.[1]

It seems that moderate production of ROS by cancer cells acts as an inducer of hypoxia, and it has been understood from a large number of papers that hypoxia and related processes play key roles in progression of cancer.[13,16,18-21] By contrast, ROS overload to the TME could act as an inhibitor for the release of hypoxic mediators from cancer cells,[19,22] Interestingly, hypoxia, in an indirect reciprocal feedback (through induction of autophagy responses), reduces ROS production by cancer cells[19] (Figure 1).

3 | EVIDENCE FOR PRO-TUMOR ACTIVITY OF OXIDATIVE STRESS

Cancer associated fibroblasts (CAFs) are key components of tumor stroma,[23] which in the initial tumorigenic stages, presumably play antitumor roles through TME remodeling functions; while with an increase in the rate of tumor growth, the cells play a diverse role by acting as tumor promoters.[24] CAFs express and secrete a myriad of factors related to reprogramming cancer cells along with cells within cancer stroma, like macrophages and endothelial cells to facilitate cancer cell invasive traits.[23,24] Oxidative stress plays a cardinal role for differentiation of fibroblasts toward CAFs. The NADPH oxidase (NOX) system is a main source of ROS within the cells. Cancer cells have highly compatible NOX systems.[25,26] A type of NOX that has been identified to play an important role in cancer progression is NOX4. NOX4 has been attested to play roles for transdifferentiation of fibroblasts into their activated CAF phenotypes.[27]

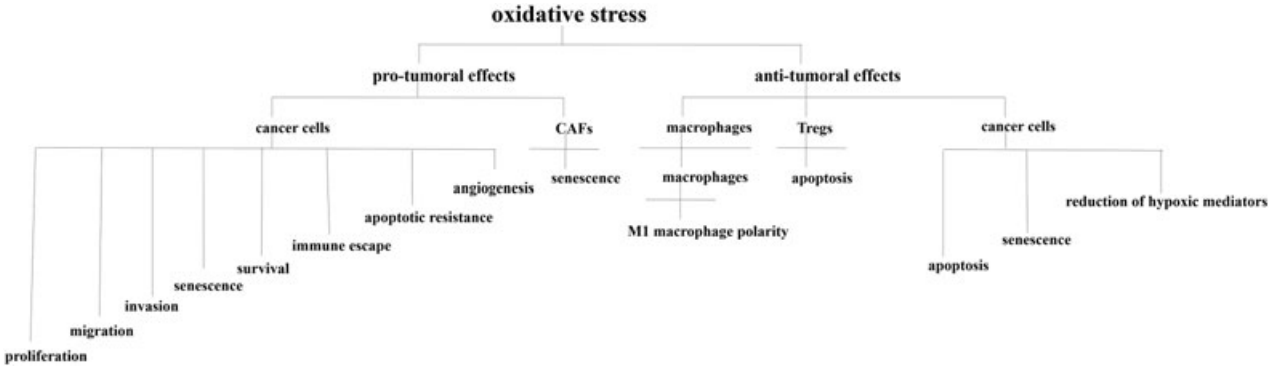

FIGURE 1 Evidence for pro- and anti-tumoral roles for oxidative stress. Oxidative stress could target cancer cells and cancer associated fibrolasts (CAFs) to be tumorigenic. For suppression of tumor, macrophages, regulatory T cells (Tregs) and cancer cells are targeted by oxidative stress

Oxidative stress facilitates crosstalks between CAFs and cancer cells. Oxidative stress induces release of high-energy nutrients from tumor stroma essential for fueling cancer cells to facilitate their growth and survival.[28] ROS accumulation in cancer cells promotes immune escape in the cells, resistance to apoptosis, and cancer recurrence.[29-31] In addition, cancer cells' release of ROS to the TME is detected by CAFs for promotion of angiogenesis-related mediators, like VEGF.[2] Oxidative stress also induces senescence in both CAFs and cancer cells. Senescent CAFs release numerous cytokines, proteases, and growth factors to promote invasion and migration of cancer cells.[28] Senescence may also take another way by suppressing tumor progression[32] (Figure 1).

Oxidative stress could also exhaust natural killer (NK) cell functioning, providing an immune escape within the TME for cancer cell invasion. To do this, cancer cells release H_2O_2 to the TME, which is able to switch off the function of NK cells.[7]

4 | DISRUPTION OF THE REDOX BALANCE WITHIN THE TUMOR AS A PROMISING THERAPEUTIC APPROACH

There is evidence from most of the reports studied so far that disruption of the redox balance in the tumor would be a promising therapeutic approach. It is interesting to note that cancer cells are highly compatible to maintaining a redox balance for attaining progression-related features. These cells have high rates of oxidative stress as well as increased activity of antioxidative related enzymes.[33] When the rate of ROS production in the cells reaches an undesired state, the antioxidative machinery is activated to keep the cells in a proactive position. This is a striking characteristic for cancer cells, allowing them to acquire resistance to oxidative inducers. Therefore, cancer cells can easily adopt to new environments because they have highly compatible oxidative and antioxidative machineries, allowing them to induce a new redox balance for the promotion of tumor growth. To maintain a redox balance, cancer cells have a high-quality NOX system for the promotion of tumor growth and invasiveness.[25,26]

The current research has focused on the disruption of the redox system in cancer cells. Photodynamic therapy[34] and nanoparticle delivery techniques[35] are examples of the techniques used in the immunotherapy of cancer, and their focus is to mediate over-increase of ROS deposition within the TME. One of the important ways to reach to this aim is by manipulating NOX activity in cancer. Overrelease of ROS to the TME is an inhibitor for release of hypoxic mediators.[19,22] These mediators play cardinal roles for amplification of cancer-promoting events. A point in this context is to apply therapeutic procedures specifically on cancer cells and their related milieu (ie TME). Overload of ROS on normal cells around cancer can induce mitochondrial dysfunctions in the cells, which, in turn, through promoting a vicious cycle could increase the rate of mutations in mitochondrial DNA, favoring cancer progression in normal cells.[36]

Another point to consider is that due to oxidation-induced NK exhaustion resulting in immunosuppression, patients receiving oxidative overloading therapy are recommended to also receive factors for activation of NK cells. There is evidence that when NK cells are activated, the cells become resistant to oxidative overloading therapy. These cells are activated by application of interleukins 2 and 15 inducers. These inducers would maintain the redox balance within NK cells as well as cytotoxic T lymphocytes (CTLs) through upregulation of peroxiredoxin-1 in the cells.[7] Therefore, to have an appropriate therapeutic response, the redox system is needed to be disrupted within cancer cells, but this system must be maintained in a balance for tumor suppressor cells like NK and CTL cells.

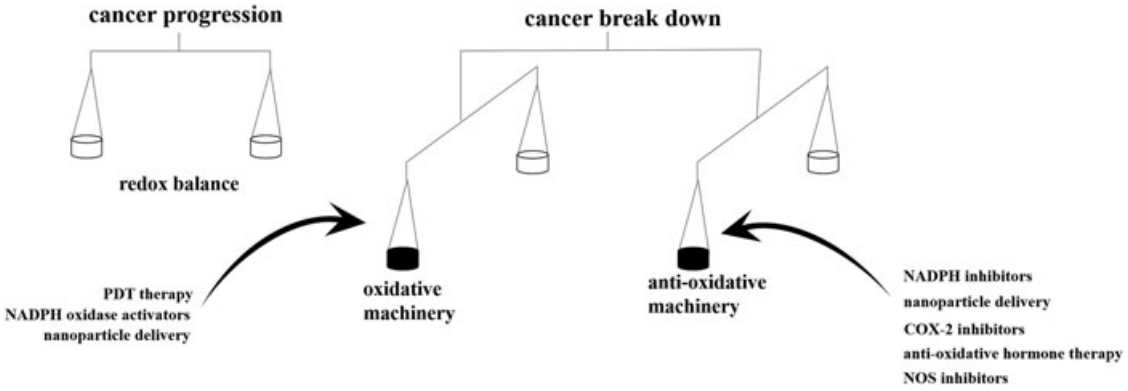

FIGURE 2 A schematic diagram illustrating possible relationship between redox system and cancer. A balance in the system is considered as a promoter of cancer, while any disruption in this system to either over-oxidation or over-antioxidation could be a therapeutic approach for cancer

Cancer-targeted therapy can also be applied through over release of antioxidative related molecules to the tumor milieu. This is also applicable for the disruption of the redox system in cancer cells. This antioxidative delivery could be applied through exogenous administration of antoxidative hormones like melatonin, which has long been known for its tremendous anticancer potentials.[1,9] Inhibitors of oxidative inducers like cyclooxygenase 2 (COX-2), nitric oxide synthase, and NOX system are other tools for shifting the redox system toward an antioxidative overloading (Figure 2).

An important point to consider is that oxidative system is one of (not specific) the targets for these anticancer approaches. So, it may target signals that are more potent than oxidative targeting for retarding cancer. For example, melatonin, as the most potent anti-oxidative hormone for treatment of cancer, could take several roles independent of its antioxidative function. Another point is that induction of one pathway by oxidative or antioxidative systems could diversely activate an undesirable pathway in favor of cancer progression. For example, ROS intrusion to the TME could induce apoptosis in Tregs, and there is evidence their its being more pro-active of these apoptotic cells in promotion of immune escape than their live counterparts.[37] This is also applicable for cancer cell apoptosis mediated by oxidative stress. Apoptotic cancer cells release apoptotic vesicles for stimulation of invasion in CAFs.[38] Increase of the activity for caspase-1 in tumor associated macrophages (TAMs) is also tumorigenic through increase of lipid deposition within the cells along with release of lactate to the TME.[39] However, there is no compelling evidence for a possible relationship between oxidative/anti-oxidative overloading with apoptosis induction in the TAMs, which is needed to be investigated in future studies. The point we could focus on here is that cancer cells, along with the cells within the stroma of tumor, are equipped with sophisticated mechanisms to make the stroma conditioned for modulating any alterations in oxidative/anti-oxidative status in their favor. Therefore, the knowledge presented in this review could not be deemed as a concept of a cancer targeted therapy for disrupting the redox system, although it is important and would be a dominant player. Instead, this is needed to be applied in adjuvan e with other therapeutic strategies like chemo- or radio-therapy to disrupt the accessory mechanisms activated by cells within the TME, and thereby having a desirable anti-cancer therapy. We hope that with broadening knowledge regarding dominant players in cancer would make the road smoother for cancer-targeted therapies.

5 | CONCLUSION

Oxidative/anti-oxidative overloading therapy has focused on the three criteria: (1) to disrupt the redox balance in cancer through cancer cell overloading with either oxidative or anti?oxidative machinery; (2) to maintain the activity of tumor suppressor cells within the TME; and (3) to prevent the influence of such an approach on normal cells or tissues around the tumor.

CONFLICTS OF INTEREST

All of the authors declare that they have no conflicts of interest.

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REFERENCES

1. Mortezaee K. Human hepatocellular carcinoma: protection by melatonin. *J Cell Physiol*. 2018;233:6486-6508.

2. Sosa V, Moliné T, Somoza R, Paciucci R, Kondoh H, LLeonart ME. Oxidative stress and cancer: an overview. *Ageing Res Rev*. 2013;12:376-390.
3. Kim E-H, Na H-K, Kim D-H, et al. 15-Deoxy-Δ 12, 14-prostaglandin J 2 induces COX-2 expression through Akt-driven AP-1 activation in human breast cancer cells: a potential role of ROS. *Carcinogenesis*. 2008;29:688-695.
4. Liu Y, Borchert GL, Surazynski A, Phang JM. Proline oxidase, a p53-induced gene, targets COX-2/PGE 2 signaling to induce apoptosis and inhibit tumor growth in colorectal cancers. *Oncogene*. 2008;27:6729-6737.
5. Lu C, Laws K, Eskandari A, Suntharalingam K. A reactive oxygen species-generating, cyclooxygenase-2 inhibiting, cancer stem cell-potent tetranuclear copper (II) cluster. *Dalton Trans*. 2017;46:12785-12789.
6. Shen YQ, Guerra-Librero A, Fernandez-Gil BI, et al. Combination of melatonin and rapamycin for head and neck cancer therapy: Suppression of AKT/mTOR pathway activation, and activation of mitophagy and apoptosis via mitochondrial function regulation. *J Pineal Res*. 2018;64:e12461.
7. Mimura K, Kua L-F, Shimasaki N, et al. Upregulation of thioredoxin-1 in activated human NK cells confers increased tolerance to oxidative stress. *Cancer Immunol Immunother*. 2017;66:605-613.
8. Min K, Kim HS, Park EJ, Kwon TK. Melatonin enhances thapsigargin-induced apoptosis through reactive oxygen species-mediated upregulation of CCAAT-enhancer-binding protein homologous protein in human renal cancer cells. *J Pineal Res*. 2012;53:99-106.
9. Mortezaee K, Khanlarkhani N. Melatonin application in targeting oxidative-induced liver injuries: a review. *J Cell Physiol*. 2018;233:4015-4032.
10. Genard G, Wera A-C, Huart C, et al. Proton irradiation orchestrates macrophage reprogramming through NFκB signaling. *Cell Death Dis*. 2018;9:728.
11. Wang X, Luo G, Zhang K, et al. Hypoxic tumor-derived exosomal miR-301a mediates M2 macrophage polarization via PTEN/PI3Kγ to promote pancreatic cancer metastasis. *Cancer Res*. 2018;78:3841.
12. Chan JSK, Sng MK, Teo ZQ, Chong HC, Twang JS, Tan NS. Targeting nuclear receptors in cancer-associated fibroblasts as concurrent therapy to inhibit development of chemoresistant tumors. *Oncogene*. 2018;37:160-173.
13. Tzeng HT, Su CC, Chang CP, Lai WW, Su WC, Wang YC. Rab37 in lung cancer mediates exocytosis of soluble ST2 and thus skews macrophages towards tumor-suppressing phenotype [published online ahead of print May 1, 2018]. *Int J Cancer*. https://doi.org/10.1002/ijc.31569
14. Tan YS, Sansanaphongpricha K, Xie Y, et al. Mitigating SOX2-potentiated immune escape of Head and Neck Squamous Cell Carcinoma with a STING-inducing nanosatellite vaccine. *Clin Cancer Res*. 2018b;2807:2017.
15. Costa A, Kieffer Y, Scholer-Dahirel A, et al. Fibroblast heterogeneity and immunosuppressive environment in human breast cancer. *Cancer Cell*. 2018;33:463-479. e10
16. Albini A, Bruno A, Noonan DM, Mortara L. Contribution to tumor angiogenesis from innate immune cells within the tumor microenvironment: implications for immunotherapy. *Front Immunol*. 2018;9:527.
17. Mensurado S, Rei M, Lança T, et al. Tumor-associated neutrophils suppress pro-tumoral IL-17+γδ T cells through induction of oxidative stress. *PLoS Biol*. 2018;16:e2004990.
18. Joseph JP, Harishankar MK, Pillai AA, Devi A. Hypoxia induced EMT: a review on the mechanism of tumor progression and metastasis in OSCC. *Oral Oncol*. 2018;80:23-32.
19. Biancur DE, Kimmelman AC. The plasticity of pancreatic cancer metabolism in tumor progression and therapeutic resistance. *Biochim Biophys Rev Cancer*. 2018;1870:67-75.
20. Tan B, Shi X, Zhang J, et al. Inhibition of Rspo-Lgr4 facilitates checkpoint blockade therapy by switching macrophage polarization. *Cancer Res*. 2018a;0152:2018.
21. Fels B, Bulk E, Pethő Z, Schwab A. The role of TRP channels in the metastatic cascade. *Pharmaceuticals*. 2018;11:48.
22. Liu Y, Zhen W, Jin L, et al. All-in-One theranostic nanoagent with enhanced reactive oxygen species generation and modulating tumor microenvironment ability for effective tumor eradication. *ACS Nano*. 2018;12:4886-4893.
23. Ahirwar DK, Nasser MW, Ouseph MM, et al. Fibroblast-derived CXCL12 promotes breast cancer metastasis by facilitating tumor cell intravasation. *Oncogene*. 2018;1:4428-4442.
24. LeBleu VS, Kalluri R. A peek into cancer-associated fibroblasts: origins, functions and translational impact. *Dis Models Mech*. 2018;11:dmm029447.
25. Block K, Gorin Y. Aiding and abetting roles of NOX oxidases in cellular transformation. *Nat Rev Cancer*. 2012;12:627-637.
26. Farhood B, Goradel NH, Mortezaee K, et al. Intercellular communications-redox interactions in radiation toxicity; potential targets for radiation mitigation. *J Cell Commun Signal*. 2018:1-14.
27. Hanley CJ, Mellone M, Ford K, et al. Targeting the myofibroblastic cancer-associated fibroblast phenotype through inhibition of NOX4. *J Natl Cancer Inst*. 2018;110:109-120.
28. Jezierska-Drutel A, Rosenzweig SA, Neumann CA. Role of oxidative stress and the microenvironment in breast cancer development and progressioneditor. *Adv Cancer Res*. 2013;119: 107-125. Elsevier.
29. Gu H, Huang T, Shen Y, et al. Reactive oxygen species-mediated tumor microenvironment transformation: the mechanism of radioresistant gastric cancer. *Oxid Med Cell Longevity*. 2018;2018:2018-2018.
30. Qiao Y, Wan J, Zhou L, et al. Stimuli-responsive nanotherapeutics for precision drug delivery and cancer therapy [published online ahead of print May 4, 2018]. *Wiley Interdisc Rev Nanomed Nanobiotechnol*. https://doi.org/10.1002/wnan.1527
31. Thommen DS, Schumacher TN. T cell dysfunction in cancer. *Cancer Cell*. 2018;33:547-562.
32. Pérez-Mancera PA, Young ARJ, Narita M. Inside and out: the activities of senescence in cancer. *Nat Rev Cancer*. 2014;14: nrc3773-558.
33. Kong H, Chandel NS. To claim growth turf, mTOR says SOD off. *Mol Cell*. 2018;70:383-384.
34. Xiong H, Zhou K, Yan Y, Miller JB, Siegwart DJ. Tumor-activated water-soluble photosensitizers for near-infrared photodynamic cancer therapy. *ACS Appl Mater Interfaces*. 2018;10:16335-16343.
35. Sengupta M, Pal R, Nath A, et al. Anticancer efficacy of noble metal nanoparticles relies on reprogramming tumor-associated macrophages through redox pathways and pro-inflammatory cytokine cascades [published online ahead of print May 24,

2018]. *Cell Mol Immunol*. https://doi.org/10.1038/s41423-018-0046-7

36. Song N, Kim AJ, Kim HJ, et al. Melatonin suppresses doxorubicin-induced premature senescence of A549 lung cancer cells by ameliorating mitochondrial dysfunction. *J Pineal Res*. 2012;53:335-343.
37. Maj T, Wang W, Crespo J, et al. Oxidative stress controls regulatory T cell apoptosis and suppressor activity and PD-L1-blockade resistance in tumor. *Nature Immunol*. 2017;18:1332-1341.
38. Itoh G, Chida S, Yanagihara K, Yashiro M, Aiba N, Tanaka M. Cancer-associated fibroblasts induce cancer cell apoptosis that regulates invasion mode of tumours. *Oncogene*. 2017;36:4434-4444.
39. Niu Z, Shi Q, Zhang W, et al. Caspase-1 cleaves PPARγ for potentiating the pro-tumor action of TAMs. *Nat Commun*. 2017;8:766.

How to cite this article: Farhood B, Najafi M, Salehi E, et al. Disruption of the redox balance with either oxidative or anti-oxidative overloading as a promising target for cancer therapy. *J Cell Biochem*. 2019;120:71-76. https://doi.org/10.1002/jcb.27594