Published in final edited form as:

Semin Radiat Oncol. 2019 January ; 29(1): 1–5. doi:10.1016/j.semradonc.2018.10.010.

Manipulations of Redox Metabolism for Enhancing Radiation Therapy Responses: A historical perspective and new hypothesis

Douglas R. Spitz, PhD^{1,*}

¹—Free Radical and Radiation Biology Program, Department of Radiation Oncology, Holden Comprehensive Cancer Center, Carver College of Medicine, the University of Iowa, Iowa City, IA 52242

Abstract

Since the recognition during the 20th century that cancer cells demonstrated fundamental alterations in the regulation of oxidative and glycolytic metabolism, many basic as well as translational scientists have proposed that targeting metabolic differences in cancer versus normal cells could be exploited to improve cancer therapy outcomes. With the recognition that dysregulation of mitochondrial redox metabolism leads to the increased steady-state levels of superoxide and hydrogen peroxide which could contribute to both aging and cancer; radiation biologists have pursued many avenues of targeting oxidative metabolic pathways to both selectively radiosensitive cancer cells as well as protect normal tissues during cancer therapy. Recent advances in exploiting redox metabolism for improving radiochemotherapy both from a basic and translational science point of view are the focus of the papers in this current issue of *Seminars in Radiation Oncology*. The historical perspective underlying these areas of research as well as a unifying hypothesis for further advancing this research into clinical trials will be presented in this overview.

Introduction

Since the discovery that free radical scavengers could protect against radiation induced injury in animals¹, scientists studying radiation biology have been at the forefront of the field of redox biology and medicine. This seminal observation also led to the free radical theories of oxygen toxicity², aging³, and cancer^{4,5}. In addition, for the past 60 years these theoretical constructs and resulting experimental data have also driven the development of several modern approaches for enhancing cancer therapy responses while protecting normal tissues from radiochemotherapy. This work has also led to a paradigm shifting theoretical construct for understanding the relationship between oxidative metabolism and gene expression pathways that could be very useful moving forward for continuing to refine metabolic manipulations directed at improving radiochemotherapy.

*-to whom correspondence should be address: Douglas R. Spitz, PhD, Professor and Director, Free Radical and Radiation Biology Program, Department of Radiation Oncology, Free Radical Metabolism and Imaging Program, Holden Comprehensive Cancer Center, B180 Medical Laboratories, Carver College of Medicine, The University of Iowa Iowa City, Iowa 52242, douglas-spitz@uiowa.edu, 319-335-8001: Office Phone, 319-335-8019: Fax.

Radiation biology and redox metabolism

For many years it has been well recognized that the deposition of energy from ionizing radiation leads to the formation of free radicals directly on critical target molecules and well as indirectly from the radiolysis of H_2O to form hydroxyl radical.⁶ These free radicals are known to lead to covalent changes in critical bio-molecules that significantly contribute to radiation-induced cell killing as well as transformation and normal tissue injury.⁶ In the latter half of the 20th century it has also become well-recognized that the initial free radical damage caused by ionizing radiation is accompanied by the induction of oxidative metabolic dysfunction that persists for many months and years following exposure, leading to normal tissue injury and genomic instability.^{6,7} The recognition that these radiation-induced late normal tissue damage effects are indistinguishable from similar pathologies induced during aging, has led to the proposition that the random stochastic free radical damage caused by ionizing radiation during cancer therapy may accelerate the onset of the persistent metabolic oxidative stress that has been associated with aging.⁶⁻⁸

The “Horse and Cart” model for selectively targeting metabolism, signal transduction, and gene expression in cancer cells while protecting normal tissues

Albert Szent-Györgyi was one of the first scientists to propose that the life force necessary to maintain living systems was derived from easily oxidizable substrates providing for the movement of electrons from higher energy orbitals to lower energy orbitals releasing energy that could be harnessed by biological systems.⁹ This theoretical construct together with the chemosmotic hypothesis proposed by Peter Mitchell¹⁰ coupled to the discovery that mitochondria could produce superoxide ($\text{O}_2^{\bullet-}$) and hydrogen peroxide (H_2O_2)^{11,12} can now be unified with the free radical theories of cancer and aging⁶⁻⁸ for the purpose of improving cancer therapy.

The “Horse (oxidative metabolism) and Cart (gene expression)” model provides a novel unified theoretical approach for understanding the fundamental regulation of mitochondrial oxidative metabolism, signal transduction, and gene expression in aging, cancer, and normal tissues injury (Figure 1).^{8, 13, 14} The essential oxidation/reduction (redox) metabolism which extracts, stores, and moves the electrons necessary for maintaining living cells occurs in the mitochondria/cytosol and can be considered the “horse” that is connected by redox sensitive signaling pathways to the “cart” representing the nuclear gene expression pathways (Fig. 1A). Given this model, it would be predicted that the mechanistic relationship between gene expression and glucose/ O_2 metabolism would be based on the ability to extract electrons from food sources via metabolic oxidation/reduction reactions to the generate ATP and reducing equivalents for biosynthesis (i.e., NADH/NADPH), while consuming O_2 by 4 electron reductions to make H_2O . The cellular proteins necessary to carry out these metabolic processes are regulated by the flow of ATP, reducing equivalents (in the form of NADH and NADPH), and reactive by-products of oxidative metabolism (i.e., $\text{O}_2^{\bullet-}$, H_2O_2 , organic hydroperoxides, aldehydes etc.) through redox sensitive signaling pathways to

coordinately regulate the gene expression program required to maintaining cellular structure needed for normal function.

In normal cells, redox metabolism (horse) and gene expression (cart) are tightly coupled via non-equilibrium steady-state fluxes of reactive metabolic by-products and electron carriers through redox sensitive signal transduction pathways (Fig. 1A). Thus, the flow of electrons from reactions governing energy production and biosynthesis directly regulate gene expression pathways governing assembly of the protein and lipid structures necessary to maintain normal cellular functions and differentiation (Fig 1A). When this non-equilibrium steady-state is disrupted, the reactive by-products of oxidative metabolism, such as $O_2^{\cdot-}/H_2O_2$, as well as reactive oxidative damage byproducts (i.e., aldehydes and organic hydroperoxides), produced by the “horse,” can cause covalent damage in the genome, that if unrepaired or mis-repaired will lead to the gradual deterioration of the “cart” (Fig. 1B). The gradual deterioration of the “horse and cart” relationship can lead to dysfunction cellular processes on multiple levels, due to stoichiometric mismatches between protein expression and the assembly of the mitochondrial/cytosolic metabolic machinery needed to maintain the efficiency of electron flows, leading to steadily increasing levels of reactive species produced as byproducts of oxidative metabolism as a function of time. This increasing inefficiency in oxidative metabolism and increasing steady-state levels of reactive species can lead to the exponential deterioration of the genome during aging leading to senescence and death (Fig. 1B). The increasing levels of reactive species and damage products that occur during aging are also accelerated by radiochemotherapy-induced damage and can be targeted (Fig 1B, red X's) to inhibit normal tissue injury/regeneration during cancer therapy.

In this context the 5 papers in this issue of *Seminars in Radiation Oncology* address strategies being explored for targeting metabolism for the purpose of protecting against normal tissue responses while enhancing tumor responses. The first of these papers by Schoenfeld et al. discusses the proposal to exploit pharmacological doses of ascorbate (given IV to blood levels of ~20 mM) to enhance metabolic oxidative stress in cancer tissues while protecting normal tissues from radiation-induced injury.¹ The underlying mechanism for this approach is proposed to be the increased presence of redox active metal ions in cancer tissues making high levels of ascorbate selectively act as a prooxidant generating H_2O_2 leading to cancer cell radiosensitization, while retaining antioxidant function in normal tissues protecting against radiation injury. In the paper by Aykin-Burns et al. a similar approach to selectively protecting normal tissues while enhancing cancer cell therapeutic responses is proposed using vitamin E analogs where the differential redox biology of tocopherols is being exploited.² In a similar line of investigation the paper by Hillman explores the redox biology of soy isoflavones for inducing radiosensitization while mitigating inflammatory responses leading to radiation-induced normal tissue injury.³ In a final investigation along these same lines of inquiry, Mapuskar et al. discuss the utilization of small molecule superoxide dismutase mimics to inhibit radiation-induced normal tissue injury while preserving cancer cell responses based on fundamental differences in oxidative metabolism leading to the formation of superoxide.⁴

Cancer biology and cancer therapy responses

The proposed “horse and cart” model predicts that degenerative diseases associated with aging, including cancer development, arise from the disruption of metabolic homeostasis where metabolic oxidation/reduction reactions are losing efficiency as a function of time and reactive by-products are formed from one-electron reductions of O_2 (electron leak) in mitochondrial electron transport chains leading to the formation of $O_2^{\bullet-}$ and H_2O_2 which together with redox active labile metal ions (Fe^{+2} and Cu^{+1}) to catalyze oxidation of critical biomolecules leading to the formation of organic hydroperoxides, alkoxy/hydroperoxyl radicals, and aldehydes. This gradual dysregulation of metabolic oxidation reactions also disrupts the coordinated production of energy and reducing equivalents necessary for cell survival, proliferation, biosynthesis, and differentiated function that results in the acceleration of aging related pathologies including carcinogenesis. This model allows for the proposal that the flow of electrons during metabolism are both necessary for living systems as redox signaling molecules and detrimental in mediating damage to the genome causing increased metabolic inefficiency accelerating the processes of senescence, as well as onset of degenerative diseases associated with aging (Fig 1BC).

In process of carcinogenesis, this model predicts that the cellular and metabolic dysregulation leading to malignant transformation is due to the age-related increases in steady-state levels of reactive oxygen species (i.e., $O_2^{\bullet-}$ and H_2O_2) and toxic products arising from free radical reactions that lead to immortalization of cells capable of cell division (possibly involving the induction of telomerase) as an adaptive response to the stress caused by the accumulation of oxidative damage to the genome. Once immortalization has occurred the transformed cell has adapted to the dysfunctional relationship between oxidative metabolism, signal transduction and gene expression; but also exhibits significant genomic instability, loses the ability to perform differentiated function, loses control of cell proliferation, and continue to progress to malignancy. In addition, the natural extension of this hypothesis is that continued targeting of only the malignant cell genomic dysregulation without targeting the malignant cell's metabolic dysfunction (Fig 1C) will significantly limit the potential success of stopping cancer cells from killing the organism (Fig 1C). This theoretical construct predicts that the most efficient way to target frailties in cancer cell metabolism to selective increase the production of reactive species while compromising the protective pathways; would be to focus on exploiting the biochemical hubs of cancer cell redox metabolism including NAD(H)/NADP(H) levels, electron transport chain activity, glutathione and thioredoxin dependent thiol metabolism, folate metabolism, and redox active metal ion metabolism.⁸

In the context of this metabolic targeting strategy the paper by Lewis et al. provides a rigorous overview of NAD⁺ metabolism in the context of the cellular responses to ionizing radiation as well as presenting novel combined modality therapy approaches that target NAD⁺ metabolism to enhance radiation therapy responses.¹⁹ In the paper by Ashcraft et al. the authors explore the novel preclinical as well as clinical evidence supporting exercise modulation of cancer therapy responses as well as the potential biological mechanisms involving alterations in oxidative metabolism that may provide account for these effects.²⁰

Bibliography:

1. Patt HM, Tyree EB, Straube RL et al.: Cysteine Protection against X Irradiation. *Science* 1949; 110(2852):213–4. [PubMed: 17811258]
2. Gerschman R, Gilbert DL, Nye SW et al.: Oxygen poisoning and x-irradiation: a mechanism in common. *Science* 1954; 119(3097):623–6. [PubMed: 13156638]
3. Harman D: Aging: a theory based on free radical and radiation chemistry. *J Gerontol.* 1956; 11(3): 298–300. [PubMed: 13332224]
4. Oberley LW, Buettner GR: Role of superoxide dismutase in cancer: a review. *Cancer Res.* 1979; 39(4):1141–9. [PubMed: 217531]
5. Oberley LW, Oberley TD, Buettner GR: Cell differentiation, aging and cancer: the possible roles of superoxide and superoxide dismutases. *Med. Hypotheses* 1980; 6(3):249–68. [PubMed: 6253771]
6. Spitz DR, Azzam EI, Li JJ, Gius D: Metabolic oxidation/reduction reactions and cellular responses to ionizing radiation: a unifying concept in stress response biology. *Cancer Metastasis Rev.* 2004; 23(3-4):311–22. [PubMed: 15197331]
7. Spitz DR, Hauer-Jensen M: Ionizing radiation-induced responses: where free radical chemistry meets redox biology and medicine. *Antioxid Redox Signal.* 2014; 20(9):1407–9. [PubMed: 24354361]
8. Zhu Y, Dean AE, Horikoshi N, et al.: Emerging evidence for targeting mitochondrial metabolic dysfunction in cancer therapy. *J Clin Invest.* 2018; 128(9):3682–3691. [PubMed: 30168803]
9. Szent-GYÖRGYI A *Electronic biology and cancer* Marcel Decker Inc, New York, NY, 1976, pp. 34–35.
10. Mitchell P: Chemiosmotic coupling in oxidative and photosynthetic phosphorylation. 1966. *Biochim Biophys Acta.* 2011; 1807(12):1507–38. [PubMed: 22082452]
11. Forman HJ, Kennedy J: Superoxide production and electron transport in mitochondrial oxidation of dihydroorotic acid. *J Biol Chem.* 1975; 250(11):4322–6. [PubMed: 165196]
12. Boveris A, Cadenas E: Mitochondrial production of superoxide anions and its relationship to the antimycin insensitive respiration. *FEBS Lett.* 1975; 54(3):311–4. [PubMed: 236930]
13. Allen BG and Spitz DR: Physiologic and pathologic functions of mitochondrial ROS. In *Mitochondria and Cell Death, Cell Death in Biology and Diseases*, (Hockenbery, editor) Humana Press, Springer Science+Business Media New York, NY 2016, DOI 10.1007/978-1-4939-3612-0.
14. Allen BG and Spitz DR: Metabolic production of H₂O₂ in carcinogenesis and cancer treatment In *Redox-Active Therapeutics, Oxidative Stress in Applied Basic Research and Clinical Practice* (Batinic-Haberle, Reboucas, Spasojevic, St. Clair, and Warner, editors), Springer International Publishing Switzerland 2016; DOI 10.1007/978-3-319-30705-3.
15. Schoenfeld JD, Alexander MS, Waldron TJ, Sibenaller ZA, Spitz DR, Buettner GR, Allen BG, Cullen JJ: Pharmacological Ascorbate as a Means of Sensitizing Cancer Cells to Radio-Chemotherapy While Protecting Normal Tissue. (this issue *Seminars in Radiation Oncology*).
16. Aykin-Burns N, Pathak R, Boerma M, Kim T, Hauer-Jensen M: Utilization of vitamin E analogs to protect normal tissues while enhancing anti-tumor effects (this issue *Seminars in Radiation Oncology*)
17. Hillman GG: Soy isoflavones protect normal tissues while enhancing radiation responses. (this issue *Seminars in Radiation Oncology*)
18. Mapuskar KA, Anderson CM, Spitz DR, Batinic-Haberle I, Allen BG, Rebecca Oberley-Deegan R: Utilizing Superoxide Dismutase Mimetics to Enhance Radiation Therapy Response While Protecting Normal Tissues. (this issue *Seminars in Radiation Oncology*).
19. Lewis JE, Singh N, Holmila RJ, Sumer DB, Williams NS, Furdui CM, Kemp ML, Boothman DA: Targeting NAD metabolism for enhancing radiation therapy responses. (this issue *Seminars in Radiation Oncology*).
20. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW: Exercise as adjunct therapy in cancer. (this issue *Seminars in Radiation Oncology*)
21. Floberg JM, Schwarz JK Manipulation of glucose and hydroperoxide metabolism to improve radiation responses. (this issue *Seminars in Radiation Oncology*).

22. Luo M and Wicha MS Targeting cancer stem cell redox metabolism to enhance therapy responses.
(this issue **Seminars in Radiation Oncology**).
23. Naz S, Kishimoto S, Mitchell JB, et al. Imaging metabolic processes to predict radiation responses.
(this issue **Seminars in Radiation Oncology**).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

The “horse and cart” model for understanding the fundamental relationship between mitochondrial oxidative metabolism, redox-regulated signal transduction, and gene expression in degenerative diseases associated with aging and cancer. (A) The essential redox metabolic processes occurring in the mitochondria and cytosol can be considered the “horse” and gene expression can be considered as the “cart”. In normal cells, oxidative metabolism (horse) and gene expression (cart) are tightly coupled via the nonequilibrium steady-state fluxes of reactive metabolic by-products and electron carriers through signal

transduction pathways. (B) When this nonequilibrium steady-state is disrupted, $O_2^{\bullet-}$ and H_2O_2 as well as highly reactive oxidative damage products from oxidative metabolism (the horse) can cause the deterioration of the genome (the cart). If this disrupted oxidative metabolism continues to progress leading to the assembly of inefficient metabolic structures, the persistent exponential deterioration of the genome will inevitably lead to cancer induction and/or senescent death. (C) The dysregulated oxidative metabolism in cancer cells, which are immortalized and incapable of normal differentiated function will eventually drag the living system off the cliff into the valley of end stage malignancy and organismal death.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript