Homeostatic control of redox status and health

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Abstract
Research on oxidants and electrophiles has shifted from focusing on damage to biomolecules to the more fine-grained physiological arena. Redox transitions as excursions from a steady-state redox set point are continually ongoing in maintenance of redox balance. Current excitement on these topics results from the fact that recent research provided mechanistic insight, which gives rise to more concrete and differentiated questions. This Commentary focuses on redox eustress and the feedback restoration of steady state as concepts in active maintenance of physiological health, with brief discussion of redox stress response to viral infection, exemplified by COVID-19.

**KEYWORDS**
COVID-19, hormesis, oxidative eustress, parahormesis, redox biology, steady state

1 | INTRODUCTION

Homeostatic mechanisms are an essential feature of the hallmarks of health,\textsuperscript{1} and health is envisaged as an active biological process.\textsuperscript{2} Achieving physiological health relies on evolved mechanisms to maintain homeostasis by resistance, tolerance, and resilience, which are of homeodynamic character.\textsuperscript{3,4} The constant physiologically ongoing alert for homeostasis is viewed as eustress, distinct from nonphysiological distress, which is a principal distinction introduced by Selye.\textsuperscript{5} The evolution of the concept of stress and stress responses has recently been summarized.\textsuperscript{6}

Oxidation–reduction (redox) reactions constitute essential components of life processes. Biochemical research in oxygen, iron, copper, sulfur, selenium and nitrogen, free radical oxidations and defense mechanisms has revealed astounding diversity and flexibility of use of redox reactions in energy capture, escaping toxicity of oxygen and to the production of chemical weapons against biological entities recognized as adverse. It is not surprising, therefore, that chemical species competent for biochemically controlled oxidations have been also adopted for signaling in fast and reversible processes. As life in the presence of oxygen is made possible by a sophisticated and complex integration of different energetically expensive mechanisms, the same concept holds for the control of physiological processes involved in redox signaling.

In this scenario, redox homeostasis is a constantly ongoing challenge.\textsuperscript{7} Thus, maintenance of redox homeostasis as an indispensable component of health requires that events in which a given oxidation is part of a physiological signal must be under control of counteracting biochemical reactions switching off the signal and restoring the redox steady state.\textsuperscript{8} The condition where the steady state of specific redox couples is shifted toward oxidation...
in the frame of a controlled pathway has been defined as oxidative eustress to pinpoint the intrinsic physiological relevance of the reaction.9 This marks the difference with the original definition of oxidative distress when oxidations overwhelm the counteracting reactions that are not anymore able to restore the homeostatic redox steady state.

1.1 | Conceptual background: redox steady state

_Panta rhei_, everything flows, attributed to Heraclitus of Ephesus (fifth century B.C.), is the essence of the concept of flow equilibrium as pioneered in biophysics by von Bertalanffy to characterize the open metabolic system.10 The flow equilibrium, known as steady state, is in contrast to thermodynamic equilibrium, in which net flux is zero. Maintenance of steady-state requires continuous monitoring of flux in order to balance inflow with outflow. Fluctuation and discontinuity are hallmarks of the metabolic steady state. The open metabolic system is characterized by oscillations around a set point which, in turn, is subject to change and adaptation. Spatiotemporal control is centerpiece.

In terms of the impact on “physiology of health” defined according to Bernard and Cannon as maintenance of _milieu intérieur_ or homeostasis, respectively, we can also refer to Greek philosophy of Stoics referring to _Ataraxia_—the absence of distress—a concept elaborated by the Latin poet Horace (first century B.C.) in the notion of _Aurea Mediocritas_—Golden Mean—indicating as optimally desirable the middle between extremes.8

1.2 | Eustress for maintenance of redox steady state set point

A variety of reactive oxidants and electrophiles interact with the cellular machinery of macromolecules, notably proteins and nucleic acids, in redox regulation.11 In particular, reactive oxygen species12 and various electrophiles13 are involved in redox signaling, as are reactive nitrogen14 and sulfur15 species. A veritable redox network of molecular interactions forms the redox architecture of physiological function16 in a reactive species interactome.17 The minimization of the physiological range of excursion from the steady state set point has been defined by the notion of “Homeodynamic Space”18 or “Goldilocks Zone”.19 In terms of stress physiology, this range is the range of redox eustress, on constant alert for redox homeostasis.7 If the excursion occurs in the oxidative direction, it is oxidative eustress, which evolves to distress when not feedback controlled. While oxidative eustress has been studied in detail (see a book on the topic20), the actual relevance of a reductive stress has been questioned,21 although responses22 and molecular mechanisms have been proposed.23 It may be assumed, indeed, that under the metabolic conditions of aerobic metabolism the excursions to the oxidative side of the balance are predominant. In this respect, the reactions toward a more reduced state are restricted to those increasing the nucleophilic tone operating to shut down the electrophilic signaling brought by the signaling oxidative eustress. The cornerstone mechanism is the feedback activation of the nuclear factor Nrf2 operated by electrophiles.24,25

1.3 | Redox stressor sensing Nrf2 and hormesis

The widely recognized link between eustress activated by different stressors and the homeostatic feedback response to stress is the nuclear factor Nrf2 (Figure 1).

Electrophiles, of which hydroxynonenal produced by oxidative degradation of polyunsaturated lipids is prototypical, as well as oxidants such as hydrogen peroxide, operate by interacting with the Kelch-ECH associated protein 1 (Keap1).26,27 This primes the transfer of Nrf2 to the nucleus and activates the expression of more than 200 genes which, besides increasing antioxidant defense, shifts metabolism toward catabolism, energetically more favorable to contrast the energetically expensive response to injury. Thus, Nrf2 operates by antistress mechanisms restoring the homeostatic steady state challenged by the stressor and the associated inflammation.27 Activators of Keap1, including nutrients and drugs, are the players of a hormetic response.28,29 When insufficient, this regulatory mechanism is associated with stable alteration of the homeostasis, accounting for a disease status that corresponds to that produced by insufficient feedback control. In summary, reasoning on eustress and nucleophilic response, we envisage the health-supporting activity of hormetic stimuli as one of the significant hallmarks of physiological health.1

The basic sequence of events supporting the dynamic redox equilibrium is, therefore, the following: stressor (or signal) -> increase of oxidants and/or electrophiles -> signal transduction by a redox-sensitive functional shift in the target -> feedback activation of a response switching off the signal -> reestablishment of homeostasis. The failure, therefore, to rearrange the redox steady state constitutes a condition of altered homeostasis and is seen as decreased health condition. In essence, we propose that a major hallmark of physiological health is the
capability to maintain a redox steady state escaping from an excess of oxidations primed by the response to the stressor.

1.4 Redox homeostasis and COVID-19: an exemplary case

The deviation from redox homeostasis upon the exposure to a stressor and the subsequent feedback response operating to restore the redox status has been observed in the pathophysiology of influenza virus infection, and it can be efficiently represented in the paradigmatic case of SARS-CoV-2 infection and COVID-19, as has been laid out extensively. Here, we briefly discuss the formation of oxidants and the nucleophilic response as major players in the COVID-19 affliction.

When a viral particle present in inhaled ambient air droplets interacts with the specific receptors and enters cells, the cellular NADPH oxidase system is activated. It can be assumed that, at least for a minimal viral load, this could be sufficient to irreversibly damage the virus. Thus, this oxidative distress to the virus is sufficient to operate as a primary component of innate antiviral defense. Moreover, this offset of redox homeostasis toward oxidation activates the inflammasome, the cornerstone of innate immunity, which accounts for the first part of host resistance to disease and evolving, through different steps of inflammation, toward adaptive immunity. Finally, this defense mechanism could evolve to the cytokine storm and the final derangement of tissue homeostasis, multiple organ failure, frailty and respiratory distress when poorly controlled. In this perspective, the cellular response to SARS-CoV-2 includes a positive oxidative burst, while oxidations produced by an excessive inflammatory response are detrimental. The multiple organ failure typical of lethal COVID-19 is seemingly operated by an oxidative cell death likely corresponding to ferroptosis, a mechanism of cell death due to lipid peroxidation primed by insufficient activity of GPx4.

In this light, COVID-19 can be viewed in the broad concept of diseases due to an excess of reaction to injury operated by an excess of inflammation and the associated oxidative status. Notably, clinical conditions such as diabetes, obesity, and old age are associated with hyperactivation of inflammasome and an increased vulnerability to COVID-19.

Only a minority of subjects exposed to SARS-CoV-2 become severely sick and die, which introduces the notion of tolerance, seen here as the functional integration of biological and metabolic events not directly connected to combat the intruder but to prevent the excess of response while assisting the mechanism of resistance to the pathogen, operated by inflammation. In other words, tolerance operates to restore homeostasis. Activation of the Nrf2 pathway is seen as a strategy against COVID-19 and against all diseases where a poorly controlled inflammation has a pathogenetic role. In this scenario, molecules competent for alkylation of sensor thiols of Keap1 and the activation of Nrf2 emerge as central players in recovery of the redox steady state, contributing to the tolerance versus several degenerative diseases.

In conclusion, the feedback response to a functionally useful oxidative eustress operates by oxidants and electrophiles increasing the nucleophilic tone, and this prevents the evolution toward a damaging oxidative distress. In other words, the primary mechanism of restoration of redox homeostasis is hormetic (Figure 1). Chemical species derived from nutrition or by new chemical synthesis are competent for contributing to restoration of redox homeostasis. For this mechanism, the term “parahormesis” has been proposed for chemicals not intrinsically toxic but only mimicking, due to their electrophilic character, the effect of potentially toxic electrophiles on Keap1. We expect that the use of Nrf2 inducers will be soon validated by solid clinical evidence regarding the evolution of degenerative diseases and possibly the mitigation of incidence and outcome of viral infections.
1.5 Open questions

This Commentary focused on redox eustress as a concept in physiology. Several questions need to be considered for further understanding, which include: (a) What determines the redox set point for a given cell and its subcellular organization in spatiotemporal terms? (b) What defines the bandwidth of physiological eustress range, that is, the extent of the Golden Mean, which characterizes the borderline fringes for transition to distress? and (c) What orchestrates the various stress response mechanisms?

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