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Redox biology: Interface of the exposome with the proteome, epigenome and genome

Young-Mi Go, Dean P. Jones*

Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, Emory University, 205 Whitehead Research Center, Atlanta, GA 30322, USA

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ABSTRACT

The exposome is the cumulative measure of environmental influences and associated biological responses throughout lifespan, including exposures from the environment, diet, behavior and endogenous processes. Much of the direct interaction of an individual's exposome involves redox biology as the body responds to environmental, dietary and behavioral risk factors of disease. The present commentary addresses this critical interface and the need for redox biologists to lead development of concepts and strategies to sequence the exposome.

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Scientific foundation for the exposome

In 1981, Doll and Peto published an important epidemiologic study on the causes of cancer, providing quantitative estimates of avoidable risks [1]. Life-style and other environmental factors were divided into a dozen categories, and for each category the evidence relating those particular factors to cancer onset rates was summarized (Fig. 1A). Christopher Wild extended this to the concept of the exposome in 2005, pointing out the need for a conceptual grid to facilitate definition of the exposome throughout lifespan [2,3]. Wild's definition has been expanded to include health behaviors and consequences of environmental exposures, such as mutations and epigenetic changes and associated biological responses throughout lifespan, including endogenous processes such as oxidants generated as a response to the microbiome [4].

Surprisingly, after 30 years of considerable scientific progress including development of capabilities to sequence the human genome and obtain detailed knowledge of all types of exposures, we have limited applications of this wealth of analytic methods and mechanistic knowledge to predict health risks and disease on a personalized basis. A primary scientific limitation is the lack of a system to acquire and use knowledge of relevant timing, intensity and duration of exposures and associated biologic responses and outcomes. Without such a system, the best one can obtain is a

projection based upon long-distant memories or loose associations of individual properties with population averages. Planning for the exposome is underway [3,5,6] and the present commentary represents a call to redox biologists to help lead development and implementation. Active participation of redox biology is essential to provide mechanistic substance to the diverse exposures and integrated biological responses of the exposome. Indeed, redox biology is a critical interface of the exposome and the proteome, epigenome and genome.

Redox biology at the interface

The interface between the exposome and the proteome, epigenome and genome involves the interaction of exogenous agents with the metabolic and macromolecular structures which constitute a living organism (Fig. 1B). The metabolome and redox proteome provide a network structure that allows an individual to utilize essential nutrients and adapt to environmental challenges [7,8]. Reversible oxidation and covalent modifications of the proteome occur continuously as part of an evolved structure providing defensive barriers and signaling of transcriptional responses, DNA repair and epigenetic acclimatization. The considerable wealth of expertise and experience in these central processes suggests that redox biologists can provide great insight to direct development of the conceptual grid needed to sequence the exposome.

* Corresponding author. Tel.: +1 404 727 5970; fax: +1 404 712 2974.

E-mail address: dpjones@emory.edu (D.P. Jones).

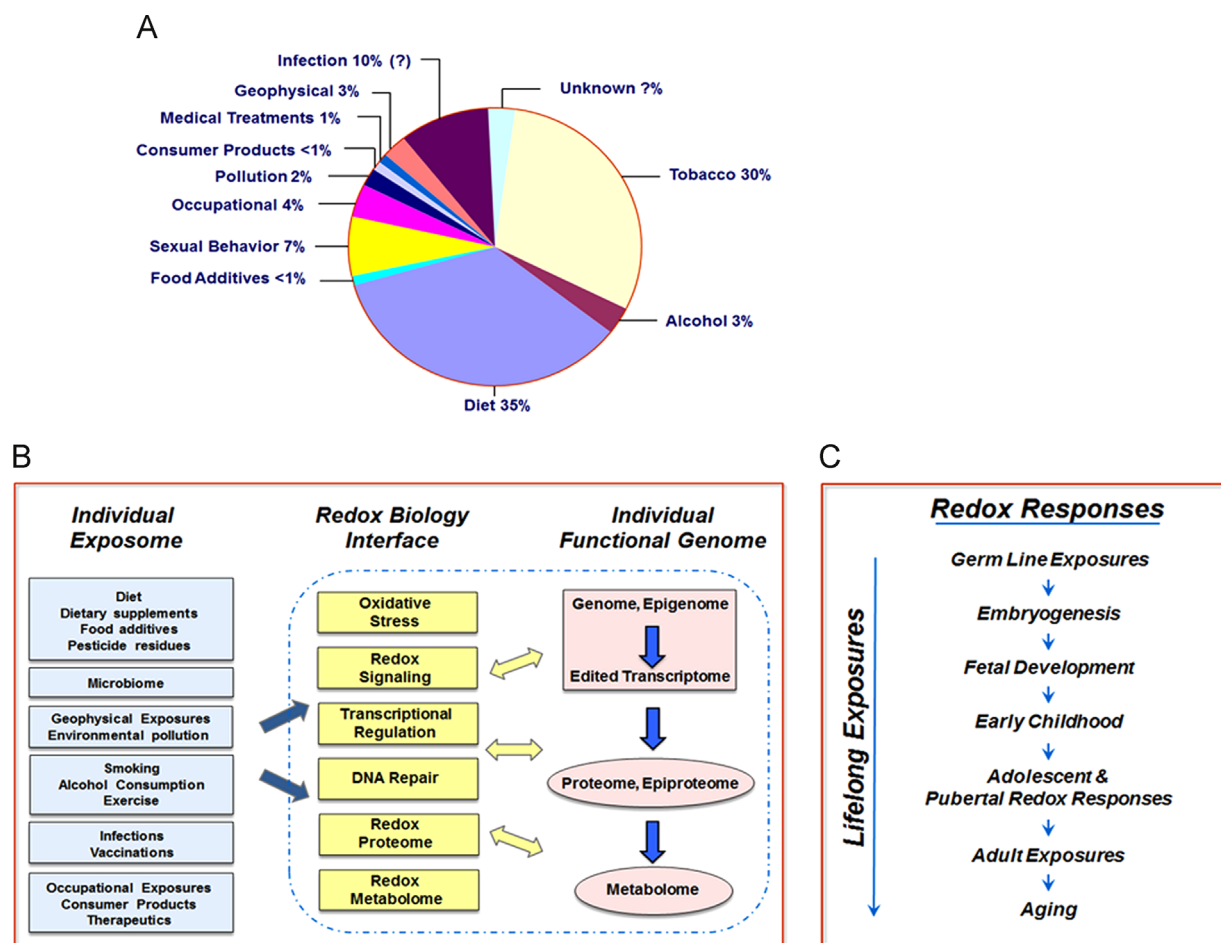


Fig. 1. Redox biology is at the interface between an individual's exposome and functional genome. (A) Epidemiology of disease provides a framework for systematic evaluation of association of exposures with disease. The landmark Doll and Peto's study [1] of factors associated with cancer illustrates a framework to begin sequencing cumulative lifelong exposures and responses as conceptualized by the exposome. (B) Redox biology encompasses mechanisms linking exposures to the functional genome. Indeed, redox mechanisms provide the first line of defense against environmental challenges. Real life involves a cumulative series of multiple exposures, and many of these affect the organism by common mechanisms. Hence, development of the conceptual grid to sequence the exposome will benefit from active leadership by redox biologists knowledgeable in these response mechanisms. (C) The conceptual grid to study the exposome can benefit from life cycle research in nutrition, development and aging. Research studies to sequence the human exposome can benefit from decades of research on developmental ages, which are vulnerable to nutrient deficiency, infection and other exposures. Application of universal biomonitoring to existing longitudinal studies may be especially useful to obtain an initial draft of the human exposome. Panel A redrawn from Doll and Peto [1].

Redox systems biology

The chronologic record of exposures must be mirrored by measures of the adaptive redox networks [7]. Currently, there are few approaches to capture and characterize adaptive and maladaptive responses in chronobiology of humans. miRNA in plasma might be an accessible readout, or accessible buccal, skin or peripheral blood cells might provide useful epigenomic signatures. At the very least, detailed studies of model systems with systematic variations of exposure sequences with integrated redox metabolomics, redox proteomics, and redox epigenomics, would provide a foundation for understanding and integrating temporal exposure-response patterns and providing a knowledgebase for long-term impacts.

Quantitative methods are essential to build a knowledgebase of redox impacts of cumulative exposures. This constitutes a considerable challenge for redox biology because quantification for long-term use requires absolute references, i.e., in terms of International Systems of Units (SI; <http://physics.nist.gov/cuu/Units/units.html>). Use of relative indicators of oxidant production is common in redox biology, and design of experiments is standard in which induced changes are expressed relative to controls. While such relative measures are useful to characterize responses,

snapshot measures of an individual are difficult to interpret against populations or evaluate within an individual over time without sound absolute reference. Hence, an important contribution to sequencing the exposome will be the development of quantitative redox measures for long-term studies to evaluate impact of exposures. This can be facilitated by inclusion of absolute references whenever possible in scientific publications.

Use of absolute quantitative references will also enhance development of redox systems biology. Redox systems biology is founded upon quantitative principles. Presently, however, there are few databases of redox properties of biomolecules, reaction rates of common redox reactions, or abundance measures of redox components. There are limited efforts to develop redox pathways and the complex multidimensional network structures that will be needed to understand and predict redox responses as components of the exposome. Redox biology must provide key leadership to develop such resources and guide their implementation.

Sequencing the exposome

The conceptual grid needs to address the spectrum of exposures, timing and duration of exposures and acute and chronic

responses to exposures. The spectrum of exposures can be expanded from epidemiologic studies, broadly including infections, vaccinations and other exposures, but will need thoughtful, detailed development to provide the granularity essential to capture relevant personal health characteristics for essentially all individuals. Convenient tools will be needed to prompt reliable entry of information into cumulative personal data records for such information, i.e., to be reliable in a reference data library structure to allow use for personal health predictions.

Timing of exposures can be addressed through a life cycle approach as commonly used in nutrition and toxicology. This highlights the natural progression from pre-fertilization exposures, to embryonic and fetal exposures, to exposures of newborns, early childhood, preadolescents and adolescents, young adults, middle-age adults, older adults and individuals with advanced age (Fig. 1C). This is exemplified by recent data showing that a wave of oxidant generation occurs in the development in *Caenorhabditis elegans* [9]. Intuitive life cycle constructs are available to establish the conceptual grid, e.g., timing approaches used in reproductive biology, pediatrics, geriatrics and other disciplines.

Development of methods to conveniently quantify intensity and duration of elements of the exposome poses an important challenge. For this, it may be necessary to use global biomonitoring such as provided by high-resolution metabolomics [10,11]. With these new methods, one can obtain snapshots of exposure including > 20,000 chemicals measured by liquid chromatography-high-resolution mass spectrometry. This provides opportunity to understand interactions of dietary, environmental and microbiome-related chemicals with redox systems. Routine use with entry of data into cumulative libraries can provide a long-term chronological record of individual exposures and responses.

The path forward

Cooperation will be needed among scientists and scientific organizations to distribute responsibilities and assure systematic coverage in sequencing the exposome. A starting point lies in systematic consideration of the existing knowledgebase of the temporal nature of exposures, lifecycle and connecting redox mechanisms. Oxidant and antioxidant exposures are frequently addressed in reproductive organs, during fertilization and implantation, early embryogenesis, and fetal development. Redox mechanisms contribute to mutagenesis, teratogenesis and environmental mechanisms of endocrine disruption,

fetal alcohol syndrome, autism, childhood tumors, asthma and other health outcomes. Similar scientific substance is available for obesity and type II diabetes, cardiovascular, pulmonary, renal, liver, neurodegenerative and other disease processes. Central roles of redox signaling, redox compartmentation and redox-dependent epigenetic modifications, are present and responsive to dietary, environmental and infectious exposures. Engagement of redox biologists in development of the conceptual grid for cumulative lifelong health exposures will assure that sequencing the human exposome is available to complement the human genome for future predictive health and personalized medicine.

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