Available online at www.sciencedirect.com
SCIENCE DIRECT
Mutation Research 597 (2006) 32–38
Fundamental and Molecular Mechanisms of Mutagenesis
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A systems biology approach to multicellular and multi-generational radiation responses

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Received 2 March 2005; received in revised form 30 June 2005; accepted 14 September 2005
Available online 18 January 2006

Abstract

Recent studies have highlighted crosstalk between irradiated cells and non-irradiated bystander cells and have uncovered high-frequency phenotypes of genomic instability in the progeny of irradiated cells that cannot be solely explained by radiation-induced mutation. It is difficult to explain these multicellular and multi-generational phenomena using the current paradigm of radiation biology. Radiation-induced bystander effect is a type of multicellular response to radiation that illustrates that the unit of function in multicellular organisms is neither the genome nor the cell. Cell function in complex three-dimensional tissues is coordinated by soluble signaling peptides and by small molecules within the context of insoluble scaffolding provided by the extracellular matrix. Adaptive response and radiation-induced genomic instability could thus result from persistent signaling perturbations following radiation exposures. A model of radiation response based on the systems biology principles of network interconnectivity and spatial organization should reconcile the apparent contradiction of these cellular phenotypes within the higher order structure of tissues and organisms.

Keywords: Ionizing radiation; Systems biology; TGFβ; Extracellular matrix; Genomic instability

1. Introduction

The challenge in predicting radiation health effects in humans is to understand how cellular responses occurring in a multicellular context are integrated to produce an organism response. Experimental studies, detailed elsewhere in this volume, show that radiation exposure elicits responses that can produce effects in non-irradiated bystander cells or can lead to a high frequency of genomic instability in the progeny of irradiated cells. This has motivated a substantial effort to both describe and quantify these non-targeted responses. One may argue that, more importantly, those data have heightened awareness that many types of cell interactions contribute to long-term radiation effects, and that multicellular responses are poorly integrated into the current paradigms of radiation effects and their consequences in terms of human health.

Understanding how cell and molecular responses to ionizing radiation produce individual organism response may be difficult in reductionism models that emphasize components and pathways, rather than on network interconnectivity and tissue context that produce complexity.

Abbreviations: ECM, extracellular matrix; MMP, matrix metalloproteinases; TGFβ1, transforming growth factor β1

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doi:10.1016/j.mrfmmm.2005.09.008

Even cell function is an elaborately branched signaling network mediated by receptors, ligands and small molecules that can activate DNA repair, alter chromatin organization, switch on cell cycle checkpoints and modulate various cellular metabolic processes [1]. Likewise, tissue function is the culmination of multicellular network coordinated by soluble endocrine, autocrine and paracrine signals and linked through a scaffolding of extracellular matrix that dynamically maintains homeostasis by regulating tissue composition, function, and phenotype. Just as DNA damage elicits a dramatic transition in signaling within a cell, each irradiated tissue has its own set of signals and cell types, distinct from that of the unirradiated tissue and different from that of other irradiated tissue. The sum of these events occurring in different organs, highly modulated by genotype, results in the organism response, but predicting this response for individuals remains an elusive.

Thus, one may consider the problem from a systems biology viewpoint, i.e. how is the whole greater than the sum of its parts? Key differences between systems biology and current 'analytical' paradigms are that systems biology places emphasis on networks versus components, distributed versus centralized effort, and redundancy versus uniqueness [2]. Systems biology attempts to organize multiscale data obtained following environmental perturbations, e.g. radiation, and use that data to build a descriptive and mechanistic model of the biological phenomena [3]. Top-down analysis of the radiation response of any organism, much less humans, is beyond present capabilities because neither the tools nor detailed, global data are available. Yet, it is feasible to use systems biology concepts to place radiation-induced bystander effect, adaptive response and genomic instability into the context of an irradiated system (i.e. tissue). Radiation-induced bystander effects are a type of multicellular responses to radiation, while adaptive response and multi-generational radiation-induced genomic instability may result from persistent network perturbations following radiation exposures.

The goal of systems biology is to analyze the whole, rather than the parts. Since there is a profound prejudice against waste, complexity and redundancy in human enterprise, we tend to impose these same constraints on biological functions. And as humans, we value individuals, uniqueness, and independence, and thus tend to frame biological problems in such terms. Systems biology provides a means to incorporate redundant, multifactorial and contradictory mechanisms into achieving meaningful goals. Three systems biology principles will be discussed as we interpret them to relate to radiation biology: information layering, scaffolding, and robustness. Neither comprehensive, nor expert, the intent of this commentary is to induce discussion rather than to instruct.

2. Information layering: reiterative, recycled and redundant processes

Recasting radiation biology in terms of system biology begins by regarding the tissue, organ or organism as the primary responder rather than the cell or molecular event. This is a fundamental shift from most current models because it de-emphasizes the well-characterized effects of ionizing radiation on a central cellular target, DNA. Most models place DNA damage, in particular double-strand breaks, as the pivotal event that initiates the radiation response and subsequent effects. Although a great deal has been learned about mechanisms of DNA damage and repair machinery, this focus has led to a virtual 'blind spot' where cell–cell interactions have no place in modern radiation biology, which leads in turn to a certain skepticism that irradiated cells can produce effects in unirradiated cells. This last is blatantly at odds with modern cell biology and extracellular signaling via ROS, cytokines, peptide hormones, chemokines, matrikines and growth factors and the cross-talk required between cell types to execute tissue, organ and organism functions.

We previously postulated the existence of a coordinated multicellular damage response program based on the rapid and dynamic cell biology that occurs in irradiated tissues [4]. Although some events may appear to augment damage, we believe that in most cases tissue damage response programs are directed towards restoring tissue function. A main feature of the program is that individual cell responses are coordinated by extracellular signaling. In normal tissue, a major role of extracellular signaling is to inhibit carcinogenesis by eliminating abnormal cells and suppressing neoplastic behavior. Since oxygen metabolism results in continuous bombardment of DNA and proteins by reactive oxygen species by-products, this program(s) is likely operative at all times, but is co-opted, and possibly corrupted, by the exigencies of acute radiation damage. Tissue pathology and organ failure result when radiation response severely disrupts communication between cells or among different cell types [5,6].

Thus, radiation-induced bystander effects and genomic instability can be seen as, respectively, positive and negative cellular manifestations of multicellular damage responses [5]. Bystander effects are evidence of the extracellular signaling that results from such multicellular programs that attempt to re-establish