# A Systems Biology Approach to Radiation Biology

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Biological responses to radiation are complex. Part of the complexity is that the initial physical damage due to energy deposition is not homogeneously distributed at the molecular level. But more importantly to understanding space radiation risks, the type and time scales of biological responses for cells, tissues and organs are different. Both cell interactions and heterogeneous, multicellular responses contribute to long term radiation effects, but are poorly integrated into the current paradigms of radiation effects on human health. Some animals are remarkably resistant to radiation, certain tissues exhibit little to no functional response while others undergo marked cell loss, and health risks like cancer are highly dependent on the individual and the tissue type. The same amount of energy elicits vastly different p53 responses in cells from different tissues (*1*); two tissues with essential identical functional radiation response, i.e. p53-dependent apoptosis, initiate very different p53-dependent transcriptional programs (*2*); and the same amount of energy deposited by different radiation sources elicits different transcriptional events (*3*).

A multiscale view of radiation effects is a tradition in radiation biology. The three 'R's' of radiobiology, repair, repopulation and re-oxygenation, describe how cellular, tissue and organismal radiation effects contribute to efficacy of radiotherapy. The response to DNA damage is an elaborately branched signaling network mediated by receptors, ligands and small molecules that can activate repair, alter chromatin organization, switch on cell cycle checkpoints and modulate various metabolic processes (*4*). Since the initial physical and chemical events due to energy deposition are similar within the genome of any given cell within an organism, the different responses of cells are generally interpreted as differences in the individual cells response to DNA damage as a function of DNA repair capacity.

Equally important is the response of that cell to being damaged, which includes activation or suppression of specific signals, signaling pathways, and receptors that can act not only on the exposed cell, but neighboring (i.e. bystander) or distant (i.e. abscopal) cells. Just as DNA damage elicits a dramatic transition in signaling within a cell, each irradiated tissue has its own set of signals, distinct from that of the unirradiated tissue and different from that of other irradiated tissue. The tissue response to damage is the culmination of many cell types that generate a multicellular network coordinated by soluble endocrine, autocrine and paracrine signals and linked through a scaffolding of extracellular matrix (ECM) that dynamically maintains

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homeostasis by regulating tissue composition, function, and phenotype. The sum of these events occurring in different organs, highly modulated by genotype, may restore homeostasis or affect health.

The major challenge is to understand how cellular responses to radiation are integrated in a multicellular context. Systems biology is an approach to use high density data to ask not what has changed, but how do specific events interact and affect the biology of the whole tissue/organ/organism? Systems biology attempts to organize multiscale data obtained following environmental perturbations like radiation, and touse such data to build a descriptive and mechanistic model of the biological phenomena (*5*). The key difference between systems biology and current analytical paradigms is the emphasis is on integration. Systems biology thus embodies multiplicity and redundancy rather than reductionism (*6*). Systems biology builds networks while molecular biology identifies components. Systems biology predicts consequences from distributed contributions while cell biology generates hierarchical models. Rather than trying to explain observable phenomena by reducing them to interplay between elementary units (e.g. cells, signaling pathways) investigated independently, systems biology conceives of problems in terms of organization and tackles phenomena not resolvable into local events (*7*).

A systems radiation biology model uses networks to predict the health effects of human travel in the complex radiation environment of space. To re-cast radiation biology in terms of systems biology, one begins by critically evaluating how radiation changes networks between cells, tissues and organs. Most biophysical models of radiation risk place DNA damage, in particular double-strand breaks, as the pivotal molecular event that initiates the radiation response and subsequent effects. A key feature of systems biology approach is recognition that systems respond to stimuli at multiple levels and each critical response has several back-ups. A network view of radiation biology incorporates interactions between target cells like the epithelial cell in solid tumor carcinogenesis that are highly modulated by non-target tissues, e.g. stroma or immune system. Energy deposition and damage may initiate the biological responses, but multicellular networks dictate whether homeostasis is restored or pathology ensues. Thus system failure lies less with the components, e.g. cells that are individually dispensable, than with the system performance which determines the return to homeostasis.

Network information dictating phenotype, function and response to stimuli can reside extracellularly. For example, extracellular matrix (ECM) consists of a complex, fibrillar network of large, generally insoluble, proteins that serve as a scaffold for cell adhesion and a reservoir of many peptide growth factors. In contrast, cytokines have transient actions that are frequently a function of release from cells, while growth factors may be activated to either maintain homeostasis or mediate response to stimuli. Thus the extracellular space provides an adhesion scaffold that contains solid state information (i.e. ECM), reserve messengers (i.e. growth factors), transitional signals (e.g. cytokines), and dynamic modifiers (e.g. matrix metalloproteinases (MMPs). ECM remodeling, similar to that elicited by wounding, is generated within hours of radiation exposure and can persist for months after a single exposure. The pattern of activity and

production of soluble and insoluble proteins is rapidly altered by radiation exposure, creating a rapid and widespread network of signals that can recruit circulating cells or modulate cell phenotype. Fundamental changes in scaffolding may persist from radiation exposures that modify subsequent behaviors. These changes can persist for decades after therapeutic radiation doses as evidenced by compromised wound healing and tissue composition (8, 9). It is possible that a coordinated cellular response of tissues and organs could be based on a scaffold of ECM and soluble factors. The failure of such an extracellular network could compromise damage signaling, generate aberrant cells, and increase proliferation (10). But redundancy operating at multiple levels produces a robust system that has a high likelihood of repair and recovery.
The ideas endorsed by systems biology have been embraced for decades by multidisciplinary investigators whose research on radiation effects in animals and humans provide the basis for contemplating human exploration despite the complex radiation environment of space. Integrating multiscale radiation biology into understanding of the truly dynamic processes that maintain or impair homeostasis remains very challenging. Nonetheless, new efforts are underway to systematically describe the genetic, molecular and cellular networks affected by radiation and integrate their consequences using systems biology modeling to predict health effects like cancer and degenerative diseases.

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