Chapter V: Radiation Chemistry: Origins of life on earth, SPEs, GCI, gamma rays

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Introduction:

Astrophysicists continue to speculate about the "Big-Bang" theory of formation of the universe, the galaxy, and specifically, our solar system. If all elements of the periodic table originated from the initial "Big-Bang" event, then current theory maintains that concatenation of collections of such atoms formed all structures of the solar system including the sun and planets, as well as moons, asteroids, and comets. The celestial bodies consist of different combinations of solids, gases, and frozen substances and maintain relative positions in the solar system with varying orbits around a central star, in our case, the sun.

The fields of astrophysics, and astrochemistry also facilitate a way to help describe the evolution of responses to ionizing irradiation. The physics in the formation of the universe is also relevant to the topics of nuclear fission and fusion. Hydrogen fusion to form Helium is the major event occurring in the sun, which generates the energy that sustains life on Earth. This same fusion reaction on our sun leads to formation of solar proton events (SPEs) (sunspots) and the x-irradiation that precedes each periodic burst of proton irradiation in our solar system. SPEs are discussed in detail in the chapter in this web-based textbook on space irradiation and how proton irradiation exposure complicates prolonged space missions including the planned Mars Mission. Also important, is the role of galactic cosmic irradiation (GCI). GCI results from supernova and other destructive events in the so-called death of stars. GCI events occur at thousands of times per day, at irregular intervals, and are responsible for the high linear energy transfer (LET) irradiation events detected by the measurement devices on unmanned spacecraft including those in recent Mars Missions ("curiosity rover"), on the space station, and in the past space shuttle missions. GCI causes a periodic fluence of charged particles that will penetrate any spacecraft outside the Earth's magnetic field and lead to formation of neutrons in the space vehicle. Managing ionizing irradiation of all types from x-rays to high LET particle irradiation including GCI is a main focus for planning any travel outside the Earth's atmosphere. Finally, fusion is also the man-made reaction leading to the tremendous energy release in thermonuclear weapons – a topic central to the field of radiation countermeasures and this web-based textbook.

The origin of life on Earth, is extremely relevant to understanding all current radiation biology, as well as directing the development of radiation countermeasures for events such as radiation terrorism or radiation accidents. Events, which produce a massive imbalance in radiation protective mechanisms that have evolved over billions of years reveal the highly sophisticated and complex mechanisms by which cells, tissues, organs, and organisms could arise and persist in the primordial Earth's environment of ionizing irradiation.

When did the radioprotective magnetic field around the Earth develop? The iron core of the Earth facilitates the magnetic field. This field directs charged particles and atoms including protons and high LET particles to the magnetic poles of the Earth. The magnetic field minimizes charged particle radiation exposure on the planet surface. Human irradiation exposure consists of primarily x-rays (photons) both from solar x-ray bursts penetrating the Earth's atmosphere and from the decay of unstable elements (gamma irradiation photons) existing in the planet itself since the formation of the Earth. These elements include Uranium 235, Radium, and other elements described in the physics section of this web-based textbook.

Radiation Chemistry and Single Celled Organisms

Fossil evidence documents the existence of single cell organisms on the planet Earth, billions of years ago. Whether the first chemistry events resulting in the creation of single cell organisms required water is less controversial.

One theory is that the recently formed and cooling planet Earth was struck by a large asteroid containing ice (water), and this event resulted in the formation of oceans and land masses. Laboratory experiments to duplicate the creation of first nucleic acids, (building blocks of DNA) have suggested that this chemistry requires the presence of water.

Modern listings of the Taxonomy of organisms describe the simplest single cell organisms, prokaryotes, represented as archaeobacteria. The nucleus of such single cells contains chromosomes, structures which facilitate replication of DNA and lead to reproduction. The modern simplest organisms, bacteria, also have no mitochondria or energy producing organelles; however, communication between bacteria includes gene transfer between bacteria, which occur through mechanisms of virus-like particle transfer of genes (bacteriophages). Bacteriophages may carry genetic material, including those associated with resistance to ionizing irradiation. The so-called "simple" single cell organisms (bacteria) are actually quite sophisticated.

Complex interaction between fields of single cell organisms (bacteria) can result in complex interactions with other bacterial taxa and with complex organisms. In Modern Medicine, the concept of biofilm-producing bacteria, has gained great relevance with respect to understanding infectious diseases.

Strains of bacteria, such as pseudomonas aeruginosa, which can produce biofilms or multiple layers of colonization of single cell organisms can produce more severe diseases, compared to other strains of the same bacteria taxa that do not form biofilms. Biofilms relate to the complex "vegetation" on cardiac valves, which follow childhood infections "Scarlet Fever" caused by Streptococcus, and can lead to valvular calcification late in life (Streptococcal origin of Rheumatic heart disease). Pseudomonas aeruginosa strains, which form biofilms presents a more complex challenge for antibiotic therapy in patients with asthma, those with chronic intubation for ventilator care, and in Cystic Fibrosis patients. The intestine response to ionizing irradiation is different with biofilm forming bacteria in the gut, which can produce more severe toxicity to the irradiation damaged intestinal epithelium, compared to other strains of bacteria that do not form biofilms. Thus, the "simplest" organisms can function in families, colonies, and complex structures that can change the health and the irradiation response of the most complex organisms including humans.

The evolution of multi-cellular organisms according to the Phylogenetic tree for animal and plant species is based on cellular and tissue complexity. Perhaps, the most relevant event in the origin of life on Earth, which affects radiation biology, was the genesis of mitochondria. These cells with mitochondria are called Eukaryotes. Eukaryotes are more complex single celled organisms that contain mitochondria, most clearly represented by yeast. Two yeast species saccharomyces cerevisiae (17), and saccharomyces pompe, are the two most commonly studied yeast strains in radiation biology. Induction of mutations in both these categories of yeast by ionizing irradiation

and other drugs has led to the development of hundreds of clonal lines of yeast mutants, which show specific causes of their ionizing irradiation repair process. The complexity of the response of these primitive eukaryotes to ionizing irradiation has been a subject of great interest, well summarized in papers by Nickoloff, et al. (9-10, 15-17). The discovery of critical radiation repair genes in mammals followed the initial discovery of analogs of these genes in yeast ranging from rad50, rad51 to other so-called orthologues, and paralogues (7), of these genes initially described mutant yeast strains. The data led to profound discoveries with respect to mammalian cellular responses to ionizing irradiation, and also led to discovery of targets for molecular biologic approaches to intervention in radiation damage and repair.

Studies of bacteria and yeast exposed to high doses of ionizing irradiation led to some of the most important studies with respect to understanding DNA repair. The best example is the bacterial species Deinococcus radiodurans (1-3) an extremely radiation resistant strain of bacteria. The D. radiodurans genome is a collection of radiation repair and stress response genes. Extremely rapid proliferation and evolution of bacterial (and yeast) sub-strains during irradiation facilitated rapid selection of a resistant strain and led to basic molecular biology and understanding of DNA repair. How Deinococcus radiodurans repairs ionizing irradiation induced DNA strand breaks represents understanding the ultimate adaptation of a species to ionizing irradiation. The evolution of life on Earth from the first single cell organisms followed a similar, but slower adaptation to exposure to a high level of ionizing irradiation.

DNA Repair Genes

All forms of radiation (x-ray, protons, neutrons, and high LET particles (those in galactic cosmic irradiation)) cause both single and double stranded DNA breaks. Much research has demonstrated that the critical effects in cell death result from double strand breaks. Mammalian cells have two primary mechanisms by which to repair double strand breaks: homologous recombination and non-homologous end joining (4, 8). The former process is the dominant one and results in the lowest frequency of errors in the repair process. Double strand break repair requires a complex system of molecular biologic events, which initiate both recognition of the site of the break and localization of the ataxia telangiectasia mutation (ATM) kinase at the site of the break. A scaffold of 22 proteins is part of the Fanconi Anemia complex and establishes a platform for attachment of DNA repair enzymes (8). While there are thousands of such double strand breaks in every cell that naturally occur during cell division, in the absence of external radiation exposure, defects in one or more of the proteins involved in the repair process can result in or can lead to cell death, or carcinogenesis (15-17). Fanconi Anemia patients, who have absence or mutation in one or more of the 22 proteins, demonstrate a shift from homologous recombination (HR) to non-homologous end joining (NHEJ) as the primary mechanism for repair of double strand breaks (8). NHEJ is known to be error prone and can lead to increased misrepair, mutations, and ultimately higher frequency of carcinogenic events. When combined with genetic defect in p53 or an absence of a critical detoxification enzyme, an increase in such mutations can lead to reproductive failure, embryonic death, and carcinogenesis (8).

Constant low level ionizing irradiation exposure can lead to an increase in DNA double strand breaks, but recent studies have demonstrated that irradiation doses as high as 400 x background do not lead to significant increases in magnitude of homologous recombination (4).

The evolution of the DNA repair mechanisms that are utilized in the mammalian response to chronic low level irradiation demonstrates a high degree of successful adaptation to continuous low dose exposure. The current consensus of opinion is that in the absence of other carcinogenic cofactors (cigarette smoking, genetic propensity to cancer) humans can tolerate chronic ionizing irradiation exposure levels found in Uranium miners, nuclear reactor workers, and the anticipated cumulative radiation dose from a NASA planned Mars Mission. What is not known is the effect of sporadic rather than continuous high LET radiation exposure. Furthermore, the high level of adaptation to continuous low dose, or sporadic radiation in mice, the species in which most of the experiments are being carried out, may not be applicable to human exposure. These subjects are a focus of significant current investigation.

Communication of Cellular Radiation Damage by Altered Transcription (RNA)

There has clearly been a revolution in the understanding of transcription. The discovery of multiple forms of RNA including small interfering RNA, RNA spliced variants, and non-translated RNA has added a new layer of complexity in understanding radiation effects on molecular biology of mammalian cells. Most studies have demonstrated ionizing radiation induction at the level of transcripts or suppression of levels of others associated with the acute, subacute, and late radiation response (5). In addition, much recent work has focused on the field of epigenetics, in which the identification of regions in DNA that will be transcribed into mRNA, can be separated from those "silent" regions by the level of protection of DNA by methylation of the nucleic acids, which prevent early transcription associated enzymes from binding and initiating the process of transcription. While there are species-specific differences in the cellular response to irradiation, most transcription follows time dependent patterns of induction or suppression of specific categories of transcripts. A relatively uninvestigated area has been the role of ionizing irradiation on reverse transcription. The discovery of retroviruses (RNA C-type viruses) that utilize enzymes to reverse the process by turning RNA into a copy cDNA that can integrate into the nucleus and essentially transpose genes from the virus into cells (like bacteriophages do in bacteria). The effects of radiation on this process can also be quite relevant. In animal models, such as mice, which have multiple endogenous C-type viruses, radiation effects on this process may be more relevant than similar process in higher mammals including humans. However, transposons have been discovered in mammalian and human cells, and the phenomenon of "jumping-genes" may be part of the process of the mammalian response to low dose rate or continuous low dose rate irradiation.

Ionizing Radiation Effects on Translation of Proteins

Proteins involved in the irradiation response including inflammatory cytokines, stress response proteins, and proteins involved in metabolism, and cellular communication are remarkably affected by ionizing irradiation. The elevation or suppression of protein levels can occur by direct effects on DNA, which increase or decrease the level of transcription of the RNA for a specific protein, at the level of RNA transcription regulating the level of protein being produced, and at other multiple levels including the formation of effective or inactive proteins. Furthermore, elevated or suppressed levels of some proteins can result in downstream effects that will elevate or suppress other proteins (6).

Ionizing irradiation induced changes in translation and functioning of proteins (6) may not necessarily follow the same directions and correlate with the changes in direction and magnitude of RNA transcripts (5). The molecular biologic techniques for quantitating specific RNA transcripts and specific proteins have been utilized in radiobiology. The methods now make such studies of the time course and kinetics and response to irradiation quite feasible (Methodology for these assays has been widely utilized for studying RNA transcript responses (5), and protein translation (6).

The Language of Lipids (Oxidized Lipidomics)

A major discovery of the last decade has been the importance of communication of ionizing irradiation damage through oxidized lipids (13-14). A seminal discovery was the understanding of the importance of mitochondria in initiating irradiation-induced apoptosis. The molecular biology and biochemistry of mitochondrial mediated apoptosis began with an understanding of the role of cytochrome-c binding in the inner mitochondrial membrane to cardiolipin (12). Irradiation-induced changes in the nucleus, which mediated signaling from nucleus to mitochondria including transport of bax, p53, and other mediators of nuclear damage, resulted in oxidative stress at the mitochondrial membranes (11-14). Specifically, the inner mitochondrial membrane contains significant quantities of the lipid cardiolipin, which was demonstrated to bind to cytochrome-c and hold it in place in the electron transport cascade. During "normal" cellular metabolism electron transport through the cytochrome system leads to generation of adenosine triphosphate (ATP) and energy consumption. What was only recently appreciated is the importance of oxidative stress at the mitochondrial membrane resulting in oxidation of cardiolipin. Cytochrome-c transformation into a peroxidase was demonstrated in these initial studies (12-14). The peroxidative functions of cytochrome-c then oxidized cardiolipin and mediated the disassociation of cytochrome-c from cardiolipin. Oxidized cardiolipin is transported from the inner to the outer mitochondrial membrane and leads to signals initiating mitophagy. Mitochondrial destruction (mitophagy) on an individual basis was demonstrated to increase with the overall level of cellular oxidative stress. Enough mitophagy (enough of a percentage of the total cellular mitochondria undergoing mitophagy) leads to apoptosis of cells. Mitochondrial membrane permeability associated with mitophagy results in leakage of the cytochrome-c from the mitochondria into the cytoplasm. Thus, this biochemical interaction was demonstrated as being critical to understanding irradiation-induced apoptosis. Stated simply, cardiolipin holds cytochrome-c in the mitochondrial membrane, and when this interaction is disrupted by oxidative stress, the freed cytochrome-c leaves the mitochondria, enters the cytoplasm, and initiates the cascade of apoptosis by activation of Caspase-3, and ultimately, poly-adp-ribosyl polymerase (PARP). It is this latter reaction that results in DNA fragmentation and cellular death.

Oxidation of cardiolipin by ionizing irradiation in Eukaryotes is only the first step. A continuous cascade of oxidized lipids and phospholipids has been demonstrated and leads to formation of many lipid signaling molecules (14). A very interesting product of this oxidation is the production of hepoxillin-A3, which is a leukotriene-like molecule that calls neutrophils into the site of its accumulation. In particular, in the irradiated intestine, hepoxillin-A3, in addition, to leukotriene B4, and IL-8 calls neutrophils into the damaged lumen of the intestine for interaction

with bacteria. In the post-irradiation environment of edema from the release of other inflammatory mediators, neutrophils can be trapped in the swollen intestinal villi, release myeloperoxidase, and exacerbate intestinal injury.

The importance of oxidized lipids and lipid mediators is further emphasized by the interaction of gut and lung pathogens in the irradiated tissue microenvironment. Several recent publications have demonstrated the importance of the action of specific subsets of bacteria with damaged tissue. In particular, pseudomonas aeruginosa, of specific strains, which can produce biofilm and have 15–lipoxygenase, an enzyme, has no substrate with bacteria themselves. Microbes with enzymes for which there are no substrates in the bacteria themselves are not uncommon, but in the context of irradiation injury, 15-lox containing bacteria have been demonstrated to "hijack" the substrate for this enzyme in pulmonary and recently in intestinal epithelial cells initiating the biochemical process of ferroptosis. The multiple death pathways in irradiation-induced killing, which are described in another chapter in this textbook show the importance of ferroptosis as one of the irradiation-induced death pathways in cell killing. To understand that microbial pathogens can utilize this pathway to exacerbate cell killing, and thus enter the bloodstream initiating a process of infection and ultimately sepsis, makes the total approach to developing radiation mitigators and treatment of radiation injury more complex.

Complex Interactions of the Ionizing Irradiated Mammalian with Microbiome Cellular Responses (Lung, GI tract), and the Importance of Combined Injury – Infection

It has become increasingly apparent that the radiation response of complex organisms involves the interaction of responses with that of microbes that colonize the aero-digestive tract. The prominence of this interaction has gained importance with the advent of sophisticated methods for analyzing the taxa in the microbiome of the human intestine, oral cavity, and lung. Appreciation of the specific 16sRNA species with respect to the bacterial taxa in the intestine has facilitated a sophisticated analysis of intestinal bacterial community in fecal material, as well as that in the intestine (18). Specific microbes have now been associated with interaction of human tissues causing oral cavity and oropharyngeal cancers (Human Papillomavirus), gastric cancer (Helicobacter pylori), and in animal models the role of Helicobacter pylori and helicobacter hepatica in colon carcinogenesis in TGF-β response inhibited mouse strains. More recently, changes in the microbiome have been associated with autoimmune diseases, congenital diseases, diseases of neurodegeneration, and most recently, the inability of certain individuals to respond to immunomodulatory drugs such as PD-1 inhibitors (programmed cell death-1 inhibitors).

The intestinal microbiome shows critical functions during the process of digesting foods, processing of nutrients, and absorption of specific digestive products. Imbalance in the intestinal microbiome can follow specific diseases including those that cause intestinal pathology such as Clostridium difficile, which can cause chronic malabsorption and diarrhea. Other pathogens such as Clostridium typhi disease in which a toxin produced by a bacteria inhibits water absorption in the intestine, is a dramatic example of imbalance in the intestinal microbiome. Recent evidence indicates that the microbiome changes in response to total body irradiation (18). These data have potentially dramatic effects not only on the capacity of individuals to recover from total body irradiation, but also influence the application of radiation countermeasures.

In the current approach to management of ionizing irradiation casualties in a radiation terrorist event estimate the radiation dose sustained by the intestine will be critical to determine whether such individuals received broad spectrum antibiotics, or are sent home to shelter in place. Application of broad spectrum antibiotics is a principle derived from the management of patients receiving total body irradiation in preparation for bone marrow transplantation. Clearing the intestine of the normal bacteria community has been the logic, and has dictated the use of antibiotics and anti-fungal agents as radiation countermeasures. The logic is that radiation damages the intestinal barrier function in the ilium primarily, but also in the jejunum, and as such barrier function breakdown facilitates transport of intestinal lumen microbes into the blood. In the setting of leukopenia that follows irradiation exposure, absence of neutrophils and monocytes allows greater proliferation of bacteria in the blood and potentially systemic infection, sepsis, and death. Thus, the logic of using broad spectrum antibiotics. However, such antibiotics deplete the normal intestinal microbiome, which may be necessary to maintain the proper balance of different taxa and potentially facilitate intestinal healing.

The concept of "good bacteria" and "bad bacteria" has gained prominence from understanding of the deleterious role of Pseudomonas aeruginosa specific biofilm forming classes of this microbe. Studies are in progress to determine whether Pseudomonas aeruginosa actually gains a proliferative advantage compared to other bacterial taxa in the intestine after total body irradiation, and whether competition between taxa is necessary to facilitate a balance. It is not known at present whether total body irradiation causes indirect effects to produce imbalance in the components of the microbiome or direct effects. Such indirect effects would include the change in synthesis, release, or processing of bile salts and pancreatic enzymes (18), or by secretion into the intestinal lumen of inflammatory cytokines, and delivery of a proliferative advantage for a certain taxa of organisms. Direct effects such as radiation killing or stimulation of growth of specific taxa of bacteria are unlikely given the relatively low magnitude of total body irradiation doses in these experimental models, and in view of the evolution of bacteria at a time when the planet was sustaining extremely high doses of radiation. Bacteria representing the intestinal microbiome have evolved over a millennia, as have their human hosts.

One conclusion from this discussion would be that administering broad spectrum antibiotics and anti-fungal agents to irradiated humans, while seeming logical, may in fact be deleterious, because it can produce an imbalance in the microbiome that would be desirable for healing radiation injury.

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