BIOLOGICAL RESPONSE TO RADIATION THERAPY

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1 Introduction

Rarely has a great scientific discovery resulted in more useful uses and risks to human health than the discovery of ionising radiation. X-rays were first employed in medical diagnosis and therapy after their discovery. Unfortunately, radiation safety systems have lagged behind the constantly expanding use of radiation sources in terms of development and application. Several occurrences of erythema, dermatitis, and baldness have been documented among x-ray operators and their patients within the first six months of their use. In 1902, the first report of skin cancer linked to x-rays was published, followed by experimental confirmation eight years later. The British Roentgen Society issued the first radiation safety advice in 1915, followed by similar recommendations from the American Roentgen Ray Society in 1922. Radiation biologists study the nature and sequence of processes that occur when ionising radiation is absorbed, as well as the biological repercussions of any damage that occurs and the mechanisms that amplify, compensate for, or repair the damage. More information regarding the effects of ionising radiation on living systems has been accumulated over a century of radiobiological research than nearly any other physical or chemical agent.

2 Molecular Responses

2.1 The body's reaction to DNA and linage:

The present perspective on studies of DNA damage and cell cycle response following ionising radiation (IR) and its application in radiation oncology has been greatly influenced by the avalanche of information in cellular biochemistry and molecular biology. When DNA is damaged by IR, mammalian cells respond by activating two critical physiological functions: cell cycle regulation and DNA repair. Most cells have repair pathways that are always active and are controlled by cell cycle checkpoints. The cell must choose between DNA repair and cell death after recognising damaged DNA and assessing the damage. The goal is to

protect the genome's integrity. Cancer-prone syndromes show that people with either repair or checkpoint abnormalities are at a considerably increased risk of developing cancer. They are also more radiosensitive to IR in general.

Cells generally react to IR radiation in three ways: cell cycle arrest, cell cycle arrest, and cell cycle arrest, even at dosages considerably below the typical fractionated daily dose given clinically. This will provide cells enough time to fix their DNA. In fact, a single double-strand break (dsb) can cause cell cycle halt. NF-K13, on the other hand, is important for shielding cells from proapoptotic stimuli such dsbs. As with other drugs that create dsbs, inhibiting NF-K13 causes radio sensitization through increased apoptosis. The size and duration of the damaging stimulus are likely to influence the final decision to begin apoptosis rather than cell cycle arrest. There's additional evidence that entering the cell cycle is required to start apoptosis in cells with DNA damage.

2.2 DNA repair:

Effective DNA repair is critical for the genome's long-term stability. The DNA-dsb is the most major DNA damage linked to reproductive cell death in response to IR. Dsb can also be generated by normal endogenous mechanisms such oxygen free radicals, DNA replication, or topoisomerase failure, in addition to IR. Mis rejoining events such as dicentric chromosomes and ring chromosomes, both of which lead to a mitotic catastrophe within 1-2 turns of the cell cycle, are linked to persistent damage. The dsb could also result in significant translocations or the insertion of genetic material outside of its original place. These key events, which may include oncogene activation and deletion or down-regulation of housekeeping genes, are often persistent during the next cell divisions. Biophysical experiments reveal a link between radiosensitivity and both unrejoined dsb fractions and rejoining kinetics. Even while the majority of cells that progressively rejoin the breaks appear to be IR sensitive, other radiosensitive cell lines rejoin the breaks regularly.

2.3 Apoptotic vs clonogenic cell killing:

In recent years, the manner of cell death caused by DNA damage triggered by anticancer treatments, including radiotherapy, has been highlighted. The discovery of the function of wild-type TP53 in inducing apoptosis in response to DNA damage has sparked a huge interest in programmed cell death. There is clear doubt that after DNA damage that is dependent on wild-type TP53, lymphoid tissues and lymphoma cells die a quick apoptotic death. New ideas have arisen as a result of the fact that apoptosis is thought to be linked to genetically specified pathways. One of these ideas is that the genotype of normal or tumour cells can predict DNA-damaging chemical susceptibility.

In a Clonogenic experiment, both genotypes may demonstrate similar cell survival. If clonogenic survival is considered as the endpoint for cell death, neither TP53 status nor the ability of the cells to undergo apoptosis appears to

play a significant impact in the susceptibility of these cells to DNA-damaging chemicals, according to the findings of this review.

A recent review looked at the ambiguous role of apoptosis in non-lymphoid normal tissues for maintaining the balance between cell production and cell loss. Apoptosis contributes just a small amount to cell turnover in mammalian normal tissues, with a few exceptions. Several processes control cell death in tumours, such as necrosis produced by insufficient angiogenesis.

2.4 Critical issues:

New pathways involved in cell cycle checkpoints and DNA repair will almost certainly be discovered in the near future. However, converting this knowledge into clinically viable medicines faces numerous challenges.

—The application of recent understanding, as seen above, to the in vivo and human condition is still largely unknown.

—It is necessary to determine the relative importance of abnormalities in the various signalling pathways involved in cell cycle checkpoints and DNA repair for radiosensitivity.

The radiosensitivity of people who are heterozygous or have polymorphisms for some of the genes involved in the complex machinery of cell cycle checkpoints and DNA repair differs from the general population. It is necessary to gain a better understanding of how common these abnormalities are among cancer patients.

2.5 Clinical potentials:

The goal of future research is to figure out how DNA repair can be quantified and modulated to help improve radiation therapy, using both rapid and sensitive predictive assays and specific sensitization of tumour cells by knocking out critical repair pathways. Because DNA is the primary target for therapeutic doses of radiation, having a basic understanding of repair pathways in normal and tumour cells is critical. In 1994, the first gene known to play a substantial role in dsb repair in mammals was discovered, and this field has a lot of study promise. In recent years, major progress in DNA repair research has switched the focus from prokaryotes and yeast to mammalian or human cells.

Many aspects, such as the identification of additional key proteins, signalling pathways, alternative mechanisms of repair, activation/ inhibition of pathways and proteins, the role of the cell cycle and proliferation, relocalization of proteins, the role of the 3D nuclear architecture, the effects of high-LET (linear energy transfer) and multiple damage sites, and heterogeneity within individuals and cell populations, are still unknown. The knowledge gathered could pave the way for future advancements in tumour and normal tissue response prediction and prognosis. Similarly, identifying critical targets that are preferably down- or up-regulated in tumour cells could improve tumour therapy by modulating the repair process.

3 CELL AND TISSUE RESPONSE TO DOSES ABOVE AND AROUND 1 GY

Radiation destroys cells by causing several types of DNA damage. Damage to DNA appears to be the primary source of IR cell death and mutations, according to the research. In addition to a significant degree of base damage, each 1 Gy dose of low-LET radiation causes roughly 1000 initial single-strand breaks (ssbs) and 25-50 initial double-strand breaks (dsbs). The number of unrepaired or misrepaired dsbs breaks, which are regarded to be the most common type of cellular damage, correlates most strongly with cell death. Only approximately 1-2 percent of dsbs, however, are truly fatal. The majority of ssbs and dsbs are fixed correctly.

Various models based on assumptions about target inactivation have been presented to characterise the dose-response relationship for cell death. The exponential and multi-target single hit survival curves are examples of such models. In fact, for most experimental cell survival data produced using clonogenic experiments, a combination of these two is more appropriate. The linear quadratic model provides an even better description of radiation cell killing to single dose fractions of a size for clinical usage. The a/13 ratio, where a and p are cell specific under established conditions, but may vary with radiation quality, dose rate, and other dose modifiers, determines the curvature of the survival curve. There have been suggestions for alternative repair models.

The changing of the dose-response function with changes in irradiation volume is known as a volume effect. It is well understood that if the dose-response function is steep, there will be very little volume effect, such as in the case of spinal cord damage. Otherwise, there is a volume effect for most organs and endpoints. There could be a volume effect threshold. Radiation hepatitis, nephritis, and pneumonitis are examples of endpoints where this is most likely the case. The dose-volume effect is also determined by the organ and tissue architecture, as well as the presence of functional subunits. According to the arrangement of the functional subunits, tissue architecture is categorised into serial and parallel types.

4 Stem cells, colonogenic cells and proliferation

Stem cells: Self-renewing and differentiating cells that can produce all the different types of cells in a lineage, and sometimes pluripotent cells that can regenerate all cell lineages in a tissue or tumour.

Transit Amplifying cells: Proliferating cells with a poor potential for self-renewal and a high likelihood of terminal differentiation.

Clonogenic cells: are cells that can reproduce themselves. In tests, cells are identified by their ability to form a colony of more than 50 cells under a specific growth environment.

Differentiation cells: Cells that have undergone qualitative changes in their phenotypic as a result of the initiation of new gene product production, which

eventually leads to functional competence.

Understanding how stem cells are regulated is crucial in cancer research. Stem cell research lays the groundwork for oncology treatment development. Because the cells are rapidly eliminated, oncogenic lesions acquired by cells undergoing terminal differentiation have little impact on a tissue. Stem cells, on the other hand, are permanent residents of the tissue and so have the potential to develop harmful alterations over time and become a tumour. New treatment techniques focused at the fundamental cause of cancer will arise from understanding the processes driving proliferative regulation and differentiation within multiple cellular systems. Squamous cell carcinomas and colorectal carcinoma are two tumour histologies where the stem cell notion has been established.

Stem cell research is significant for a variety of reasons: I) The same systems that regulate stein cell proliferation get dysregulated during cancer growth. 2) Rapidly dividing bone marrow, gut, and skin tissues are the first to be impacted by cancer treatment and are frequently dose limiting in radiotherapy and other cytotoxic drugs. Isolation of viable stem cells might be employed to repopulate such tissues, or growth factors could be used to save them. 3) For stem cell gene therapy, trustworthy markers must be used to identify stem cells. The stem cell is an undifferentiated cell with a variety of qualities or options that enable it to proliferate and maintain its own population.

5 Cell and tissue response to doses above and around 1 gy

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Highly conformal radiotherapy employing intensity-modulated radiation treatment (IMRT) has been available in ordinary clinical practise since the mid-1990s. We require information regarding the dose-volume fractionation responsiveness of the normal tissues at risk in order to identify the best shape for the dose distributions. This knowledge is currently incomplete, and research must focus on gathering dose-response data and developing acceptable models. The nature of the volume effect, which is organ or tissue specific and also particular to a given endpoint, determines the dose-volume effect. Radiation causes a variety of problems in most organs. The collection of relevant and large enough databases to develop dose-volume impact models and obtain tissue- and end-point-specific parameter estimations is a critical challenge for the near future. The inclusion of inhomogeneous dosage distributions should be a goal of new models. The late tissue effects of IR censorship must be taken into account while modelling. There are various survival models that adjust for censoring, however the problem is that survival models cannot model dose-volume-response relationships. Finding early-appearing surrogate endpoints for the underlying late and mostly irreversible morbidity is one method to avoid the censoring dilemma.

6 CELL AND TISSUE RESPONSE TO LOW RADIATION DOSES

Within the last decade, advances in clonogenic test methodology have made it possible to analyse cell survival with enough precision to resolve variations in radiosensitivity at doses below 1 Gy. When cell survival is near to 100%, the number of 'at risk' cells in a colony-forming experiment must be precisely quantified. This can be accomplished by employing a fluorescence-activated cell sorter (FAGS) to plate a precise number of cells or by using microscopic scanning to determine an exact number of cells after plating. The phenomena of low-dose loperradiosensitirity (FIRS) was discovered to be a prevalent feature of radiation cell survival below 0.5 Gy using these methods.

Over the dose range of 0.5-1 Gy, HRS precedes the appearance of a relative resistance per unit of dose to cell killing, a process known as enhanced radioresistance (IRR). The HRS/IRR characteristics are visible after low-LET radiation but not after high-LET radiation. HRS/IRR has been found in around 80% of the 45 cell lines studied thus far. There has been no link found between

the presence of HRS and histological type, p53 status, apoptosis, cell cycle time, or GI arrest. In general, the cell lines that are most radioresistant to 2 Gy show the most pronounced low-dose HRS. The cell lines tested in vitro comprise of colorectal adenocarcinoma, bladder carcinoma, prostate carcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, neuroblastoma, glioma and melanoma. In addition, a non-malignant lung epithelial cell line has been discovered.

6.1 CLINICAL POTENTIALS

The goal of future study is to figure out how DNA works. Repair can be quantified and modulated to help improve radiation therapy through both rapid and sensitive predictive assays and specific sensitization of tumour cells through knockout of critical repair pathways. Because DNA is the primary target for therapeutic doses of radiation, understanding repair pathways in normal and tumour cells is critical. In 1994, the first gene known to play a substantial role in dsb repair in mammals was discovered, and this field has a lot of study promise. In recent years, major progress in DNA repair research has switched the focus from prokaryotes and yeast to mammalian or human cells. However, there are still a lot of things that aren't evident.

The knowledge gathered could pave the way for future advancements in tumour and normal tissue response prediction and prognosis. Identifying key objectives is a similar process. Modulation of the repair, which is preferably down- or up-regulated in tumour cells, may have the potential to improve tumour therapy. There is a need for creative biochemical studies as well as the use of recent discoveries in genomics and proteomics in this study area, which contains intricate interactions between molecular targets.

7 Bystander Effect

A cell or target that has not been irradiated (bystander) may respond as if it has been irradiated. This phenomenon, which has primarily been observed in vitro in numerous assays employing diverse endpoints, is known as bystander effect "However, it is also known as "untargeted effect" or "intercellular communication." The phrase "Bystander effects, which occur when the gene product of a transfected DNA travels from the transfected cell into neighbouring cells, have already been utilised in other study fields including in gene therapy. Cells may respond to the bystander signal by inducing apoptosis, genetic instability, or delayed death, as well as enhancing call proliferation. DNA damage, chromosomal aberrations, altered gene expression, or mutations are all examples of DNA damage.

In radionuclide therapy and other cases when the dome distribution is diverse, killing bystander cells may be advantageous. The enhanced cell death could be minor or non-existent, but it appears to be cell type dependent: in cultures with keratinocytes and other cell lines, up to 50% of the cells were

killed without being physically irradiated. The development of permanent chromosomal mutations within irradiated cells could be a more critical implication of the bystander effect, and these mutagenic features, which may be particular to high LET radiation, should be recognised.

Much of the current duren comes from sources with high LET radiation. Because this sort of radiation causes highly complicated and clustered damage, there may be discrepancies in data and debates over the mechanisms.