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A review of radiation genomics: integrating patient radiation response with genomics for personalised and targeted radiation therapy

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Literature Review

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Abstract

Background: The success of radiation therapy for cancer patients is dependent on the ability to deliver a total tumouricidal radiation dose capable of eradicating all cancer cells within the clinical target volume, however, the radiation dose tolerance of the surrounding healthy tissues becomes the main dose-limiting factor. The normal tissue adverse effects following radiotherapy are common and significantly impact the quality of life of patients. The likelihood of developing these adverse effects following radiotherapy cannot be predicted based only on the radiation treatment parameters. However, there is evidence to suggest that some common genetic variants are associated with radiotherapy response and the risk of developing adverse effects. Radiation genomics is a field that has evolved in recent years investigating the association between patient genomic data and the response to radiation therapy. This field aims to identify genetic markers that are linked to individual radiosensitivity with the potential to predict the risk of developing adverse effects due to radiotherapy using patient genomic information. It also aims to determine the relative radioresponse of patients using their genetic information for the potential prediction of patient radiation treatment response.

Methods and materials: This paper reports on a review of recent studies in the field of radiation genomics investigating the association between genomic data and patients response to radiation therapy, including the investigation of the role of genetic variants on an individual's predisposition to enhanced radiotherapy radiosensitivity or radioresponse.

Conclusion: The potential for early prediction of treatment response and patient outcome is critical in cancer patients to make decisions regarding continuation, escalation, discontinuation, and/or change in treatment options to maximise patient survival while minimising adverse effects and maintaining patients' quality of life.

Introduction

Radiogenomics is a term that has been used interchangeably to describe two recently emerging multidisciplinary fields of scientific research; imaging genomics and radiation genomics. These two research areas have the potential for the development of a more personalised and targeted radiation therapy for cancer patients.[1–157] Imaging genomics refers to the study of the use of high throughput methods to assess the association between imaging characteristics of a disease (e.g., imaging phenotype and radio-phenotype) with genomic data (e.g., gene-expression patterns, mutations and other genomic data).[6,9–14,17] These associations have the potential to provide comprehensive inter-tumour, intra-tumour and peri-tumour information without the need of invasive procedures such as biopsy.[9] In contrast to imaging genomics, radiation genomics is the study investigating the association between genomic data and patients response to radiation therapy.[1–5,7–16,20,26,32,33,62,66] This field aims to identify genetic markers (i.e., genes and gene sequences that are up-regulated or down-regulated due to radiation exposure) linked to individual radiosensitivity with the potential to predict the risk of developing adverse effects (both acute and late effects) due to radiation therapy based on a patient's genetic information. It also aims to determine the relative radioresponse of patients using their genetic information for the potential prediction of patient treatment response.[1] By combining imaging genomics and radiation genomics studies, there is the potential to be able to predict a patient's radiotherapy response and the risk of developing adverse effects based on their imaging characteristics.

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A closely related field of study is radiomics, which has also recently emerged as a promising tool for discovering new imaging biomarkers by high-throughput extraction of quantitative image features such as shape, histogram and texture that captures tumour heterogeneity.[10,17] Radiomics can be applied to any type of clinical images (e.g., computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET)) and can be used in a variety of clinical settings (i.e., diagnosis and evaluation of treatment response). Imaging genomics uses radiomic's computer-extracted imaging features and biotechnology to correlate imaging characteristics and genetic markers.[3,10,17] With current technological advancements in imaging and genome sequencing, scientific research in these newly emerging fields of radiogenomics and radiomics have the potential to revolutionise radiation therapy for cancer patients by personalising treatments to maximise an individual patient tumour control probability while minimising the normal tissue complication probability. This narrative review paper reports on recent radiation genomics studies investigating the association between patients genomic data and their response to radiation therapy, including the investigation of the role of genetic variants on an individual's predisposition to enhanced radiosensitivity (i.e., relative susceptibility to the harmful effect of ionising radiation) and/or tumour response to radiation therapy.

Radiation Therapy of Cancers and Inter-Patient Response to Treatment

Since the inception of its clinical use, radiation therapy has become a significant mode of cancer treatment, especially in the treatment of localised tumours.[1,18] The radiation utilisation rate (percentage of cancer patients who received radiotherapy as part of their treatment during their illness) has been increasing steadily with a global goal of reaching about 50% in most developed countries.[158] The success of radiation therapy is dependent on the ability to give a total tumouricidal radiation dose to the clinical target volume, however, the radiation dose tolerance of the surrounding healthy tissues becomes the main dose-limiting factor.[2] According to Suit,[19] a 5% increase in radiation dose to the clinical target volume will typically increase the tumour control probability by about 5–10%, however, the likelihood of incidence and severity of surrounding normal tissue radiation damage may also rise with the increase in dose. A key challenge in radiation therapy is the ability to optimise the target dose or deliver a maximal dose to the target while minimising the dose to the surrounding normal tissues of the patient, allowing a balance between the cure and toxicity of a treatment.[1,2] Although substantial advancements have been made in recent years in radiation therapy with the advent of Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) to significantly conform the radiation dose to the planning target volume during radiotherapy, normal tissues are still subjected to non-negligible levels of radiation dose that could result in organ toxicity and can compromise organ function.[3,20]

The observed radiation toxicities in patients present itself at different times, and includes both early and late toxicities. The early, or acute, toxicity usually occurs during treatment or within 90 days after treatment and tends to be transient and healing. However, the late toxicities (which may occur months or years after treatment) are of a particular concern due to its persistence and ability to impact the quality of life of patients and may lead to chronic disability.[1] As long-term cancer survival rates are on the rise,[3] the late side effects from radiation therapy complications has become a major concern. Approximately 5–10% of patients will develop severe side effects that results in a significant impact on their quality of life.[6] Although, dose–volume histogram (DVH) constraints to organs-at-risk (OAR) are usually chosen during the radiation treatment planning process in order to keep the risk of developing a grade 3 or higher side effects below 5%, radiation-induced toxicities continue to develop in some patients.[21,22]

Inter-patient variability of response to radiation therapy

A large amount of variability in toxicities, in both prevalence and severity, exists in inter-patient response to radiation therapy despite the use of uniform site-specific treatment protocols.[2] While the majority of patients develop toxicities within a clinically acceptable range, others exhibit hypersensitivity and have been observed to develop severe toxicities at standard radiation doses.[23] Although this variability can be somewhat attributed to patient characteristics such as age, nutritional status, medication, recent surgery and comorbidities, the range of toxicity among patients has led to the suggestion that a component of this variability may be explained by common genetic variants.[2,24] Inter-patient radiation therapy response are complex polygenic phenotypes determined by interactions between multiple loci, gene products, and external factors (age, medication, recent surgeries, anatomy, ethnicity, dosimetric factors).[2] As a result of increased understanding of radiation response, the biological mechanisms behind the phenomenon, and the need to explain the large inter-patient variability despite uniform treatments protocols, researchers have shifted their focus towards the impact of specific genetic variants on radiosensitivity. One of the strongest pieces of evidence delineating the relationship between genetics and radiosensitivity was that patients with rare disorders such as ataxia telangiectasia, Nijmegen breakage syndrome, Fanconi anemia and Bloom's syndrome exhibited significant cellular and clinical radiosensitivity and experienced high normal tissue reactions when treated with radiation therapy.[25] These syndromes are all related to germline mutations in genes related to the deoxyribonucleic acid (DNA) damage detection. Although these rare conditions may not be relevant when considering the overall variability regarding susceptibility to radiotoxicity, it provides a proof of principle that clinical radiosensitivity can be influenced by genetic factors.[25,26]

It has also been observed that susceptibility to radiotoxicity is a heritable trait. In recent studies,[27,28] depending on the control of confounding factors such as treatment parameters (e.g., radiation dose and tissue volume irradiated), concurrent treatments (e.g., chemotherapy), medications and patient factors (e.g., comorbidities, smoking, age and ethnicity), Barnett et al.[30] estimated that heritability (the proportion of total phenotypic variation between individuals in a given population due to genetic variation) contributes around 60–80% towards patients radiosensitivity and Vaisnav et al.[27] estimated over 80% towards patients radioresistance. Scott[29] used chromosome damage assay to investigate if the degree of chromosomal radiosensitivity in breast cancer patients is a familial characteristic. He tested 69 blood relatives of 24 patients and observed that 23 of 37 (62%) first-degree relatives of 16 radiosensitive patients were also radiosensitive, whereas only 1 of 24 (4%) first-degree relatives of 8 'normal' responding patients was radiosensitive. However, evidence of radiation

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therapy hereditary-associated toxicity is difficult to obtain due to the need for prospective toxicity data of cancer survivors and their close family, along with data of confounding factors which are not always well documented.[30]

At present, radiation therapy is delivered using standard treatment regimens with regards to prescription dose, fractionation protocols and some adjustments made on the dose distribution based on the DVH values of the OAR without consideration of an individual patient's propensity towards radiosensitivity/radiotoxicity or radioresistant. The potential to be able to predict an individual patient's radiosensitivity (the risk of developing side effects) or tumour response (risk of treatment failure or success) to radiation based on genetic information, and the potential to take into account this inter-patient variability during the radiation treatment planning process will allow both physicians and patients to make more informed decisions and to tailor radiation treatment protocols to individualised patient need. Therefore, several genetic association studies[7,8,31–35,60–67] briefly described below, have been performed, aiming to find genetic markers associated with individual patients' response to radiation treatment and their disposition to radiation-related toxicities.

Genomics and Biological Response to Radiation Therapy

Radiation genomics studies are involved with the investigation of the association between genomic data and patients response to radiation therapy.[1–157] These investigations have aimed to identify genetic markers (i.e., up- or down-regulated genes and gene sequences due to radiation exposure) that are linked to radiation response with the potential to predict the risk of developing adverse effects due to radiation therapy, and also to determine the relative radioresponse of patients that may be undergoing radiation therapy.[1] According to Imadome et al.,[86] genes involved in radiotoxicity include those which are involved in cellular processes such as cellular regulation, mitotic cyclin, stress response, immune response, chromosome maintenance, apoptosis and DNA repair. Current radiation genomics research has aimed to generate predictive models of radiation therapy response which attempts to capture toxicity trends and tumour control factors that can assist physicians in selecting the optimal personalised treatment based upon patient genetic characteristics,[20] while also taking into consideration the clinical, physical and biological factors of the individual patient.

Mechanism of sensitivity to ionising radiation

Radiosensitivity is the relative susceptibility of cells, tissues or organs to the effects of radiation.[22] It is considered to be a complex polygenic trait dependent on the interactions of various genes involved in multiple cell processes, type of radiation, the cell's position in the cell cycle, its DNA damage repair capacity, level of oxygenation and the expression of both oncogenes and growth factors.[4] The blockage of the various DNA repair pathways has also been associated with increased radiosensitivity.[1] High radiosensitivity is often attributed to excessive proliferation, abnormal differentiation, senescence and slow DNA damage repair. It has been observed that single nucleotide polymorphisms (SNPs) constitute a proportion of the genetics underlying variance in normal tissue radiosensitivity. As SNPs in coding regions are capable of altering protein function and SNPs in regulatory regions can affect the rates of gene expression and protein synthesis, SNPs have the potential to affect the phenotype of normal tissue radiosensitivity.[23] It has been observed in clinical studies that some genetic alterations express themselves selectively through certain tissue reactions, whereas others such as those observed in patients with radiosensitive syndromes (such as ataxia telangiectasia) cause more systemic effects, leading patients to exhibit an overall enhancement of clinical radiosensitivity.[23]

Mechanism of resistance to ionising radiation

Radioresistance, on the other hand, is a process in which tumour cells or tissues adapt to radiation therapy-induced changes leading to resistance to ionising radiation. It is the main cause of radiation therapy failures and poor prognosis characterised by tumour recurrence.[87] Numerous studies[88–119] have discovered various underlying mechanisms which contribute to radioresistance development. The DNA damage response can be promoted by the phosphatidylinositol-3 kinases (PI3K) signalling pathway to protect cells against genome instability following radiation exposure.[106,107] Cell cycle checkpoint molecules, including 14–3-3σ, can arrest cells to promote radioresistance.[108] Alteration of oncogenes, such as the cell adhesion molecule vitronectin (VTN),[109,110] and tumour suppressors, such as miRNA (miR-29c, miR-22)[59,60] are associated with radioresistance. Changes in the microenvironment (cytokine levels, hypoxic conditions, immunosuppressive processes) induce radioresistance.[113–116] Glucose and mitochondria metabolism are known primary contributors to radioresistance.

Glucose metabolism and radioresistance

The success of radiation therapy primarily depends on glucose metabolism.[88–105] Cancer development and progression are closely associated with metabolic syndromes (obesity, cardiovascular diseases, diabetes)[88] and metabolic reprogramming resulting from the activation of oncogenes or the inactivation of tumour suppressor genes.[89,90] According to the Warburg effect, even in the presence of oxygen, cancerous cells undergo active glycolysis characterised by increased glucose uptake and high lactic acid concentrations.[6,94,95,97] In addition, the production of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) and decrease of Oxidative Phosphorylation (OxPhos) not only increases glycolysis dependence, but also reduces intracellular reactive oxygen species (ROS) levels.[96] When exposed to radiation for an extended period of time, AKT kinase alters the glucose metabolic pathway resulting in radioresistance.[98] Glucose Transporter 1 (GLUT1) protein, which is essential for glucose metabolism, is associated with radioresistant tumour cells through oncogene activation, tumour suppressor inactivation, hypoxia stimulation and regulation of MPK and PI3K/AKT signalling pathways.[91–93]

Accumulation of lactic acids occurs after radiation therapy when glucose metabolism is altered, associated with radioresistance by inhibiting the activation and differentiation of immune cells,[99,100] releasing hyaluronic acid which promotes cell migration, clustering and neovascularisation,[101] and inducing Monocarboxylate Transporter 1 (MCT1) which transports lactate through the cell membrane.[102,103] Soluble Adenylate Cyclase (sAC) promotes Lactate Dehydrogenase (LDHA) release to accelerate cell proliferation and radioresistance through BRAF/extracellular signal-regulated kinases (ERK)1/2 signaling pathway activation,[120] while LDHA A inhibitor (FX-11)[121] and miR-34[122,123] inhibit LDHA expression to improve radiosensitivity. Pyruvate Kinase M2 (PKM2), which regulates

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glycolysis through the conversion of phosphoenolpyruvate and intracellular adenosine diphosphate (ADP) into pyruvate and intracellular adenosine triphosphate (ATP) in cancer cells, is associated with radioresistance and can be inhibited through its inhibition using miR-133[124] and dichloroacetate.[125] Radioresistance can also result from the upregulation of the hexokinase 2 (HK2) enzyme to induce glycolysis for tumour progression. However, Ad2-deoxy-D glucose (2-DG) can reduce this radioresistance by inhibiting the expression of HK2 and disrupting the tumour radiation-induced DNA damage repair process and induce cell apoptosis.[104,105]

Mitochondrial metabolism and radioresistance

Cancer cells radioresistance is also associated with mitochondrial metabolism energy production processes resulting from increased mutations (size, morphology, functions, energy metabolism), respiration, and ATP levels.[126] Studies show that enhancing both the antioxidant enzyme Manganese Superoxide Dismutase (MnSOD)[127] and glial cell antigen 2 (NG2),[128] which protect cells from ROS damage or mitochondrial oxidative stress, promotes radioresistance. Increasing or inhibiting the decrease of mitochondrial membrane potential (MMP) induces radioresistance by the regulation of growth differentiation factor-15 (GDF15),[135] mitogen-activated protein kinases/ERK signalling[136] and overexpression of mitochondrial ATP-sensitive potassium channel (MtKATP).[137]

Mitochondrial metabolism and radiosensitivity

Radiosensitivity can be induced by increasing mitochondrial oxidative stress using Sorafenib,[129] ceramides[130] or diisopropylamine dichloroacetate (DADA)[131] by inducing intracellular ROS levels. Alterations of mitochondrial proteins (e.g., adenosine monophosphate family protein 3A ATAD3A, NAD + dependent protein deacetylase SIRT3, mitochondrial MAPK phosphatase MKP1) involved in apoptosis and radiation signal transduction as a result of radiation therapy can also potentially overcome radioresistance. Radiosensitisation can be achieved by silencing ATAD3A to enhance ionising radiation-induced apoptosis and inhibit DNA damage repair,[132] utilising cyclin-dependent kinase (CDK1)-mediated phsophorylation of SIRT3,[133] and co-suppressing MKP1 and human epidermal growth factor receptor 2 (HER2) to induce apoptosis.[134] Histone deacetylase inhibitors[138] and paclitaxel[139] are found to reduce MMP resulting in radiosensitivity.

Genetics Association Studies

Studies in the field of radiation genomics primarily analyse SNPs, single nucleotide variations located in either coding or non-coding regions of a DNA sequence,[31] in an attempt to build reliable predictive models of radiation therapy response in relation to individual genomic data. However, the analysis of an individual SNPs in relation to a specific endpoint (e.g., erectile dysfunction in prostate cancer radiotherapy) had initially yielded results of small impact and minimal efficiency. This initial drawback has been overcome with the advent of microchips, containing up to two million tags, allowing researchers to analyse all common variants at the same time.[7] In recent years, radiogenomics studies are moving towards machine-based learning methods to simultaneously investigate multi-SNP associations and predictions using SNPs that do not individually reach statistical significance. In addition, these approaches allow for correlations or interactions among significant SNPs, something not often accounted for in single-SNP association tests due to statistical power limitations. However, these are preliminary studies but presents proof-of-principle to demonstrate the feasibility of the methods.[8] Currently, there are two main approaches to genetic association studies; namely, candidate gene studies and genome-wide association studies (GWAS). Whereas the candidate gene approach focuses on the associations between genetic variation within pre-specified genes of interest and phenotypes or disease states, GWAS can scan the entire genome for common genetic variation.

Candidate gene approach to genetic association studies

The candidate gene approach to conducting genetic association studies focuses on associations between genetic variation within pre-specified genes of interest [e.g., *NBS1* (Nijmegen breakage syndrome, ataxia telangiectasia mutated (ATM), etc.] and specific phenotypes or disease states. This approach is relatively cost-effective and uses prior knowledge of the gene's biological functional impact on the trait or disease in question to reduce the number of genes under study to a manageable quantity. Candidate gene studies were initially used in radiation genomics to study SNPs located within or near genes that play a role in underlying processes for radiation response (i.e., DNA damage repair, cell cycle checkpoint control, inflammation, apoptosis, growth signalling and free radical scavenging).[32] Talbot et al.[34] carried out a candidate gene association study and replicated the result using three additional cohorts, a total of 2,036 women who scored for adverse reactions to radiotherapy for breast cancer. They identified that alleles of the class III major histocompatibility complex (a set of cell surface proteins essential for the acquired immune system to recognise foreign molecules in vertebrates) region is associated with overall radiotherapy toxicity in breast cancer patients.

The candidate gene studies approach have found some significant associations between genomics data and radiation exposures, however, some of these results are yet to be clinically validated to be a reliable prediction of radiosensitivity or radioresponse.[36–59] As a result of the complex biological pathways and individual risks associated with the interaction of multiple genes, most SNPs show low effect sizes and low penetrance.[60,61] The proposed drawback with the candidate gene approach is the methodological approach used and the limited number of SNPs investigated that limits the identification of many important loci. It is estimated that 88% of SNPs that affect various complex traits are located in non-coding sequences,[62] not previously anticipated to be of importance towards radiotoxicity, and many genes contain hundreds of common SNPs.[63] Polygenic models of complex diseases also suggest that hundreds of SNPs are required to develop predictive models with high sensitivity and specificity, depending on allele frequency and individual effect size.[3,64]

Genome-wide association studies (GWAS)

To overcome the limitations of the candidate gene studies, researchers have moved towards GWAS which primarily uses a meta-analysis or a two-stage study design to observe the broad set of common genetic variants across an individual's genome.[32] The meta-analysis approach takes advantage of existing datasets which consist of two or more primary GWAS studies. The two-stage

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approach, on the other hand, utilises a single cohort randomly divided into a stage one discovery group, which genotypes for millions of SNPs throughout the genome, and a stage two replication group, that uses the selected top SNPs from the previous stage to undergo secondary analysis. Genotyping (investigating the genetic constitution of an individual organism) microarrays used in the GWASs have been designed to take advantage of linkage disequilibrium blocks, so that by genotyping a few hundred thousand SNPs, one can indirectly survey nearly all genetic variation in the genome, thus, making the GWASs quite cost-effective.[32] Although this technique has been proven to be effective at detecting associations with common causative alleles, false positives are frequent and few significant associations have been able to be replicated due to population stratification, genotyping artifacts, genetic linkages, rare minor allele frequencies, phenotype prevalence, poor genotype call rates and tissue end-point heterogeneity.[65] The need for larger sample sizes to identify SNPs with low minor allele frequency and multiple cohorts to validate SNPs initially discovered through previous GWAS studies led to the establishment of the Radiogenomics Consortium.[4,20,26,66] By creating a link between existing collaborative groups (RAPPER, GenePARE and Japan RadGenomics) through collaboration and sharing of resources, this group aims to perform a meta-analysis of existing data to validate SNPs associated with radiosensitivity or radioresponse confirmed by previous studies.[60,66,67] Ultimately, the genetic predictors of radiation therapy adverse effects can be used to develop an assay to predict patients at high risk of radiotoxicity and explain possible molecular pathways. Moreover, technological advancements will also increase the speed of capture of genetic determinants and lead to the identification of additional SNPs that lie in or near genes not previously assumed to be associated with radiotoxicity.

Genomic Alterations Impacting Tissue Radiosensitivity or Radioresponse

Structural variants studies

Structural variants are genomic alterations, other than nucleotide substitutions, which change the organisation of DNA, potentially impacting normal tissue radiosensitivity and the risk of development of radiotoxicity. SNPs' small insertions and deletions (indels) which affect coding sequences, non-coding introns or intergenic regions are primarily used in radiation genomics as they make up 90% of naturally occurring genome variation with 10 million SNPs among our 3 million base pairs estimated by the HapMap consortium.[7] Recent evidence shows that common variants (i.e., SNPs present with at least 1% population prevalence) are associated with a risk of developing late radiotoxicity,[28] however this contrasts previous findings that rare variants in DNA damage response genes have a greater effect on radiotoxicity.[4] This shows that the two types of SNP variants (common and rare) are not mutually exclusive in their role of affecting radiotoxicity as genotyping common variants acts as a driving force for the subsequent discovery of rare variants with similar functions within the same locus.[68] Copy number variation (CNV), in which sections of the genome are repeated, is another type of structural variant associated with radiotoxicity with a more substantial impact on gene expression. The limited overlap between SNP and CNV indicates potential complementary effects.[69,70]

Gene expression studies

Gene expression is the processing of information contained within a gene into ribonucleic acid (RNA) or protein structures, and it is associated with individual radiotoxicity through messenger RNA (mRNA) transcript expression, microRNA (miRNA), and long non-coding RNA (lncRNA).[71–79] By combining mRNA signatures with mRNA panels, it was determined that DNA damage response, cell cycle, chromatin organisation and RNA metabolism correlate with radiosensitivity while cellular signaling, lipid metabolism and transport, stem-cell state, cellular stress and inflammation are correlated with radioresistance.[73] miRNA's (small non-coding RNA molecules responsible for silencing and post-transcriptional regulation of gene expression), have been found to play important role in cellular response to radiation damage.[74–76] This is consistent with findings that miRNA has oncogenic, tumour suppressor and disease progression roles.[77] miR-20a, miR-205 and miR-29a have been found to regulate the PI3K/Akt survival pathway to enhance radioresistance through cell cycle progression, cell survival and differentiation.[80] The main challenge with studying gene expression is the ability to quantify transcripts as expression levels are low.[3]

Epigenetics studies

Epigenetics are modifications of the chromatin (DNA and associated histone proteins) that indirectly change DNA sequence and expression through DNA methylation, histone methylation and acetylation and non-coding RNA modification. Both inherited and acquired epigenetic biomarkers play an important role in radiation response because of their dynamic nature, complex interplay between cell types and immune cells and the variability between different tissues and cells in response to the environment.[3] According to Weigel et al.,[81] diacylglycerol kinase alpha (DGKA) is an epigenetically deregulated kinase involved in radiation response and may serve as a marker and therapeutic target for personalised radiotherapy. In a review, Weigel et al.[82] again demonstrated the important role for epigenetic mechanisms such as DNA methylation, microRNAs and histone modifications in the development of fibrotic disease. Other studies[83–85] have also shown that radiation exposure can significantly regulate DNA methylation and histone modifications, which can potentially lead to altered gene expression to promote radiosensitivity.

Biomarkers for Characterisation of Patient's Radiosensitivity and Radioresistance

Biomarkers are characteristics objectively measured and evaluated as an indicator of normal biological processes, pathological processes or pharmacological responses to a therapeutic intervention.[21] With the advent of high throughput sequencing technologies to screen for a variety of biological molecules, biomarkers can be identified to characterise individual patient radiation treatment response and to stratify patients for optimisation of radiation treatment plans via either dose reduction or dose escalation.[20] Radiation genomics has the potential to establish predictive biomarkers to inform patients and physicians about possible propensity to radiotoxicity effects or treatment response from therapeutic radiotherapy interventions.[3] One of the concerns with biomarkers is the variability in collected data and the non-linear relationship of biological response to radiation therapy which makes clinical effects difficult to determine using

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the predictive models.[3] However, REQUITE which is an ongoing multicenter prospective observational study attempts to validate potential biomarkers in order to develop clinically useful statistical models to predict patient's risk of developing long-term side effects following radiation therapy alongside clinical and treatment planning parameters.[33,140] Several biomarkers (BRCA1/2, ATM, RAD51, nibrin (NBN), TP53, Cdh1, XRCC1/2/3, APE1, CHEK2, MLH1, MSH2/3, PTEN, EpCAM, FLCN) [1,36–38,40–46,56–59,80,141–151] have been identified for use in the field of radiation genomics and some are briefly presented here.

Oncogenes–radiotoxicity

Transforming growth factor 1 (TGFB1)

TGFB1 gene is believed to be the main component of normal tissue injury after radiation therapy, as it encodes a pro-fibrotic cytokine which stimulates differentiation of fibroblasts, production of extracellular matrix and inhibits epithelial repair.[30] The studies[2,4,24–26] on C-509 T polymorphism in TGFB1, which represents one of the most studied SNPs, show that this polymorphism promotes chronic inflammatory and fibrotic reactions, however, there are other data suggesting a lack of association.[60,65–67]

DNA damage repair genes–radiotoxicity

X-ray repair cross-complementing (XRCC 1/2/3) protein genes

The X-ray repair cross-complementing (XRCC) protein genes are involved in DNA damage repairs and Guo et al.[1] have explored their role as a biomarker for radiosensitivity. Although *XRCC1, XRCC2 and XRCC3* genes carry the same symbol, XRCC, these genes do not necessarily have similarities in biochemical function, but rather are components with different damage recovery pathways (e.g., XRCC1 is involved in DNA base excision repair whilst XRCC3 is involved in the homologous recombination of DNA double strand breaks (DSBs)).[44,56] Gene variants of both XRCC1 and XRCC3 have been associated with hypersensitivity to radiotherapy.[44] Yin et al.[151] observed that SNPs of XRCC1 rs25487 (G > A) had a significant effect on the onset of radiation pneumonitis of grade 2 or higher among patients with non-small cell lung cancer treated with radiation therapy. Another study[58] found that prostate cancer patients with the XRCC2 rs25489 G > A genotype were more likely to develop erectile dysfunction following radiation treatment. Furthermore, the rs861539 variant of XRCC3 has also been observed to be potentially associated with an enhanced risk of radiation-induced fibrosis among patients with nasopharyngeal carcinoma.[59]

RAD51 recombinase gene

The RAD51 recombinase gene family encodes several proteins involved in ATPase-stimulated homologous DNA recombination repair during the S and G2 phases of the cell cycle to restore DSB which may have resulted from exposure to ionising radiation.[1,87] SNP rs 1801320 (G > C), located in the promoter region of chromosome 19, results in upregulated promoter activity and gene expression associated with radiation pneumonitis and dysphagia following radiation therapy. This mutation in combination with XRCC1 rs25487 (G > A) is also associated with a higher likelihood of acute radiotoxicity.[36] A second RAD51 mutation, SNP rs 1801321 (G > T) of chromosome 19, was also shown to be associated with an increased probability of developing cervical cancer following radiation therapy.[37]

Tumour suppressor genes–radiosensitivity

Breast cancer genes (BRCA1, BRCA2)

Breast cancer genes (BRCA1 and BRCA2) are tumour suppressor genes, observed to not only be involved in the oncogenesis of breast cancer, but also the regulation of DNA repair and recombination pathways, cell cycle control and apoptosis.[47] There appears to be some conflicting evidence regarding the role of BRCA1 and BRCA2 in contributing to radiosensitivity as, although, *in vitro* studies [49,50] have found associations between mutations within the gene and increased cell radiosensitivity, clinical studies[48,51] have been unsuccessful in elucidating similar results. In a study by Baert et al.,[49] who used a G2 phase-specific micronucleus assay to determine whether lymphocytes of BRCA2 mutation carriers exhibit increased radiosensitivity compared to controls, found a significant increase in radiosensitivity in the cohort of BRCA2 mutation carriers compared to those without a history of breast cancer. In a similar study, Ernestos et al.[50] observed using a G2 micronucleus assay that BRCA1 and BRCA2 mutation carriers had a significantly higher amount of mean chromatid breaks per cell and a higher number of maximum breaks compared with matched controls, indicating increased radiosensitivity. However, clinical studies by Pierce et al.[51] found no difference in acute skin toxicity among a cohort of BRCA mutation carriers compared to matched controls and results from a study by Park et al.[48] indicated no correlation between BRCA mutation status and enhancement of radiosensitivity.

Tumour protein P53 (TP53)

Tumour protein P53 (TP53) regulates the expression of cytokines and cellular adhesion molecules involved in the expression of downstream genes responsible for cell cycle regulation, apoptosis and DNA repair. In response to ionising radiation cellular stress, TP53 is phosphorylated and activated by DNA damage-induced kinases leading to cell cycle arrest and apoptosis.[152] TP53 has been suspected to be associated with radiotoxicity as SNP rs3765701 (A > G) was found to be related with survival in advanced non-small cell lung cancer patients receiving chemoradiation therapy.[151] The most commonly studied SNP, rs1042522 (G > C), has the ability to induce cell apoptosis and has been found to be associated with radiation-induced telangiectasia,[41] radiation pneumonitis[40] and local recurrence and distant metastases.[42] Other recently studied SNPs causing normal tissue radiosensitivity include rs35117667 (C > T), associated with developing acute skin adverse effects, and rs17883323 (C > A), linked to high-grade urinary toxicity.[43]

MutL homolog 1 (MLH1)

MutL homolog 1 (MLH1) encodes a DNA mismatch repair protein involved in maintaining genomic stability through the repair of endogenous and exogenous mismatches in daughter strands during the S phase of the cell cycle.[149] Since MLH1 is also a regulatory autophagy signaling factor, this gene can alter radiosensitivity by inducing autophagy and inhibiting apoptosis via the mTOR/S6k1 signaling pathway.[150] This claim is supported by an in vitro study of colorectal cancer cells which discovered that MLH proficiency enhances radiosensitivity to prolonged low-dose-rate ionising radiation through inhibition of homologous recombination, enhances apoptotic and autophagic cell death pathways, reduces gene mutation rate and alters cell cycle distribution.[150]

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Phosphatase and tensin homolog (PTEN)

Tumour suppressor PTEN is a natural inhibitor of PI3K, which prevents the recruitment of pyruvate dehydrogenase kinase (PDK) and AKT to the cell membrane, thereby suppressing the PI3K/Akt radioresistance-enhancing pathway.[80] Overexpression of PTEN has been shown to promote radiosensitivity of colorectal cancer cells through the p53 signaling pathway by inhibiting cell cycle transition from G2/M to G1 phase and inducing cell apoptosis.[153] In human gastric cancer cells, depletion of PTEN was found to facilitate tumour growth, epithelial mesenchymal transition, increase in stem and progenitor cells and radioresistance enhancement.[154] This finding was confirmed in an in vitro study where the reduction of PTEN protein in colorectal cells using miR-29a, binding to the mRNA's 3′-UTR and modulating the PI3K/Akt signaling pathway was able to enhance radioresistance.g.[80]

Checkpoint kinase 2 (CHEK2)

CHEK2 was considered to be a promising biomarker of radiation genomics as it encodes a G2 CHEK which, when phosphorylated by ATM, plays a critical role in DNA damage repair. However, data suggest that CHEK2 1100delC mutations in breast cancer patients are not associated with enhanced chromosomal radiosensitivity.[146] Therefore, more studies involving other CHEK2 variants with larger sample sizes are required to determine the potential of CHEK2 as a promising biomarker of radiation genomics.

Epithelial cell adhesion molecule (EpCAM)

EpCAM gene encodes a transmembrane glycoprotein that assists in epithelial cell adhesion, but is also responsible for cell signaling, migration, proliferation and differentiation.[148] With the activation of the PI3K/Akt/mTOR signaling pathway, down-regulation of EpCAM was found to increase the radiosensitivity in cervical adenosquamous carcinoma[149] and prostate cancer cells.[148]

Tumour suppressor genes–radioresistance

Ataxia telangiectasia mutated (ATM)

ATM, a member of the PI3K-like protein kinase family, has been implicated to contribute to radioresistance as it plays a crucial role in the biological response to ionising radiation.[54] ATM is primarily involved in cellular stress responses, cell cycle checkpoint control, DNA repair, detection of DNA DSBs and apoptosis. DNA damage, such as that caused by ionising radiation, causes the activation of this protein kinase causing the phosphorylation of downstream targets such as TP53, Csk homologous kinase (CHK) and keratin-associated protein 1 (KAP-1). This activation then initiates cell cycle checkpoints, arrest, delays in the G1, S and G2 phases of the cell cycle and enables DNA repair. Consequently, individuals with mutations in the ATM gene develop ataxia telangiectasia, a syndrome which is characterised by severe responses to ionising radiation and an increased risk of cancer development. Hence, mutations within ATM leading to loss of function or aberrant expression have an increased likelihood in the pathogenesis of radiation-induced side effects. Various studies[40] using genomic data have demonstrated a relationship between SNPs in the ATM gene and various endpoints associated with radiotoxicity. Multiple studies[40,53] have analysed the relationship between genetic polymorphisms in the ATM gene and susceptibility to radiation pneumonitis in lung cancer patients treated with radiation therapy. They observed that SNP rs189037 (G > A) in the promotor section of the ATM gene, which leads to decreased ATM protein expression, was associated with increased likelihood of radiation pneumonitis following radiation therapy. However, studies[54] that involved breast cancer patients treated with radiation therapy to evaluate the relationships between SNPs and susceptibility to erythema (a common toxicity of therapy), found no significant association between ATM polymorphisms and this endpoint. In another study, Moding et al.[52] deleted the ATM from the vasculature of both a tumour and normal heart tissue of a sarcoma-bearing mouse model. The model was then subjected to irradiation to both the sarcoma and heart in order to directly compare the radiation response of ATM lacking endothelial cells of tumour and cardiac areas. It was observed that the deletion of ATM enhanced the radiosensitivity of the rapidly proliferating cells of the sarcoma, but had no sensitising effect on the quiescent cardiac endothelial cells, suggesting that cell cycle progression plays a role in ATM's effect on radiosensitivity.

Cadherin-1 (CDH1)

Cdh1 is a tumour suppressor gene that works alongside anaphase-promoting complex/cyclosome to regulate the cell cycle during the G2 phase in response to DNA damage and throughout the G1 phase to prevent the premature accumulation of Cyclin A, Cyclin B and S-phase regulators. A loss of Cdh1 function contributes to increased proliferation and metastasis, leading to cancer development, through impaired DNA repair and aberrant cell cycle checkpoints.[144] By using short hairpin RNA (shRNA) targeted Cdh1 knockdown, irradiated nasopharyngeal carcinoma cells lacking Cdh1 exhibited significantly fewer colonies compared with Cdh1 positive cells. This demonstrates that Cdh1 is directly involved in radioresistance and its knockdown can potentially enhance a cell's radiosensitivity.[145]

Folliculin (FLCN)

FLCN can alter radiosensitivity by inducing autophagy and inhibiting apoptosis involved in adenosine monophosphate-activated Protein Kinase (AMPK) and rapamycin signalling pathways, responsible for cellular energy homeostasis and cell growth, proliferation and survival. An in vitro study of renal cancer cells deficient in FLCN exhibited decreased viability after exposure to ionising radiation due to higher radiosensitivity and lower apoptotic signals.[147] Thus, autophagy inducers may enable a more effective form of therapeutic radiotherapy.

Tumour suppressor genes–radiotoxicity

Nibrin (NBN)

NBN composes the MRE complex (MRE11-RAD50-NBN) involved in damage sensing, signaling and DSB response.[1] SNP rs1805794 (G > C) of NBN's recessive allele on chromosome 8 is the primary mutation with a significant association with radiotoxicity, specifically oral mucositis (grade > 2).[38] However, no radiotoxicity association was found with breast cancer or non-small cell lung cancer patients.[39]

MutS Homolog 2 (MSH2)

MSH 2 is a tumour suppressor and caretaker gene that encodes a DNA mismatch repair protein involved in processing biologically significant clustered DNA damages induced by ionising radiation.[44] Previously, DNA mismatch repair proficiency was found to confer radiosensitivity to high ionising radiation doses, but the impact at low ionising radiation doses remained unclear. A recent study discovered that endometrial carcinoma cells with proficient

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MSH2 function exhibited increased radiosensitivity to low radiation doses (<0·2 Gy) through early G2-phase cell cycle checkpoint activation and unrepaired DNA DSBs, thus showing that MSH2 proficiency can increase the efficacy of low ionising radiation dose radiotherapy by preventing potentially mutagenic lesions from being passed onto progeny.[46] This was supported by a study which found an association between SNP rs2303428 (T > C) and the development of radiotoxicity (acute skin reactions) in breast cancer patients.[44]

MSH3

MSH 3 is a DNA mismatch repair gene that forms a heterodimer with MSH2 to correct indel loops and base pair mismatch. The role of MSH3 is essential in repairing the damage imposed by radiation therapy.[44] Using a G2 chromosomal radiosensitivity assay, mice inbred with SNP rs 48840878 (G > A) was predicted to have an increased probability of deleterious radiosensitivity effects, although no specific endpoint was determined. In addition, phosphorylation of MSH3 rs 48840878 was predicted to affect 14 different protein kinases, potentially altering the regulation of various downstream activities associated with radiotoxicity.[45] Mangoni et al.,[44] also found an association between SNP rs26279 (G > A) and the development of acute skin reactions in breast cancer patients.

Concerns With Radiation Genomics Studies

There are some challenges that exist in this new field of study that require further investigation in order to be able to develop more accurate predictive models for clinical usage. According to genes studies,[2,4,24–26,60,65–67] results on the association of SNPs in some genes such as ATM, GSTP1, SOD2, TGFB1, XPD and XRCC1 with the risk of severe erythema after breast-conserving radiation therapy have been heterogeneous and often conflicting. Kerns et al.[5] have expressed some concern on the lack of positive SNP associations reproducibility in independent validation studies, due partly to the high number of false positive findings because adjustments for multiple comparisons were not made, and also partly due to some validation studies which have been false negatives due to methodological shortcomings or a failure to reproduce relevant details of the original study.

According to West and Barnett,[4] a challenge for radiogenomic studies is to obtain cohorts of patients with good quality (i.e., complete, longitudinal, including pretreatment, and comprehensive) toxicity data along with other data on possible non-genetic risk factors (e.g., age, smoking history, alcohol use, ethnicity, weight, height). Although it may be challenging to accurately quantify non-genetic risk factors, their influence on radiotoxicity and radioresistance is essential to reliably observe the effects of radiation therapy.[4] There are a variety of non-genetic factors that can affect a patient's potential response to radiation therapy, some of which are due to treatment parameters (e.g., toxicity is directly related to radiation dose and tissue volume irradiated), concurrent treatment (e.g., chemotherapy has been observed to increase toxicity) and patient history (e.g., comorbidities such as diabetes, rheumatoid arthritis and activities such as smoking have been linked to increased toxicity). These confounding factors need to be accounted for in any radiation genomics study to ensure data integrity. Rosenstein[20] has suggested that in order to determine the effects of radiation on the adverse effects that appear post-treatment, it is essential to obtain some baseline information or pre-radiotherapy symptom assessment from patients before the start of radiation therapy. In this case, the pretreatment effects can be subtracted from the post-treatment effects giving more reliable radiation-induced effects. Commonly observed adverse effects of radiation may overlap with symptoms seen in the general population and may not be associated with radiotoxicity. A pertinent example of this is that individuals diagnosed with prostate cancers often already experience various issues related to urinary or sexual function prior to radiation treatment, which highlights the need to obtain baseline data in order to accurately understand the change experienced by the patient from the radiotherapy.[32]

Kerns et al.[32] have indicated that the measurement systems with various scales (patient-reported, physician assigned, single endpoint) and follow-up schedules used for patient assessments lack uniformity, which could also contribute to the difficulty of drawing comparisons across different studies. There is also the variation of time and grade of effect associated with the development of adverse effects following radiation therapy. According to Kerns et al.,[32] a long-term follow-up period of a minimum of 5 years is often warranted due to the extended time associated with the onset of some late adverse effects. Additionally, Rosenstein[20] has mentioned the difficulties involved in determining whether to evaluate patients based on a specific time point, grade level of toxicity, or both, or if the data should be analysed as a continuous variable. Furthermore, the endpoints of radiotoxicity are varying and incompletely understood.[4,30,66] Different centers employ various measures and scales of toxicity for particular endpoints, making it difficult to standardise the data when performing studies based on multiple cohorts. For example, urinary toxicity can be measured using hematuria, nocturia, straining urgency and other variables, leading to vast heterogeneity in data. Due to this, important efforts have been put forth in order to combine different forms of toxicity into one score known as a standardised total average toxicity (STAT) score.[35] The variability of results often observed in radiation genomics studies may also be attributed to the difference in radiation therapy protocols used at different centres, as it often leads to heterogeneity in both the incidence and severity of adverse effects. Centre-specific procedures with respect to dose–volume, radiation type and delivery methods have the potential to impact modifiers in SNP association with toxicity effects following radiation therapy. Therefore, it is important to investigate and account for these factors when undergoing SNP association studies or adjust for such factors in order to have a more accurate estimate of the magnitude of SNP effects. In order to address some of the above challenges, the Radiogenomics Consortium has created the STROGAR guideline to validate any significant associations in independent cohorts by improving the quality, transparency, and completeness of radiogenomics research reporting.[5,30] Although genetic signatures are a major contributor, they may not by itself be sufficient to comprehensively determine an individual's risk of radiotoxicity. Patient- and treatment-related factors, post-translational modification, cell signalling, the microenvironment, and interactions between multiple genetic variants also need to be taken into account to create accurate predictive assays for clinical usage.

Conclusion

Radiation therapy has become the most effective non-surgical treatment of cancer[155] and its utilisation rate has been climbing up in most developed countries. Due to technological

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advancements and hence improved radiation treatment modalities, cancer patients are now living longer after treatment. However, radiation therapy is still associated with the development of radiation-related toxicities which can impact the quality of life of survivors. Therefore, it is essential to limit any long-term adverse effects associated with radiation therapy in order to improve the quality of life of cancer survivors. Radiation genomics has the potential to provide individualised genetic information in relation to a person's response to radiation exposure and disposition to radiation-related toxicities. Such knowledge has the potential to assist in the radiation treatment planning process by tailoring the radiation prescription dose to the individual patient needs, thereby being able to achieve a high local tumour control with a low risk of normal tissue complications.[156]

The primary aim of radiation genomics investigations is to establish predictive models of radiation therapy response by attempting to capture toxicity trends and tumour control factors that can assist physicians in selecting the optimal personalised individualised treatment based upon patient's genetic characteristics, and also taking into consideration the clinical, physical and biological factors of the individual patient. Genes identified through radiation genomics studies have the potential to aid in the development of mechanistic and functional studies to enhance the understanding of molecular pathways and biological roles gene products play in the risk of development of adverse effects following radiation exposure. With such knowledge, various pharmacological agents can potentially be developed to alter one's radiosensitivity or radioresistance according to an individual's genetic disposition or a patient's radiation prescription dose can be modified based on knowledge of the individual patient level of radiosensitivity or radioresistance. Using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) genome editing technology, there is also the possibility to correct mutations that predispose an individual to radiosensitivity or radioresistance by editing specific stretches of DNA at precise locations.[157] With radiation genomics still in its infancy stages to build reliable predictive models, collaboration of both researchers and clinicians is essential to continue to refine genomics studies (i.e., GWAS studies) by creating large patient cohorts for multiple cancer types and to validate genetic loci and to explore new possibilities to help guide cancer patients in selecting the best possible personalised and targeted treatment options. The early prediction of treatment response and patient outcome is critical in cancer patients to make decisions regarding continuation, escalation, discontinuation, and/or change in treatment options to maximise patient survival while minimising adverse effects and maintaining quality of life.

Statement of Search Strategy

The following databases were searched on May to June 2018 for relevant studies from 2001 to 2018: MEDLINE, Pubmed and Web of Science. The literature search used the following terms: 'radiation therapy', 'radiotherapy', 'radiogenomics', 'radiomics', 'imaging genomics', 'radiation genomics', 'radiotoxicity', 'radiosensitivity' and 'radioresistance'. The searches were not limited by study design or language of publication. The full list of sources and the search strategy are available from the authors.

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Conflict of interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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