Impact of single-nucleotide polymorphisms on radiation pneumonitis in cancer patients (Review)

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Abstract. Radiation pneumonitis (RP) is one of the most important dose-limiting toxicities in the radiotherapy of thoracic tumors, which reduces the rate of local tumor control and overall survival and severely affects the patients' quality of life. Single-nucleotide polymorphisms (SNPs) have recently attracted increasing attention as biomarkers for predicting the development of RP. SNPs in inflammation-related, DNA repair-related, stress response-related and angiogenesis-related genes were proved to be associated with RP, with different underlying mechanisms. Radiogenomics focuses on the differences in radiosensitivity caused by gene sequence variation, which may prove helpful in investigating the abovementioned associations. In this review, we aimed to investigate the associations between RP and SNPs reported in recent studies and highlight the main content and prospects of radiogenomics.

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Abbreviations: RP, radiation pneumonitis; SNPs, single-nucleotide polymorphisms; BER, base excision repair; DSBR, DNA double-strand break repair; HR, homologous recombination; NHEJ, non-homologous end-joining; NSCLC, non-small-cell lung cancer

Key words: radiation pneumonitis, single-nucleotide polymorphisms, genetic markers

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1. Introduction

Radiation pneumonitis (RP) is the inflammation of the normal lung tissue within the radiation field following radiation therapy. RP is one of the most common complications and one of the most important dose-limiting toxicities in the treatment of thoracic tumors by radiotherapy (1). Although significant progress has been made in the treatment technologies, a considerable number of patients experience RP following thoracic irradiation. Studies have demonstrated that ~10-20% of lung cancer patients develop severe RP (grade ≥3) following radiotherapy, of whom 50% succumb to this complication (2). The main risk factors of RP include patient-related factors, such as gender, smoking and pulmonary function, and treatment-related factors, such as radiation dose, irradiated lung volume, surgery and chemotherapy (3-7). However, it remains difficult to predict the occurrence of RP for any individual patient. Based on the development of the human genome project and pharmacogenomics, it is reported that single-nucleotide polymorphisms (SNPs) in inflammation-related, DNA repair-related, stress response-related and angiogenesis-related genes, may be used as biomarkers to predict the development of RP.

2. Inflammation-related genes

Inflammation is a defensive reaction that results from tissue damage or cellular injury, and is also a key process underlying radiation-induced toxicity (8,9). Several studies have been conducted to evaluate inflammation-related biomarkers, focusing mostly on genes as described below.

Transforming growth factor-β1 (TGF-β1). TGF-β1 is a type of cytokine that has been widely investigated and plays an important role in the processes of cell proliferation and differentiation, tissue fibrosis and inflammation (10-12). Early in 1998, Anscher *et al* (13) found that patients who developed RP following radiotherapy had higher plasma TGF-β1 levels compared with those prior to radiotherapy, unlike patients who did not develop RP. As a result, the plasma TGF-β1 levels may be used as a prediction index of RP.

In recent years, with the advances in molecular biology and genetics, the association between RP and individual differences caused by gene polymorphisms has become a research focus. Yuan *et al* (14) analyzed the correlation between genetic variants of TGF-β1 in 164 cases of lung cancer patients (77.4% Caucasian) who developed RP following radiotherapy, and found that the TC/CC genotypes in TGF-β1 rs1982073 (T>C) were associated with a decreased risk of grade ≥3 RP (HR=0.390, 95% CI: 0.197-0.774, P=0.007) and grade ≥2 RP (HR=0.489, 95% CI: 0.227-0.861, P=0.013) compared with the TT genotype. However, in 2010, Wang and Bi (15) found no association between TGF-β1 rs1982073 and grade ≥2 RP in Chinese patients (P=0.84) and the plasma TGF-β1 levels were not dependent on this gene polymorphism. Subsequently, a study by Niu *et al* (16) validated and supported Wang's view and discovered that the AG/GG genotypes of TGF-β1 rs11466345 (A>G) were associated with an increased risk of grade ≥3 RP in Chinese lung cancer patients (HR=2.264, 95% CI: 1.126-4.552, P=0.022). These studies suggested the presence of significant interethnic differences in the SNPs of TGF-β1.

Abnormal cell lineage protein 28 (Lin28) B. Lin28 (including Lin28A and Lin28B) is a type of protein that binds RNA and is involved in the processes of cell growth, tumorigenesis and tissue inflammation (17-19). Lin28 binds with miRNA precursors and regulates the biosynthesis of miRNA, particularly the let-7 family miRNAs; therefore, Lin28 is the post-transcriptional inhibitor of let-7 (20). It was previously demonstrated that, inhibiting the expression of Lin28 may increase the synthesis of let-7 and reduce the expression of K-Ras, leading to high radiosensitivity of lung cancer cells (21). Therefore, Lin28-let-7 may be a regulatory site of overcoming the low tumor radiosentivity caused by activated Ras signaling. In addition, Iliopoulos *et al* (19) found that nuclear factor (NF)-κB may directly stimulate the transcription of Lin28 and decrease let-7 miRNA levels, leading to high interleukin (IL)-6 levels. Although the mechanisms underlying the association between Lin28 and inflammatory response are not clear, we may infer that Lin28 plays an important role in inflammatory response based on the regulation of IL-6 expression.

A previous study evaluated the association between Lin28 polymorphisms and the risk of grade ≥3 RP in 362 cases of non-small-cell lung cancer (NSCLC) patients receiving definitive radiotherapy (22). Lin28B rs314280 (G>A) AG/AA (HR=2.23, 95% CI: 1.01-4.94, P=0.048) and rs314276 (C>A) AC/AA (HR=2.00, 95% CI: 1.11-3.62, P=0.022) are risk genotypes of grade ≥3 RP. Among the treatment-related factors, only mean lung dose (MLD) was found to be associated with the occurrence of grade ≥3 RP. The highest-risk patients were those with the two risk genotypes and MLD ≥19.0 Gy.

Pro- and anti-inflammatory genes. There are numerous pro- and anti-inflammatory cytokines in the human body. Whether the inflammation occurs and to what severity, depends on the balance between the two types of cytokines. Thus, damage caused by radiotherapy, such as RP, likely results from the interaction between pro- and anti-inflammatory cytokines. Hildebrandt *et al* (23) investigated 59 SNPs in 37 inflammation-related genes and found that 12 SNPs were associated with RP, including 7 SNPs in pro-inflammatory genes and 5 SNPs in anti-inflammatory genes (Table I). These SNPs were all associated with an increased risk of RP, with the exception of nitric oxide synthase 3 (NOS3) rs1799983. The study also demonstrated a dose-related effect in inflammation-related SNPs. The higher the number of risk genotypes a patient carries, the higher the risk for RP. Another study also identified the association between inflammation-related SNPs and toxicity following radiotherapy in NSCLC patients (24) by evaluating 11,930 SNPs in 904 inflammation-related genes. Following double screening of the discovery and validation phases and polygenic risk score analysis, they observed that DEAD box polypeptide 58 rs11795343 affected the risk of RP. However, the specific mechanisms underlying the association between inflammation-related SNPs and RP remain unclear.

3. DNA repair-related genes

Ionizing radiation may cause DNA damage, including DNA strand breaks, base change, ribose destruction and dimer formation. Radiotherapy-induced DNA damage mainly consists of strand breaks and base alterations; therefore, the repair pathways involved in DNA damage are DNA double-strand break repair (DSBR) and base excision repair (BER) (25). The genetic variants of DNA repair-related genes may affect the capacity of the DNA repair pathways. Insufficient DNA repair capacity leads to increased DNA damage and high tissue radiosensitivity, resulting in severe radiation-related complications (26,27).

DNA DSBR genes. The ataxia telangiectasia mutated (ATM) gene is located on chromosome 11q22-23 and its mutations lead to ataxia-telangiectasia. The ATM protein is the main receptor for radiation-induced DNA injury that may detect and repair DNA DSBs and plays an important role in the DSBR pathway (28,29). Furthermore, the ATM protein is a type of serine/threonine kinase, which may phosphorylate several intermediates involved in cellular stress responses, modulation of cell cycle regulation point and apoptosis (30).

Studies *in vivo* and *in vitro* demonstrated that ATM heterozygosity or decreased expression may cause high radiosensitivity among individuals or cells (31,32); thus, ATM may be a key checkpoint of radiosensitivity. In 2009, Zhang *et al* (33) found that ATM rs189037 (G>A) and rs373759 (G>A) exhibited a significant correlation with grade ≥2 RP in Chinese patients (n=253) and the two SNPs are in linkage disequilibrium. ATM rs189037 is located in the core region of ATM promoter and its GA/AA genotypes may cause a decline in ATM mRNA expression, resulting in hypersensitivity to radiation and increased risk of RP. In addition, this research team assessed the association between p53 gene polymorphisms and the risk

Table I. Effects of gene polymorphisms on the risk of radiation pneumonitis.

Gene	SNP ID	Base change	No.	Ethnic group	Treatment	Tumor type (stage)	End point	Impact on RP	Refs.
TGF-β1	rs1982073	T>C	164	77.4% Caucasian, 16.5% black, 6.1% other	RT, RCT	NSCLC (I-IV)	Grade ≥2 and grade ≥3	CT/CC decreased risk	(14)
			179	Chinese	RT, RCT	NSCLC (I-IV)	Grade ≥2	No significant correlation	(15)
			167	Chinese	RT, RCT	NSCLC (I-IV)	Grade ≥3	No significant correlation	(16)
	rs11466345	A>G	167	Chinese	RT, RCT	NSCLC (I-IV)	Grade ≥3	AG/GG increased risk	(16)
Lin28B	rs314280	G>A	362	82.0% Caucasian, 18.0% black	RT, RCT	NSCLC (I-IV)	Grade ≥3	AG/AA increased risk	(22)
	rs314276	C>A	362	82.0% Caucasian, 18.0% black	RT, RCT	NSCLC (I-IV)	Grade ≥3	AC/AA increased risk	(22)
NOS3	rs1799983	G>T	173	Non-Hispanic Caucasian	RT, RCT	NSCLC (IIIA and IIIB)	Grade ≥2	Decreased risk	(23)
IL1A	rs1800587	C>T						Increased risk	
	rs17561	G>T							
IL8	rs4073	T>A							
TNFRSF1B	rs1061622	T>G							
MIF	rs755622	C>G							
TNF	rs1799724	C>T							
IL4	rs2243250	C>T							
	rs2070874	C>T							
IL13	rs20541	C>T							
	rs180925	C>T							
NFKBIA	rs8904	C>T							
ATM	rs189037	G>A	253	Chinese	RT, RCT	LC (I-IV)	Grade ≥2	GA/AA increased risk	(33)
			362	82% non-Hispanic Caucasian, 17.7% black, 0.3% other	RT, RCT	NSCLC (I-IV)	Grade ≥3	GA/GG decreased risk	(35)
	rs228590	C>T	362	82% non-Hispanic Caucasian, 17.7% black, 0.3% other	RT, RCT	NSCLC (I-IV)	Grade ≥3	CT/TT decreased risk	(35)
	rs373759	G>A	253	Chinese	RT, RCT	LC (I-IV)	Grade ≥2	GA/AA increased risk	(33)
p53	rs1042522	G>C	253	Chinese	RT, RCT	LC (I-IV)	Grade ≥2	Arg/Arg increased risk	(34)
RAD51	rs1801320	G>C	196	71.9% Caucasian, 21.4% black, 6.7% other	RT, RCT	NSCLC (I-IV)	Grade ≥1	CG/CC decreased risk	(37)

Table I. Continued.

Gene	SNP ID	Base change	No.	Ethnic group	Treatment	Tumor type (stage)	End point	Impact on RP	Refs.
LIG4	rs1805388	C>T	195	71.3% Caucasian, 21.0% black, 7.7% other	RT, RCT	NSCLC (I-IV)	Grade ≥3	CT/TT increased risk	(38)
XRCC1	rs25487	A>G	165	72.7% Caucasian, 19.4% black, 7.9% other	RT, RCT	NSCLC (I-III)	Grade ≥2	AA decreased risk	(40)
APEX1	rs1130409	T>G	165	72.7% Caucasian, 19.4% black, 7.9% other	RT, RCT	NSCLC (I-III)	Grade ≥2	GG increased risk	(40)
			126	Chinese	RT, RCT	NSCLC (I-IV)	Grade ≥3	GG/GT increased risk	(41)
NEIL1	rs4462560	C>G	187	Chinese	RT, RCT	ESCC (I-IV)	Grade ≥2	GC/CC decreased risk	(43)
MTHFR	rs1801131	A>C	136	Caucasian	RT, RCT, surgery	LC (IIB-IV)	Grade ≥2 and grade ≥3	AC/CC decreased risk	(48)
HSPB1	rs2868371	C>G	271	80% Caucasian, 20% other	RT, RCT	NSCLC (I-IV)	Grade ≥2 and grade ≥3	CC increased risk	(53)
VEGF	rs2010963	G>C	195	71.3% Caucasian, 21.0% black, 7.7% other	RT, RCT	NSCLC (I-IV)	Grade ≥3	CC increased risk	(60)
	rs3025039	C>T			RT, RCT	NSCLC (I-IV)	Grade ≥3	TT increased risk	

SNP, single-nucleotide polymorphism; RP, radiation pneumonitis; RT, radiotherapy; RCT, combined radiochemotherapy; NSCLC, non-small-cell lung cancer; LC, lung cancer; ESCC, esophageal squamous cell carcinoma; TGF-β1, transforming growth factor-β1; Lin28, abnormal cell lineage protein 28; NOS3, nitric oxide synthase 3; IL, interleukin; TNF, tumor necrosis factor; TNFRSF1B, TNF receptor superfamily 1B; MIF, macrophage migration inhibitory factor; NFKBIA, nuclear factor of κ-light polypeptide gene enhancer in B-cells inhibitor-α; ATM, ataxia telangiectasia mutated; LIG4, DNA ligase 4; XRCC1, X-ray repair cross-complementing 1; APEX1, apurinic/apyrimidinic endonuclease 1; NEIL1, nei endonuclease VIII-like 1; MTHFR, 5,10-methylenetetrahydrofolate reductase; HSPB1, heat shock proteins B1; VEGF, vascular endothelial growth factor.

of RP; by using ATM rs189037 and P53 as genetic markers, they were able to predict 63.2% of the patients with RP following radiotherapy (34). Xiong *et al* (35) demonstrated that ATM rs189037 AG/GG, rs228590 CT/TT and rs189037G/rs228590T/rs1801516G (G-T-G) haplotype exerted a negative effect on grade ≥3 RP in both univariate and multivariate analyses in Caucasians. However, there was no statistically significant association between the ATM rs189037 and the risk of grade ≥2 RP. This result conflicted with the findings of Zhang *et al* (33), who found ATM rs189037 to have a significant correlation with grade ≥2 RP, mainly because the variant allele frequencies and the incidence of severe RP were different between Chinese and non-Hispanic whites.

DNA DSB repair has two main pathways: Homologous recombination (HR) and non-homologous end-joining (NHEJ) (36). Thus, the genetic variants involved in the two pathways were considered to be associated with the risk of RP. Yin *et al* (37) found that the HR gene RAD51 rs1801320 (G>C) C allele was associated with a lower risk of grade ≥1 RP (HR=0.52, 95% CI: 0.31-0.86, P=0.010) compared with the GG genotype, and the NHEJ gene DNA ligase 4 (LIG4) rs1805388 (C>T) T allele increased the risk of severe RP (HR=1.96, 95% CI: 1.00-3.85, P=0.048) in patients with NSCLC (38).

BER genes. DNA BER is the major repair pathway of DNA single-strand breaks, including the apurinic/apyrimidinic (AP) site break and DNA base injury caused by radiation (25). The main enzymes involved in this pathway are DNA glycosylase, AP endonuclease, DNA polymerase and DNA ligase. AP endonuclease 1 (APEX1) may detect and incise the AP sites in the early stages of DNA damage and plays a role in the inflammatory response by regulating NF-κB (39). X-ray repair cross-complementing 1 (XRCC1) usually forms a complex with poly(ADP-ribose) polymerase, DNA ligase 3 and DNA polymerase β, connects and fills the DNA incision in the final stage. Yin *et al* (40) reported that the XRCC1 rs25487 (A>G) AA genotype was associated with a low risk of grade ≥2 RP (HR=0.48, 95% CI: 0.24-0.97, P=0.041), whereas the APEX1 rs1130409 (T>G) GG genotype was associated with an increased risk of grade ≥2 RP (HR=3.61, 95% CI: 1.64-7.93, P=0.001) in whites. In 2014, Li *et al* (41) found that the APEX1 rs1130409 G allele was associated with grade ≥3 RP, verifying the correlation between APEX1 SNPs and the risk of severe RP. The grade endpoints of the abovementioned studies may have been discrepant due to the gene heterogeneity and differences in inflammation sensitivity among different races, but the specific mechanisms remain unclear.

Nei endonuclease VIII-like 1 (NEIL1) is one of the genes encoding the human DNA glycosylase involved in the first reaction of BER. NEIL1 may combine with deoxyuridylate to repair DNA damage induced by thymidylate synthesis inhibition (42). It was previously suggested that NEIL1 rs4462560 (C>G) GC/CC genotypes may reduce the risk of grade ≥2 RP in patients with esophageal squamous cell carcinoma (43).

4. Stress response-related genes

At the molecular level, reactive oxygen species induced by ionizing radiation exert a direct damaging effect on DNA and tissue, leading to DNA DSBs and production of cytokines or growth factors, which may cause pulmonary hypoxia, inflammation, chronic oxidative stress and, eventually, damage repair delay (44-46). In addition to inflammation and DNA repair-related genes, stress response-related genes may also be involved in the regulation of the effect of radiation on lung tissue.

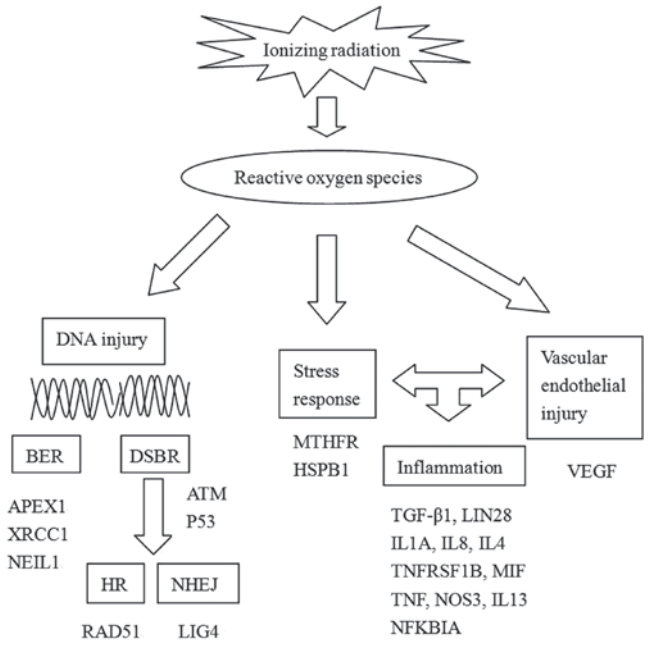

Figure 1. Mechanisms, pathways and genes involved in RP and gene polymorphisms. BER, base excision repair; DSBR, DNA double-strand break repair; APEX1, apurinic/apyrimidinic endonuclease 1; XRCC1, X-ray repair cross-complementing 1; NEIL1, nei endonuclease VIII-like 1; ATM, ataxia telangiectasia mutated; HR, homologous recombination; NHEJ, non-homologous end-joining; LIG4, DNA ligase 4; MTHFR, 5,10-methylenetetrahydrofolate reductase; HSPB1, heat shock proteins B1; VEGF, vascular endothelial growth factor; TGF-β1, transforming growth factor-β1; Lin28, abnormal cell lineage protein 28; TNF, tumor necrosis factor; TNFRSF1B, TNF receptor superfamily 1B; MIF, macrophage migration inhibitory factor; NOS3, nitric oxide synthase 3; NFKBIA, nuclear factor of κ-light polypeptide gene enhancer in B-cells inhibitor-α.

5,10-Methylenetetrahydrofolate reductase (MTHFR) plays a key role in folate metabolism, thymidine synthesis, homocysteine processing and other important metabolic pathways (47). Folate metabolism is closely related to DNA synthesis and repair and MTHFR is the key enzyme of redox reaction in cellular metabolic activity, which may irreversibly convert MTHFR to 5-methyltetrahydrofolate. Mak *et al* (48) investigated the correlation between the SNPs of MTHFR and superoxide dismutase (SOD) 2 genes and the risk of RP, and demonstrated that the MTHFR rs1801131 (A>C) AC/CC genotypes decreased the risk of grade ≥2 RP (HR=0.37, 95% CI: 0.18-0.76, P=0.006) and grade ≥3 RP (HR=0.21, 95% CI: 0.06-0.70, P=0.01). No SOD2 gene polymorphisms were found to be associated with RP risk in this study. Since the number of candidate SNPs is limited, this study was unable to fully analyze the correlation between these two genes and RP risk.

Heat shock proteins (HSPs) may be stimulated by several stressors, such as drugs or ionizing radiation, and protect the body from the injury caused by these stressors. The HSP27 protein is widely expressed in the human body at a low level.

HSP27 strengthens the cells' ability of resistance when they are exposed to oxidative stress, cytotoxic agents, thermal shock and apoptosis (49-51). Furthermore, HSP27 chaperone may also enhance the antioxidant capacity of the cell by increasing glutathione and decreasing the toxicity of oxidizing reactions (52). The plasma HSP27 levels are regulated by the HSPB1 gene; thus, HSPB1 was considered to modulate cell radiosensitivity. Pang *et al* (53) demonstrated that the HSPB1 rs2868371 (C>G) CC genotype was associated with a higher risk of grade ≥3 RP compared with the CG/GG genotype (P=0.02).

5. Angiogenesis-related genes

Angiogenesis is not only an important physiological process in normal tissues, but also a necessary step in carcinogenesis, cancer development and metastasis (54-56). Pro-angiogenic substances excreted by tumor cells and tumor stromal cells may promote tumor revascularization. Reactive oxygen species generated by radiation therapy result in vascular endothelial cell damage in normal lung tissues and lead to early inflammation and high vascular permeability (45,57,58). Subsequently, white blood cells migrate to the sites of inflammation, a series of inflammatory reactions occur and lead to increased radiation toxicity in the surrounding normal tissues. Vascular endothelial growth factor (VEGF) exerts a dual effect on the occurrence of RP: High VEGF levels stimulate the growth of endothelial cells and maintain the integrity of vascular endothelium, which may enhance the resistance to RP; on the other hand, VEGF may increase the synthesis of inflammatory cytokines through NF-κB in the damaged endothelial cells, leading to RP (59). VEGF SNPs were analyzed by Yin *et al* (60), who observed that the rs2010963 (G>C) CC and rs3025039 (C>T) TT genotypes were associated with a high risk of RP in 195 NSCLC patients.

6. Summary and radiogenomics

The recent studies on the effects of gene polymorphisms on RP risk are summarized in Table I and Fig. 1 outlines the mechanisms, pathways and genes involved. These studies, however, had certain limitations: First, they were all retrospective studies based on recorded information; thus, it was difficult to accurately classify the severity of the RP. Second, the diagnosis of RP was subjective, whereas RP should be differentially diagnosed from chronic obstructive pulmonary disease, infectious pneumonia and heart disease, taking into consideration the patients' overall condition. Therefore, the diagnosis of RP requires experienced physicians. The standard used for RP grading in the abovementioned articles was the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 or 4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf or http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). However, other researchers raised the viewpoint that the use of an objective evaluation method may more accurately determine the degree of radiation-induced toxicity, as it may avoid subjective confounders (61,62). Third, the majority of the studies adopted the candidate gene approach, with which was easy to overlook the crucial but rare SNPs. In addition, the sample size was relatively small, which may may have led to a high false-positive rate. Finally, some independent factors, which were shown in previous articles, should be kept consistent in the study to avoid adversely affecting the results, including smoking, MLD, and volume of normal lung receiving ≥20Gy radiation.

Radiogenomics analyzes the differences in radiosensitivity caused by gene sequence variations (63). Radiogenomics has two objectives: The first is to determine a way of predicting the risk of radiation injuries in patients following radiotherapy, and the second is to investigate the molecular mechanisms underlying normal tissue toxicity induced by radiation (64). Thus, radiogenomics may help achieve treatment individualization for patients treated with radiotherapy. In 2006, the RAPPER study (Radiogenomics Assessment of Polymorphisms for Predicting the Effects of Radiotherapy), which was the first nationwide radiation genomics program worldwide, was launched in UK (65). In 2009, the International Radiogenomics Consortium was founded, dedicated to the study of genetic predictors of adverse reactions following radiotherapy in various types of tumors (66).

Genome-wide association study (GWAS) is an approach to radiogenomics research. GWASs do not miss important SNPs, as they analyze SNPs with a minor allele frequency of ≥1% over the entire gene (64). Due to the large number of SNPs, it is necessary to enlarge the sample size or validate in replication studies to obtain a higher statistical power (67). Several SNPs identified in GWASs are located in non-coding regions with unknown functions (68,69), which may broaden our understanding of the mechanisms underlying normal tissue toxicity caused by radiation. Despite GWASs being effective in SNP genotyping, they are less efficient in distinguishing changes in DNA structure, such as inversions, deletions and insertions, which may exert an effect on the response to radiation (70,71). Currently available published GWAS studies mainly investigate the complications following radiotherapy in breast and prostate cancer patients, with only few studies on lung cancer.

7. Conclusion

Through accurately evaluating the patients' sensitivity to radiation and effectively predicting the occurrence of RP, we may determine an optimal individualized treatment plan for each patient. For patients at high risk of developing RP, non-radiotherapy or low-dose radiation therapy may be applied to achieve a relatively high radiation dose based on the low risk of RP. For low-risk patients, the radiation dose may be increased to achieve the best therapeutic effect. At present, preliminary studies have demonstrated that genetic polymorphisms are closely associated with RP and radiation sensitivity, but the specific molecular mechanisms remain unclear. With the development of radiogenomics and the promotion of GWAS, the molecular mechanisms of gene polymorphisms and radiosensitivity are major issues that must be addressed in the future, as they may provide a reliable molecular basis for the personalized therapy of malignant tumors.

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