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辐射敏感性和基因

RADIOSENSITIVITY AND GENES

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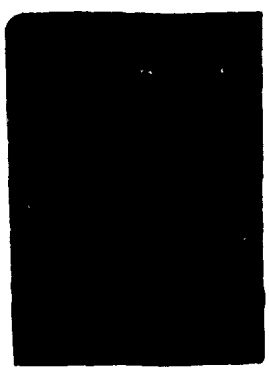

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辐射敏感性和基因

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摘　要

综述了一些癌基因、肿瘤抑制基因和 DNA 修复基因对细胞电离辐射敏感性的影响。涉及到癌基因在细胞辐射反应中的作用，尤其是那些已被广泛研究的癌基因，如 *ras* 基因家族。对于肿瘤抑制基因，主要综述了 *p*53，这是一种被认为能影响辐射敏感性的基因。一般认为细胞周期中有检点因子，并假定它能捕获 G_1 期受照细胞使之在进入 DNA 合成期前修复损伤。目前有 6 种 DNA 修复基因已在哺乳动物细胞中克隆化，但仅有一种 *XRCC*1 涉及到人类细胞 X 射线损伤修复，当这种基因转入 EM$_9$ 细胞时，*XRCC*1 能纠正高水平姐妹染色单体互换率，但其表达似乎与人类头颈部肿瘤细胞的辐射敏感性无关。辐射敏感性是一个复杂的问题，它涉及许多因素。给出了一个照射后细胞反应过程的图解，提示电离辐射引发的一系列可能事件。

RADIOSENSITIVITY AND GENES

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ABSTRACT

Reported effects of some oncogenes, tumour suppressor genes and DNA repair genes on sensitivity of cells to ionizing radiation are reviewed. The role of oncogenes in cellular response to irradiation is discussed, especially the extensively studied oncogenes such as the *ras* gene family. For tumour suppressor genes, mainly the *p*53, which is increasingly implicated as a gene affecting radiosensitivity, is reviewed. It is considered that there is a cell cycle checkpoint determinant which is postulated to be able to arrest the irradiated cells in G_1 phase to allow them to repair damage before they undergo DNA synthesis. So far there are six DNA repair genes which have been cloned in mammalian cells, but only one, *XRCC*1, appears to be involved in repair of human X-ray damage. *XRCC*1 can correct high sisterchromatid exchange levels when transferred into EM_9 cells, but its expression seems to have no correlation with radiosensitivity of human neck and head tumour cells. Radiosensitivity is an intricate issue which may involve many factors. A scheme of cellular reactions after exposure to irradiation is proposed to indicate a possible sequence of events initiated by ionizing radiation.

INTRODUCTION

The sensitivity of tumour and normal cells to ionizing radiation has long been a research focus in radiobiology as it is primarily related to the consequences of tumour radiotherapy. Both intrinsic and extrinsic factors can affect the radiation response of tumour and normal cells. Over the last 10 years, the study of intrinsic, especially genetic factors have gained increasing attention. The knowledge gained from studies of radiation damage and reqair in prokaryotes and the application of molecular techniques to the study of mammalian cells have allowed research interest to focus on the role of specific genes in radiation sensitivity. In the present paper, the reported effects of some extensively studied oncogenes, tumour suppressor genes and DNA repair genes on radiosensitivity are reviewed and a possible scheme linking various reactions induced by ionizing radiation is proposed.

1 ONCOGENES

Since Huebner and Todaro proposed the oncogene hypothesis of cancer in 1969 [1], numerous investigations have been carried out first to determine the existence and origin of oncogenes and then to study their roles in a variety of aspects and effects of their regulation. So far more than 80 oncogenes and their pseudogenes have been identified in human chromosomes [2]. The identification of oncogenes led naturally to the question of whether such genes might alter intrinsic cellular radiosensitivity and hence the curability of tumours. Among the extensively studied oncogenes in this regard are the *ras* and *myc* gene families, while othere include *raf*, *abl*, and *src*.

The *ras* gene family, so far, has eight identified members which are located on eight different human chromosome regions [2]. Radiobiological actions of the *ras* genes are of particular interest in radiation oncology due to documented association of the activated *ras* with malignant transformation in several common human neoplasms, including 90% of pancreatic carcinomas, 71% of breast cancer, 50% of colon carcinomas, 30% of acute myeloid leukaemia and 20% of lung cancer. The relationship between expression of an activated *ras* oncogene and radiosensitivity was first reported by FitzGerald et al. [3]. They studied the effect of X irradiation dose rate on the clonogenic survival of mouse embryo fibroblast cell line NIH 3T3 and its N-*ras* oncogene transformed subline and found that low dose rate (5 cGy/min)irradiation produced no signifi-

:ant differeice in survival curves between the two lines despite the seven-to eight-fold difference in plating efficiency. In contrast, high dose rate(200 cGy/min) generated statistically significantly different survival curves between the two lines. However, recent results of FitzGerald et al. [4] contrasted with their previous data. They did not find detectable increase in radioresistance of NIH 3T3 H-*ras* at the high dose rate of 116 cGy/min but demonstrated significantly increased radioresistance at low dose rate of 5 cGy/min. The reason for this difference remains to be elucidated. A more recent report [5] showed that H-*ras*-transfected cells exhibited higher survival levels than the parental rat embryo cells at a variety of dose rates, 72, 6.6, 3.5 and 1.8 cGy/min.

Sklar also found that all the NIH 3T3 cell lines transformed with *ras* oncogenes, that had been activated by a missense mutation, showed a significant increase in radiation resistance, but there was no significant difference between the different *ras* oncogenes in their effect on D_0 values, regardless of the gene type, the site of activating mutation and the method of gene transfer. The D_0 did not increase with the number or level of expression of *ras* copies in a cell since the cell line containing 20 to 50 copies of v-H-*ras* and comparably elevated messenger RNA levels had a D_0 similar to those cell lines containing two to ten copies [6~8]. Also, the possibility that the increased radiation resistance was a nonspecific consequence of transformation was taken into account but this was ruled out by comparing the survival curves of NIH 3T3 cells transformed with missense-mutation-activated *ras* transformants or an unrelated oncogene, v-*fms*. The v-*fms*-transformed cells had a D_0 value lower than that of the *ras* gene-transformed cells. This increase in radioresistance was further supported by the fact that two revertant cell lines, no longer phenotypically transformed but still containing active *ras* genes, still showed increased intrinsic resistance [9]. In a study by Samid et al., a dose-dependent correlation between the expression level of the *ras* proto-oncogene and radioresistance was observed in NIH 3T3-derived cells. These results suggested that *ras* encoded *p*21 may participate in the cellular responses to ionizing radiation.

However, other authors have reported results which question the universality of these finding. Harris et al. [10] found some *ras*-transformed cells had increased radiosensitivity and decreased repair of sublethal radiation damage. They employed two model systems: (1) normal rat kidney(NRK) cells and its derived (*ts*K-NRK) cells, which carry a temperature-sensitive K-*ras* onco-

gene, permitting modulation of cellular *ras* p21 levels and (2) NIH 3T3 cells and a subline(PAP2) previously transformed with an H-*ras* oncogene and expressing relatively large amounts of p21 protein. No major changes were found in D_0 and n, the extrapolation number, for NRK and *ts*K-NRK cells, but the survival fraction was, in general, slightly higher for NRK cells. D_0 were not significantly different for NIH 3T3 and PAP2 cells but the n was significantly higher for NIH 3T3 cells. In both systems, study on repair of sublethal damage in split-dose experiments showed that cells carrying the *ras* oncogene were less efficient than their parent cells. Grant et al. [11] reported no general correlation between *ras* expression and radiosensitivity in immortalized human retinoblast cell lines transfected with either an N-*ras* or an H-*ras* oncogene. Alapetite et al. [12] studied the influence of the presence of an activated *ras* oncogene on the *in vitro* radiosensitivity of human epithelial cells. There was little evidence of acquired radioresistance in the *ras* transfected cells. Mendonca et al. [13] investigated the radiosensitivity of several activated c-H-*ras*-containing clones that have been established after transfection of a spontaneously immortalized nontumorigenic human keratinocyte cell line. There was no general correlation between either activated c-H-*ras* expression level or tumorigenic potential and enhanced radioresistance. Also, multiple survival studies of Garden et al. [14] did not show appreciable difference in sensitivity to radiation between the rat fibroblast(Rat-1) cell line with or without *ras* oncogene expression. In conclusion these results suggest that the effect of the *ras* gene on radiation sensitivity may be species specific. Most of the studies on rat or murine cell line have shown changes in radiosensitivity, while nearly all the studies involving human cell line have shown no statistically significant changes in radiosensitivity.

Another oncogene family, the *myc* genes, is also implicated in a variety of human malignancies. The relationship of *myc* oncogene to alterations of radiation response is also controversial. Ling and Endlich [15] transfected primary rat embryo cells with c-*myc* gene and reported a higher D_0 for transfected cells as compared to their parent cells. However, when they and their colleagues transfected such cells with v-*myc*, they found it had no effect on the D_0 value of the cells [16]. Recently, FitzGerald et al. [17] reported that a clonal haematopoietic progenitor cell line transfected with and expressing the v-*myc* oncogene demonstrated increased radioresistance at low (5 cGy/min) and high

(116 cGy/min) dose rates. But Pirollo et al.[18] reported that the D_0 value for a c-*myc* transfected cell line was in the same range as that of the recipient NIH 3T3 cells. Results with a mink epithelial cell line and Syrian hamster Osaka-Kanazawa cells did not show significant effects of *myc* on radiation sensitivity[19]. It has also been reported that cells of different radiosensitivity had the same *myc* oncogene expression level[20]. However, *myc* oncogenes were demonstrated, in several cell lines, to have synergistic effect on radioresistance with a ras oncogene[15,16]. When rat embryo cells were cotransfected with a c-*myc* gene and a c-H-*ras* oncogene, higher values of D_0 were seen relative to cells untransfected or transfected either with c-*myc* or c-H-*ras* oncogene alone[16]. These results indicate that the v-*myc* oncogene may play an important cooperating role in the phenotype of radiation resistance at low dose which is within the dose range used in most clinical practice.

A study with a human laryngeal cancer and NIH 3T3 cell lines showed that the *raf* oncogene may also be associated with radiation resistance[21]. Further study with sense and antisense human c-*raf*-1 cDNA sequences demonstrated that reduced expression of endogenous c-*raf*-1 was sufficient to modulate the radiation-resistant phenotype of the same cell line. D_0 values were 3.10 Gy for the cells transfected with sense DNA and 1.91 Gy for those transfected with the antisense DNA[22]. However data with human small cell lung cancer xenografts showed that cells of different radiation sensitivity could have similar expression levels of *raf* oncogene[20].

Expression in haematopoietic progenitor cell line of the transfected oncogenes v-*erb*-B, v-*abl*, or v-*src* and in NIH 3T3 of transfected oncogenes v-*abl*, v-*fms* or v-*fos* conferred significant radioresistance. More recently FitzGerald and his colleagues[23] infected myeloid progenitor cells with murine retroviruses containing either the wild-type or a temperature-sensitive mutant v-*src*. They observed that cells infected with the temperature -sensitive v-*src* mutant did not have significantly different resistance to 5 cGy/min γ irradiation at the permissive (34℃) versus the nonpermissive temperature (39℃). This result suggests that v-*src* is not directly responsible for radioresistance. Shimm et al.[24], however, have reported that v-*src* activation increases radioresistance in cells expressing the multidrug-resistant phenotype.

These data indicate that the effects of only a limited number of oncogenes on radiosensitivity have been studied and some results are contradictory. Many

factors, including the method of gene transfer, gene expression, irradiation conditions, cell type and phase of the cell cycle, could be responsible for these contradictions. In the processes of gene transfer, some extra DNA sequences may be transferred along with the gene of interest into the target cells. This raises the possibility of interference of the expression of the gene of interest. The radiosensitivity of the transfected cells might thus not only be influenced by the activity of the transfected gene but also by the mutation of the *in situ* gene caused by the insertion or translocation. Pardo et al. [25] investigated the role of transfection and clonal selection in mediating radioresistance. They found that transfection of a neomycin-resistant marker and clonal selection can impart radioresistance to both normal and tumour cells but there was a significant clonal heterogeneity in the radiation response of human and rodent cells transfected with a *neo* vector. Thus, at minimum, radiation sensitivity following oncogene activation appears to depend on the oncogene and cell line studied, but perhaps also on other factors not yet identified.

2 TUMOUR SUPPRESSOR GENES

It has been more than 20 years since Harris et al. (1969) and Knudson (1971) first postulated the existence of tumour suppressor genes. But only in the past 6～7 years, have real studies on their identity and action emerged. According to Levine [26], a broad definition of tumour suppressor genes includes both the retinoblastoma susceptibility gene (*RB*) and *p*53, and other genes or their products that can act like tumour suppressor gene, e.g. GTPase activating protein (*GAP*), neurofibromatosis gene 1 (*NF1*), the Wilm's tumour gene 1 (*WT1*), and transforming growth factor (*TGF*-β). So far there are more than 20 tumour suppressor and related genes mapped on human chromosomes [2]. In comparison with oncogenes, the effects of these tumour suppressor genes on radiosensitivity have been little studied.

Reports concerning the roles of *p*53 and *RB* in radiosensitivity have appeared only in the past couple of years. Su and Little [27] found that human diploid fibroblast cells transfected with wild-type SV40 T-antigen (SV40T) were significantly more radioresistant than those transfected with the *neo* gene only (D_0=192±13 cGy vs. 127±19 cGy). Cell clones transfected with *RB* binding defective mutants showed moderately increased radioresistance (D_0=174±10 cGy). But cell clones transfected with three different *p*53 binding defective

mutants demonstrated no significant changes in radiosensitivity (D_0=137±11, 128±15 and 131±12 cGy respectively) as compared with *neo* gene transfected controls (D_0=127±19 cGy). These data suggest an important role of SV40T/*p*53 complex in radiosensitivity, i.e. *p*53 binding can increase the radioresistance of SV40T transfected cells. Also, *RB* binding may strengthen the role of the complex.

Jung et al.[28] examined mutations in the *p*53 gene in 3 radiosensitive and 3 radioresistant human squamous carcinoma cell lines. Interestingly they found 3 of 3 radiosensitive and 2 of 3 radioresistant cell lines having mutation in the *p*53 gene. This study suggests no role of *p*53 in radiosensitivity but it is possible that different mutation sites could result in different biological consequences. Lee and Bernstein [29] have reported that *p*53 mutations increase resistance to ionizing radiation. They examined radiation sensitivity of bone marrow cells and spleen cells from transgenic mice expressing one or two mutant alleles of *p*53, and found that expression of both mutant variants significantly increases the cellular resistance to γ radiation. But transfection of rat embryo fibroblasts (REF) with mutant *p*53 alone did not significantly alter mean parameters of *in vitro* radiosensitivity relative to control *neo* transfected REF cells [30]. Co-transfection with mutant *p*53 and *ras* genes or triple transfection with mutant *p*53, *ras* and E7 genes resulted in significant radioresistance.

It has been postulated that cell cycle checkpoints can contribute to an increase in cell survival and a decrease in abnormal heritable genetic changes following exposure to DNA damaging agents. Both *RB* and *p*53 have been demonstrated to be potential cell cycle checkpoint determinants acting in G_1 phase. Following irradiation *p*53 can arrest irradiated cells in G_1 phase which allow the cells to have time to repair DNA damage before entering S phase [31]. This could prevent the mutagenic lesions or/and the accumulation of genomic changes, which can result in cell death. This function of *p*53 was supported by the experiment that cells with wild-type *p*53 genes exhibited transient arrests in both G_1 and G_2 phases after γ irradiation, while cells without *p*53 genes or with its mutant retained only the G_2 arrest [31]. This is consistent with the fact that mutant *p*53 can function in a "dominant negative" manner, presumably by inhibiting endogenous wild-type *p*53 function [32]. But in other cases, cells retaining one wild-type *p*53 allele still mimicked the behaviour of primary diploid cells; they arrested growth in the presence of drug [33]. The data obtained so

far have indicated that wild-type *p*53 can only directly affect gene expression through transcriptional activation. The gene expression may be related to DNA damage repair following exposure to ionizing radiation [34]. Theoretically, tumour suppressor genes are thought to be able to help maintaining DNA integrity when cells are exposed to radiation and therefore support cell survival. The possible role of apoptosis and the effects of mutant *p*53 indicate that more than one mechanism may be involved. Vogelstein and Kinzler [32] proposed five *p*53 inactivation mechanisms, which may act in the progression of different tumours and are helpful to us for orienting future research.

3 DNA REPAIR GENES

DNA repair is critically important for preserving the integrity of the genetic material. The DNA repair processes are a complex set of reactions, in which DNA repair genes play important roles. So far there are six DNA repair genes identified in mammalian cells, five excision repair cross-complementation (*ERCC*) genes and an X-ray repair cross-complementation (*XRCC*) gene.

Flejter et al. [35] used cultured cells from individuals with xeroderma pigmentosum (XP) to study DNA repair gene correction. The cells exhibit sensitivity to UV radiation and defective nucleotide excision repair. They found that direct transfer of a cosmid bearing *ERCC*2 gene conferred UV resistance to XPD cells. Regarding ionizing radiation, only one dedicated human X-ray repair gene, *XRCC*1, has been cloned on the basis of its correction of a hamster mutant [36]. But no defects in this gene have been identified in genetic disease traits or in tumour tissues. A recent report on the relationship of *XRCC*1 to radiosensitivity [37] showed that expression of the polymorphic human DNA repair gene *XRCC*1 did not correlate with radiosensitivity of the cells of human head and neck tumour cell lines. But *XRCC*1 was demonstrated to efficiently correct high sister-chromatid exchange levels present in EM$_9$ cells upon transfection into EM$_9$ [38]. However, DNA repair pathways are usually regulated by a number of genes, mutations in any one of which could lead to the observed repair deficiency and therefore increase radiosensitivity of the cells. In the yeast, *Saccharomyces cerevisiae*, also many mutants have been isolated that are abnormally sensitive to killing by UV and ionizing radiation. They are placed into three epitasis groups referred to as the *RAD*3, *RAD*52, and *RAD*6 groups. These three groups of genes are thought to reflect three largely

nonoverlaping primary cellular responses to ionizing and UV radiation damage to DNA in the yeast. Loci in the *RAD3* epistasis group are involved in nucleotide excision repair and those in the *RAD6* epistasis group are required for mutagenesis, while those in the *RAD52* epistasis group are thought to reflect the existence of recombination responses to DNA damage. Game and Cox [30] tested UV-sensitive mutants from different laboratories and established the loci *RAD1* through *RAD22*. In another study Game and Mortimer [60] established the independent loci *RAD50* through *RAD57* using X-ray-sensitive mutants. Their relationships to radiation responses have insightfully and thoughtfully reviewed [61]. Recently, chromosome transfer experiments have facilitated the mapping of a human gene complementing the hamster X-ray sensitive mutants. These mutants are being extensively characterized by cross-sensitivity studies and by the use of cell extracts to correct defined DNA damage. Intensive efforts to clone human genes which correct DNA repair deficiency will undoubtedly improve our understanding of DNA repair mechanism as well as their intrinsic relationship to radiosensitivity.

So far we have reviewed investigations of the effects of oncogenes, tumour suppressor genes and DNA repair genes on radiosensitivity. The fact that ionizing radiation itself can activate a wide range of genes also needs to be elucidated. These genes are associated with many different cellular processes including signal transduction (e.g. transcription factors and certain oncogenes), intercellular signalling (e.g. cytokines), growth control (e.g. oncogenes and others), responses to tissue injury (e.g. collagenase, plasminogen activator), inflammation (e.g. interleukin-1 and *TNF*), DNA repair (e.g. *REV2* gene), responses to stress (e.g. metallothionein). All these responses are a cascade of molecular events initiated from certain early response genes (transcription factors) that regulate the subsequent activation of later response genes. Any changes in these processes may affect the cell fate after exposure to radiation.

Recently it has been postulated that radiation-induced interphase death of cells is a consequence of a metabolically active process termed apoptosis. If this postulation is true the genes involved in apoptosis control are certainly implicated in radiosensitivity. The oncogenes *bcl-2*, *myc*, the tumour suppressor gene *p53* and interleukin 6 are all reportedly involved in regulation or stimulation of apoptosis. *Bcl-2* was shown to block apoptosis when introduced into B

cells. *Myc*, on the other hand, was demonstrated to be able to stimulate apoptosis. Wild-type *p*53 can stimulate but mutant *p*53 blocks apoptosis. The effect of wild-type *p*53 can be counteracted by interleukin-6 but is enhanced by *TGF*-β. Recently a gene whose protein product is located on cell membrane, has also been reported to be able to stimulate apoptosis. It has been termed as *APO*-1 or *fas* gene and is mapped to human 10q23 or mouse chromosome 19.

Since ionizing radiation can cause DNA damage and cell membrane changes we propose that radiation-induced DNA damage in the DNA nucleoprotein conformation induces a nuclear signal that, in turn, activates a program of gene expression, and that changes in cell membrane caused by radiation also initiate a signal that cause a cascade of gene activation. In the former case, signal transduction must pass from the nucleus to the cytoplasm after exposure to radiation and then, as in the latter case, from the cytoplasm back to the nucleus. Although the signal transduction pathways are not clear at present, there are some observations supporting this proposition. Stein et al.[42] found that the induction of the human immunodeficiency virus type 1 (*HIV*-1) promoter by UV light is mediated by a nuclear signal, the heterodimer of *jun* and *fos* (AP-1) which resides in the nucleus and must be modulated there. The signal activates NF-kB, a cytoplasmic protein, which then binds to the promoter region. Certain genes induced rapidly in the presence of a protein synthesis inhibitor are referred to as early-response genes. Generally demonstrated examples of early response genes encoding transcriptional factors include the *fos*, *jun* and *egr*-1 gene families as well as a member of the steroid hormone receptor gene family. Although the induction of early response genes is very rapid, there is evidence suggesting that protein kinase C mediates X-ray inducibility of early response genes, *egr*-1 and *jun*. The expression of early response genes is probably regulated through differential signal transduction pathways which may be activated by ionizing radiation. Also the expression differs in different types of cells treated with radiation. Early response gene products may participate in subsequent events by binding to specific promoter elements of later response genes. For example, the gene for platelet-derived growth factor (*PDGF*) a chain has AP-1 and *egr*-1-binding domains whereas tumour necrosis factor (*TNF*) has elements similar to AP-1 and *egr*-1 target sequences. Therefore it is speculated that radiation induction of *PDGF* and *TNF* may be regulated by *egr*-1 and *jun*. The activation of later response

genes leads to later responses which may include growth factor and cytokine production, DNA repair and regulation of cell cycle distribution. It is still elusive how many and what genes are involved in early and later responses respectively. We here outline a general scheme for whole cascade of events initiated by radiation. Analysis of the sequence of radiation-induced cellular responses will allow us to make inferences regarding the events responsible for cellular radiosensitivity.

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