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REVIEW

Ability to repair DNA double-strand breaks related to cancer susceptibility and radiosensitivity

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Abstract Traditional radiobiology has aimed at elucidating the mechanism of radiosensitivity of cancer cells and normal cells. Because the mechanism of DNA double-strand break (DSB) repair, which is inherently important to radiosensitivity, was unknown, it has been difficult to obtain results applicable to clinical radiotherapy from traditional radiobiology research. Today, however, the molecular mechanism of DNA DSB repair has been elucidated because of the rapid advances in molecular biology. In DNA DSB repair, at least two major repair mechanisms, homologous recombination and nonhomologous end joining (NHEJ) have been reported. In the NHEJ pathway, DSBs are directly, or after processing of the DNA ends, rejoined at an appropriate chromosomal end. DNA-dependent protein kinase (DNA-PK) plays an important role in DNA DSB repair by NHEJ. We have investigated how the ability of repair of DNA DSB influences cancer susceptibility and the radiosensitivity of tumors and normal tissues by focusing on the activity of DNA-PK. In the near future, research on DNA DSB repair mechanism will be able to be applied to research on carcinogenesis, prediction of radiosensitivity of tumors and normal cells, and sensitization of tumor cells.

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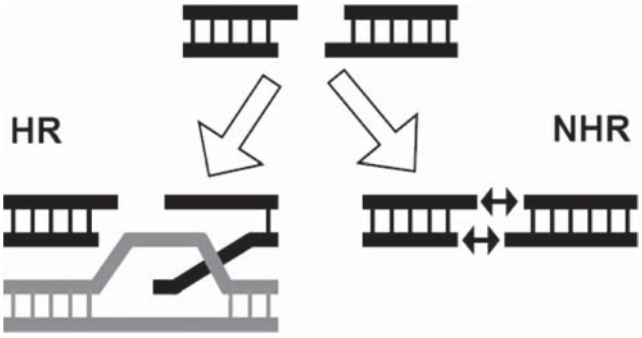
Introduction

Radiotherapy, surgery, and chemotherapy comprise three pillars of cancer treatment. Recently, the quality of life of a cancer patient has become a focus of attention, and the role of radiotherapy has therefore grown. When radiotherapy is employed, a uniform dose is applied to tumors of the same size and pathology. However, the response to radiation is often different even in tumors of the same pathology. Moreover, the seriousness of radiation complications differs greatly among patients owing to the different radiosensitivity of normal tissues. Therefore, individualized radiotherapy based on the radiosensitivity of cancer cells and normal tissues of patients is required.

To perform the individualized radiotherapy, it is necessary to know (1) the inherent radiosensitivity of the tumor cells, (2) oxygen concentration of tumor tissues, (3) tumor proliferation characteristics, and (4) number of clonogenic tumor cells.

When X-rays are irradiated to a cell, there are various kinds of DNA damage. Among them, DNA double-strand break (DSB) is believed to be one of the most serious induced by DNA-damaging agents such as ionizing irradiation. If unrepaired or repaired incorrectly, it can lead to cell death during mitosis.[1] It is recognized that the inherent radiosensitivity of tumor cells is greatly influenced by the ability of DNA DSB repair.[2]

The mechanisms of DNA repair have recently been elucidated thanks to the rapid advances in radiobiology



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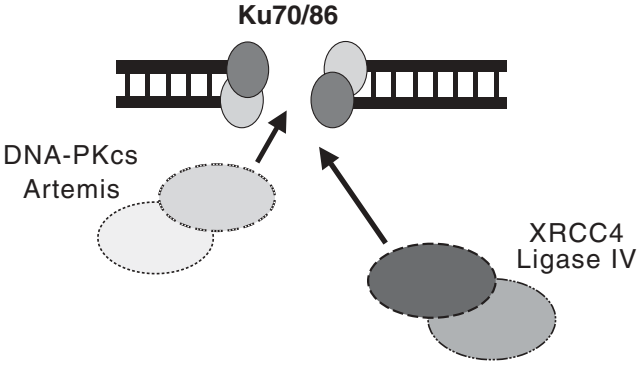

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Fig. 1. **a** Schema of the DNA double-strand break repair mechanism: homologous recombination (*HR*) and nonhomologous end joining (*NHEJ*). **b** Schema of nonhomologous end joining

during the past decade. During DNA DSB repair, at least two major repair mechanisms, homologous recombination (HR) and nonhomologous end joining (NHEJ) have been reported (Fig. 1a).[3] In the NHEJ pathway, DSBs are directly, or after processing of the DNA ends, rejoined at an appropriate chromosomal end; DNA-dependent protein kinase (DNA-PK) plays an important role in DNA DSB repair by NHEJ throughout the cell cycle.[4] DNA-PK is a serine/threonine kinase composed of DNA-PK catalytic subunit (DNA-PKcs) and a heterodimer of Ku70 and Ku86. DNA-PK binds to DSBs in DNA, phosphorylates, and activates DNA-binding proteins, including XRCC4 and DNA ligase IV, p53, and several transcription factors. Then ligase IV repairs DNA DSB (Fig. 1b).[5] HR uses homologous DNA as a repair template. Because this repair mechanism demands the presence of a sister chromatid, HR is most efficient in the S and G_2 phases of the cell cycle. In contrast, NHEJ can operate efficiently during G_1 phase because it does not require the presence of a sister chromatid.

We think that a study of DNA DSBs repair by NHEJ is important to improve radiotherapy results in cancer patients, and we have mainly studied DNA-PK, which plays a main role in NHEJ. In this review, we present our results and consider the application of these results.

DNA-PK and cancer susceptibility

The presence of genomic instability in cells is known to play an important role in the multistage carcinogenesis of various organs in both humans[6] and experimental animals.[7] Genes involved in the maintenance of genomic stability can be considered as a caretaker class of tumor suppressor genes.

The DNA repair pathway has been implicated in maintaining genomic integrity via suppression of chromosomal rearrangements.[3,8,9] Consistent with this idea, mice deficient in NHEJ components are characterized by increased sensitivity to agents causing DNA damage, chromosomal instability, and immunodeficiency; and they have a predisposition to thymic lymphomas.[10] Further loss of cell cycle checkpoints in NHEJ-deficient mice results in a shift from thymomas to pro-B cell lymphomas[11–14] or sarcomas.[12,15] These results indicate that DNA-PKcs, Ku70, and Ku86, which comprise the DNA-PK complex, are considered to belong to the caretaker class of tumor suppressor genes.[16] Therefore, it is interesting to understand how NHEJ influences the genomic integrity and carcinogenesis in a clinical setting.

In our previous study, we examined DNA-PK activity in peripheral blood lymphocytes (PBLs) from individuals with various kinds of cancer.[17] It is ideal to measure DNA-PK activity of progenitor cells for cancer from normal tissues. However, it is difficult to obtain enough normal tissue to measure DNA-PK activity. Therefore, we used PBLs for the DNA-PK activity measurement. It is a precondition that DNA-PK activity of PBLs relates to DNA-PK activity of normal tissues that are irradiated. Auckley et al. reported that DNA-PK activity in PBLs from patients with lung cancer was significantly lower than lung cancer-free controls. They also demonstrated a tight correlation between DNA-PK activity in PBLs and bronchial epithelial cells (a progenitor cell for lung cancer) that were obtained by bronchoscopy, suggesting that PBLs can be used as a surrogate cell type for other kinds of cell.[18]

In our previous study, we examined the DNA-PK activity in PBLs from individuals with various kinds of cancer (breast cancer, head and neck cancer, uterine cervix cancer, esophageal cancer, malignant lymphoma) and normal individuals before radiation therapy and chemotherapy.[17]

Age and smoking had no association with DNA-PK activity. DNA-PK activities of PBLs in patients with

uterine cervix or breast cancer were significantly lower than those in normal volunteers. There was the relation between DNA-PK activity and expression of Ku70, Ku86, and DNA-PKcs shown by reverse transcription-polymerase chain reaction (RT-PCR). A similar tendency was seen in the Western blot assay but was less clear than with RT-PCR. These results indicate that DNA-PK activity is regulated by the expression of DNA-PK.

We examined the relation between DNA-PK activity and chromosomal aberrations to elucidate why low DNA-PK activity is related to cancer susceptibility. Chromosomal aberrations were examined by cytogenetic methods. The frequency of chromosome aberrations, such as dicentric chromosomes and excess fragments, increased as DNA-PK activity decreased. Chromosome instability takes on an important role in carcinogenesis of the various organs. The DNA repair pathway has been implicated in maintaining genomic integrity via suppression of chromosomal rearrangements.[3,9]

When we summarized our results, cancer susceptibility of individuals with low DNA-PK activity is related to chromosomal instability due to the low ability of DNA DSBs repair. DNA-PK activity in PBLs can be used to select individuals for whom an examination should be performed because of their increased susceptibility to breast and uterine cervix cancer.

Association of ionizing radiation-induced foci of NBS1 with chromosomal instability and breast cancer susceptibility

The Nijmegen breakage syndrome gene (*NBS1*) is the causal gene of a hereditary disease that manifests as low height, microcephalia, immunodeficiency, and high carcinogenicity. NBS1 protein has an important role in the cell cycle checkpoint mechanism and DNA DSB repair.[19–21]

Proteins involved in DNA DSB repair usually disperse in a nucleus. When cells are irradiated, proteins for DNA DSB repair gather in areas where DNA DSBs occur and appear as a dot (a focus) with fluorescence immunostaining.

Histone H2AX is phosphorylated after irradiation and forms a focus in a DNA-damaged area within several minutes. NBS1 forms a complex with MRE11 and RAD50. The NBS1/hMRE11/hRAD50 complex relocalizes into subnuclear structures upon induction of DNA damage by ionizing radiation, the so-called ionizing radiation-induced foci (IRIF)[22,23] in 30 min.

Phosphorylation of H2AX is proposed to concentrate repair factors at sites of DNA damage, including NBS1.[24] Gamma H2AX IRIF continue to grow after exposure to X-rays and then disappear slowly over time, consistent with rejoining of DNA DSBs but with slower kinetics. Radiation sensitivity, measured as the clonogenic surviving fraction, was correlated with the fraction of gammaH2AX IRIF remaining 24 h after irradiation. Therefore, the ability to repair a DNA DSB is lower when the fraction of gammaH2AX IRIF remaining 24 hours after irradiation is high.[25]

In our previous study, we compared the formation and dissociation of NBS1 IRIF in PBLs from sporadic breast cancer patients and normal healthy volunteers.[26] We then investigated the relation between NBS1 IRIF and spontaneous chromosomal aberrations by cytogenetic methods to elucidate the mechanism of the association between NBS1 IRIF and breast cancer susceptibility. We also measured DNA-PK activity of PBLs and examined the relation between NBS1 IRIF and DNA-PK activity to elucidate the mechanism of variability of NBS1 IRIF among individuals.

Subjects consisted of 46 sporadic breast cancer patients with no other cancer and no familial breast cancer history who had undergone breast-conserving surgery and were seen because of postoperative radiotherapy. Thirty cancer-free normal healthy volunteers were also enrolled in this study. The number of persistent NBS1 IRIF per nucleus at 24 h after irradiation in invasive cancer patients was significantly higher than in the normal healthy volunteers.

To determine why the incidence of NBS1 IRIF after 24 h is related to breast cancer susceptibility after irradiation, we examined the relation between the number of persistent NBS1 IRIF per nucleus at 24 h after irradiation and the frequency of spontaneous chromosome aberrations.

The frequency of spontaneous chromosome aberrations increased as the number of persistent NBS1 IRIF increased, indicating that the number of persistent NBS1 IRIF might be associated with chromosome instability. As described earlier, the existence of chromosome instability takes on an important role in carcinogenesis. The DNA repair pathway has been implicated in maintaining genomic integrity via suppression of chromosomal rearrangements.[3,9]

The ability to repair DNA DSBs is related to the fraction of NBS1 IRIF remaining 24 h after irradiation, which is the reason the NBS1 IRIF remaining 24 h after irradiation is related to chromosomal instability. In summary, cancer susceptibility in individuals with high numbers of NBS1 IRIF remaining 24 h after irradiation is related to chromosomal instability due to less ability to repair DNA DSBs.

We also measured DNA-PK activity and examined the relation between NBS1 IRIF and DNA-PK activity

to determine the mechanism by which NBS1 IRIF is associated with chromosomal instability. There was an inverse correlation between NBS1 IRIF number and the activity of DNA-PK, which plays an important role in NHEJ; this indicates a close interrelation between HR and NHEJ in the DNA DSB repair mechanism.

cDNA analysis of gene expression related to DNA-PK activity

As already described, DNA-PK activity is associated with chromosomal instability. DNA-PK activity in PBLs is associated with the risk of breast and uterine cervix cancer. In our previous study, we demonstrated that DNA-PK activity was related to the expression of Ku70, Ku86, and DNA-PKcs, as shown by RT-PCR. There was the similar tendency demonstrated by the Western blot assay, indicating that the activity of DNA-PK may be regulated at the gene expression level.[17]

Hosoi et al. demonstrated that DNA-PK activity and protein/mRNA levels of Ku70, Ku80, DNA-PKcs, and Sp1 were significantly higher in colorectal cancer tissues than in normal tissues. Significant correlations between DNA-PK activity and protein/mRNA levels of Ku70, Ku80, DNA-PKcs, and transcriptional factor Sp1 were observed.[27] These authors suggested that DNA-PK activity and protein and mRNA levels of Ku70, Ku80, and DNA-PKcs were elevated in tumor tissues in patients with colorectal cancer because of elevated Sp1 protein levels in tumor tissues.

We therefore applied cDNA array technology to analyze the expression profiles of genes associated with DNA-PK activity in PBLs with various DNA-PK activities.[28]

Peripheral blood was collected from eight individuals, and their PBLs were separated by centrifugation. mRNA was extracted and used to synthesize cDNA. With a cDNA array filter, we evaluated the increased or decreased expression of mRNA in 536 kinds of cancer-related protein. Among the expression profiles of the 536 genes analyzed, 9 genes (*Ku70*, *Ku86*, *XRCC3*, *Granzyme B*, *cyclinD3*, *cyclinE*, *Cd346*, *Hsp90*, *Ran*) positively correlated with DNA-PK activity, and one gene (*Rbp130*) negatively correlated with DNA-PK activity. Three genes (*Cdc25B*, *Lck*, *Rab89*) were marginally correlated. Most of the genes that were related to DNA-PK activity were cell cycle-related. Our results suggest that there may be networking between the checkpoint and DNA repair molecules at the gene expression level.

Moreover, the transcription factor E2F1, which plays an important role in cell cycle progression, exhibited a strong correlation with DNA-PK activity. Rbp130, which is considered a negative regulator of E2F, showed inverse correlation with DNA-PK activity. In silico promoter analyses showed the presence of at least one E2F binding sites in the promoter regions of Ku70, Ku86, DNA-PKcs, and genes associated with DNA-PK activity. It seems that transcription factor E2F may regulate the cooperative expression of DNA-PK and proteins involved in checkpoint control.

It is also interesting that the expression of XRCC3 had a strong correlation with DNA-PK activity. XRCC3 belongs to a group of Rad 51-related proteins responsible for repairing DNA double-strand breaks by homologous recombination repair.[29] This indicates that there might be cross-talk between the two mechanisms of DNA double-strand breaks, such as NHEJ and homologous recombination.

Application of studies of DNA DSB repair to clinical radiotherapy

We discuss several applications of the DNA DSB repair mechanism to clinical radiotherapy.

Prediction of radiosensitivity of tumor tissues using immunohistochemistry

It is currently impossible to predict the radiosensitivity of tumor tissues of an individual patient precisely. If radiosensitivity of tumor tissues of an individual patient could be predicted, we could treat patients with the radiotherapy individualized biologically.

We immunohistochemically investigated the expression of proteins involved in DNA DSB repair (e.g., DNA-PKcs, Ku 70, Ku86, XRCC4, NBS1) in 134 specimens from various normal and tumor tissues with different radiosensitivity.[30,31] Immunopositivity to Ku70, Ku86, DNA-PKcs, XRCC4, and NBS1 was found in all tumor tissues examined. The staining for Ku70, Ku86, and DNA-PKcs was nuclear, whereas for XRCC4 and NBS1 it was nuclear and cytoplasmic. There were no apparent differences in the expression of these five proteins among cancerous tissues and the corresponding normal tissues. No apparent differences in nuclear staining intensity were detected in the expression of these five proteins among tumor tissues with different radiosensitivity.

Komuro et al. reported that the expression pattern of Ku protein in patients with advanced rectal carcinoma was correlated not only with tumor radiosensitivity but also disease-free survival.[32]

Thus, the results of studies analyzing the relation between Ku expression and radiosensitivity are few and

contradictory. Immunohistochemical study has the limitation of assay sensitivity. A subtle difference in expression of proteins that might influence the radiosensitivity of cells may not be detected. We are planning to examine whether DNA-PK activity in PBLs is related to acute and late complications of radiotherapy.

Radiosensitization of tumors

At present, anticancer agents, mainly platinum drugs, have been used concomitantly with radiation therapy to sensitize the radiation therapy effect. However, there are side effects associated with anticancer drugs, such as myelosuppression and kidney toxicity, that limit the quantity of drugs used. It is promising to inhibit selectively proteins involved in DNA DSB repair to sensitize tumor cells.

A remarkable report was published in 2006.[33] It reported that concomitant use of cetuximab (C225), an epidermal growth factor receptor (EGFR) inhibitor, and radiotherapy significantly improved the treatment results of patients with head and neck carcinomas. Ionizing radiation triggers EGFR import into the nucleus. During this process, Ku70 and Ku80 are transported into the nucleus. As a consequence, an increase in the nuclear kinase activity of DNA-PK and increased formation of the DNA end-binding protein complexes containing DNA-PK, essential for repair of DNA strand breaks, occurred.[34] Blockade of EGFR import by the anti-EGFR monoclonal antibody C225 abolished EGFR import into the nucleus and radiation-induced activation of DNA-PK, inhibited DNA repair, and increased the radiosensitivity of treated cells.[35]

It is expected that selective inhibitors of proteins involved in DNA DSB repair, such as cetuximab, will be discovered and applied to clinical radiotherapy.

Conclusion

The traditional radiobiology aimed at elucidating the mechanism of radiosensitivity of cancer cells and normal cells. Because the mechanism of DNA DSB repair that is important in inherent radiosensitivity was unknown, it was difficult to derive results that were applicable to clinical radiotherapy from traditional radiobiology research. However, the molecular mechanism of DNA DSB repair has now been elucidated thanks to the rapid advances of molecular biology. In the near future, research of the DNA DSB repair mechanism will be applied to the research of carcinogenesis, prediction of radiosensitivity of tumor and normal cells, and sensitization of tumor cells.

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