5 - 49 Mutant p53 in Cancer: from Molecular Mechanism to Therapeutic Modulation*

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p53 is a crucial tumor suppressor gene. As a genomic safety guard, once cells are exposed to genotoxic stress, p53 is activated, leading to a variety of different cellular responses such as cell cycle arrest, DNA damage repair, apoptosis[1]. Unfortunately, inactivation of p53 is a common event in tumorigenesis, with mutations occurring in more than 50% of human primary tumors[2]. Aside from losing its tumor suppressor function, mutant p53 (mutp53) often acquire inherent, novel oncogenic functions, which is termed 'gain-of-function' [3]. Emerging evidence suggests that mutp53 was highly associated with advanced malignancies and poor prognosis, which makes it a target for development of novel cancer therapies[4]. More importantly, mutations in p53 are correlated with poor prognosis in malignancies of breast, bladder, haematopoietic system[5–7]. Furthermore, p53 mutational spectrum differs among tumors such as colon cancer, lung cancer, breast cancer, and brain cancers.Radiotherapy is now considered to be one of the effective approaches for cancer treatment. However, many tumors exhibit resistance to radiation. Hence, it is critical to determine the role of p53 status in radiotherapy (Fig. 1). In diffuse intrinsic pontine gliomas, mutations in p53 are a major driver of increased radiation resistance, with mutp53 carrying patients less responsive to irradiation and relapsing earlier after radiotherapy with a worse prognosis[8,9]. In glioblastoma, cells carrying wtp53 in response to ionizing radiation exhibit accelerated senescence, whereas cells carrying mutp53 do not exhibit significant senescence[10]. Furthermore, transgenic mice carrying mutp53 increases resistance of various hematopoietic cell lineages to γ-irradiation and that overexpression of p53, R193P or A135V mutants increases radiation resistance of mouse hematopoietic cell by 45-57[11]. Notably, the relationship between mutp53 and radiosensitivity is controversial, since certain studies have shown that mutp53 can increase radiosensitivity or have no effect on radiosensitivity[12]. For instance, Kawashima, *et al.* introduced the p53 R273H mutant into immortalized human fibroblasts and found that cells carrying the p53 R273H mutant had higher radiosensitivity than cells not expressing p53 after X-ray irradiation. Interestingly, different mutant sites of p53 are differentially sensitive to radiotherapy. In osteosarcoma, after γ-irradiation treatment of cell lines, p53 mutations at codons 175, 244, 245, 273, and 282 are radioresistant. Mutations at codons 123, 195, and 238 have higher radiosensitivity than wtp53, and mutations at codons 130, 143, 157, 168, 277, 280, and 286 are less radiosensitive than wtp53[13].

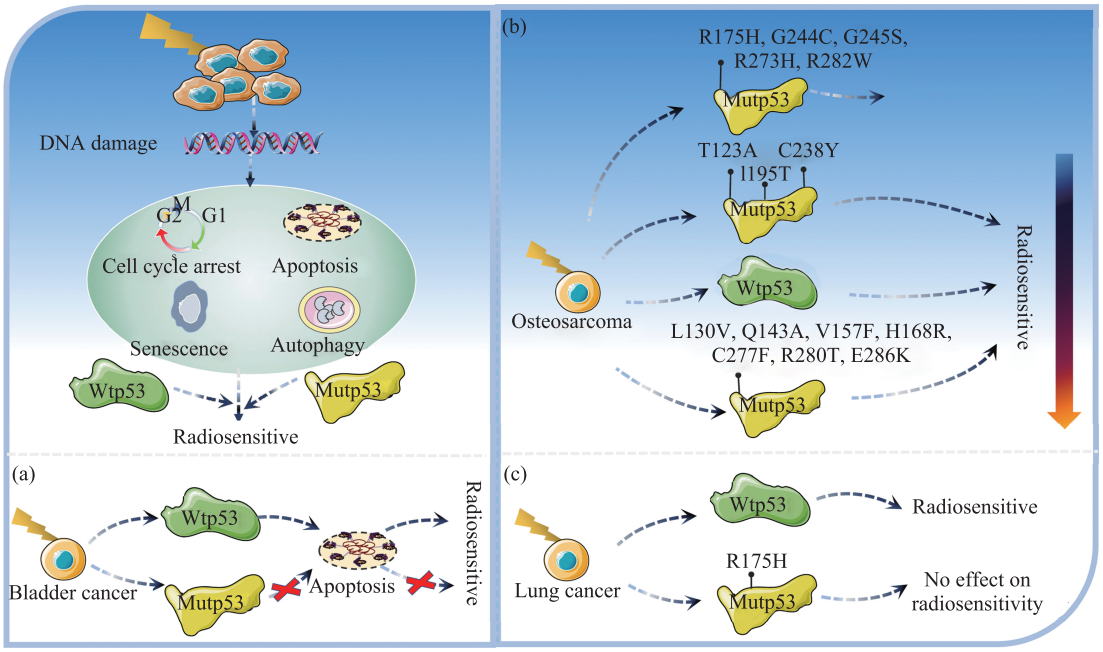

Fig. 1 (color online) **Schematic representation of the mechanism of mutp53 in radiotherapy.** Mutp53 can regulate radiotherapy through various mechanisms. In most cases, expression of mutp53 leads to radiotherapy resistance. However, under a certain context, mutp53 expression can promote radiotherapy sensitivity or have no effect on radiotherapy sensitivity.

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5 - 50 A Radiation Sensitivity Prediction Model

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Clinical trials show that carbon ion radiotherapy has excellent antitumor effects. Moreover, it is suggested that carbon ion radiotherapy is an effective treatment for tumors that are resistant to conventional X-ray radiotherapy. However, the high cost of constructing the accelerator system limits its practical application. Carbon ion radiotherapy has the capacity to treat only 0.015% of the total patient population with a newly diagnosed cancer[1]. Therefore, selecting patients who can derive the greatest benefit from carbon ion radiotherapy is of great importance.

In previous study, we obtained a NSCLC cell line with raidoresistance through fractionated X-ray irradiation and its expression patterns of mRNAs were explored with high-throughput sequencing assays. We observed the expressions of circRNA ZNF208 and lincRNA H19 were significantly upregulated in the radioresistant NSCLC cells. Then, the biological characters of these noncoding RNAs in regulating radiosensitivity were evaluated. We found that circZNF208 could regulate NSCLC sensitivity to X-ray but had no effect on NSCLC cells exposed to carbon ions[2]. Meanwhile, the radiosensitivity of NSCLC cell line was substantially augmented upon exposure to low-LET X-ray and high-LET carbon ions when the expression of lncRNA H19 was decreased[3].

Based on the results mentioned above, we constructed a radiation sensitivity prediction model which facilitates appropriate selection of patients for carbon ion radiotherapy, as shown in Table 1.

Table 1 A radiation sensitivity prediction model.

	circZNF208	**lncRNA H19**	**Radiotherapy**
Type I	low	low	X-ray
Type II	high	low	Carbon ion
Type III	high	high	Carbon ion with other modalities such as chemotherapy

According the biological characteristics of circZNF208 and lncRNA H19 in tumor, the samples or patients with NSCLC could be divided into three types. Type I, which has low expressions of circZNF208 and lncRNA H19, was suitable for X-ray radiotherapy. And carbon ion radiotherapy will be the most beneficial for patients with high circZNF208 but low H19 expressions (Type II). Moreover, if both circZNF208 and H19 have the high expressions (Type III), patients with NSCLC should be treated with carbon ion radiotherapy combined with other modalities such as chemotherapy.

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