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ORIGINAL PAPER

Mutations in the TP53 gene affected recruitment of 53BP1 protein to DNA lesions, but level of 53BP1 was stable after γ-irradiation that depleted MDC1 protein in specific TP53 mutants

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Abstract 53BP1 is a very well-known protein that is recruited to DNA lesions. The focal accumulation of p53 binding protein, 53BP1, is a main feature indicating the repair of spontaneous or irradiation-induced foci (IRIF). Thus, here, we addressed the question of whether mutations in the TP53 gene, which often affect the level of p53 protein, can change the recruitment of 53BP1 to γ- or UVA-irradiated chromatin. In various TP53 mutants, we observed a distinct accumulation of 53BP1 protein to UV-induced DNA lesions: in R273C mutants, 53BP1 appeared transiently at DNA lesions, during 10–30 min after irradiation; the mutation R282W was responsible for accumulation of 53BP1 immediately after UVA-damage; and in L194F mutants, the first appearance of 53BP1 protein at the lesions occurred during 60–70 min. These results showed that specific mutations in the TP53 gene stand behind not only different levels of p53 protein, but also affect the localized kinetics of 53BP1 protein in UVA-damaged chromatin. However, after γ-irradiation, only G245S mutation in TP53 gene was associated with surprisingly decreased level of 53BP1 protein. In other mutant cell lines, levels of 53BP1 were not affected by γ-rays. To these effects, we conversely found a distinct number of 53BP1-positive irradiation-induced foci in various TP53 mutants. The R280K, G245S, L194F mutations, or TP53 deletion were also characterized by radiation-induced depletion in MDC1 protein. Moreover, in mutant cells, an interaction between MDC1 and 53BP1 proteins was abrogated when compared with wild-type counterpart. Together, the kinetics of 53BP1 accumulation at UV-induced DNA lesions is different in various TP53 mutant cells. After γ-irradiation, despite changes in a number and a volume of 53BP1-positive foci, levels of 53BP1 protein were relatively stable. Here, we showed a link between the status of MDC1 protein and TP53 gene, which specific mutations caused radiation-induced MDC1 down-regulation. This observation is significant, especially with regard to radiotherapy of tumors with abrogated function of TP53 gene.

Keywords DNA repair · 53BP1 protein · TP53 gene · Histone γH2AX · MDC1 protein

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