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The Gain of Function of p53 Mutant p53S in Promoting Tumorigenesis by Cross-talking with H-RasV12

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Abstarc :

The loss of wild type p53 tumor suppressive function and oncogenic gain-of-function of p53 mutants have been showing important implications in tumorigenesis. The $p53^{N236S}$ ($p53^{N239S}$ in human, p53S) mutation has been shown to lose wild type p53 function by yeast assay. However, its gain of function is still not clear. By gel shift assay, we showed that mutant p53S had lost its DNA binding ability to its target promoters. Further real-time PCR data confirmed that p53S had lost the function of regulating the transcription of $p21^{Cip1/Waf1}$, cyclin G, PUMA, and Bax in response to 10Gy irradiation. These data confirmed the loss of function of p53S in mammalian cells. By xenograft assay, we showed that the p53S *per se* was not oncogenic enough to form tumor, however, cooperating with H-RasV12, p53S could dramatically promote tumorigenesis in p53 null MEFs. Further study showed that co-expression of p53S and H-RasV12 could increase the expression level of H-RasV12 and partially eliminate the elevation of stress response proteins such as Chk2, ?-H2AX, Hsp70, Rb, $p16^{Ink4a}$ caused by either p53S or H-RasV12. These data suggested that p53S cross-talked with H-RasV12 and reduced the cellular stress response to oncogenic signals, which facilitated the cell growth and tumorigenesis. Together these data provided the molecular basis for the cooperation of p53S and H-RasV12 and revealed the gain of function of p53S in cross-talking with H-RasV12. This study revealed an important aspect of gain of function for p53 mutant, therefore might shed light on the clinical strategy in targeting p53 mutant.

Key Word :
p53 mutant, gain of function, Ras, tumorigenesis, DNA damage response, cross-talk.

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