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Gadd45A, the Modulator of P53-Dependent Protective Pathway

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The tumor suppressor p53 has been known to be a genomic guardian against carcinogenic stresses caused by many of environmental mutagens while the protective mechanisms of p53 were not clarified yet. Our previous study suggested that the activation of p53 might be regulated by redox modulation of redox factor, AP1/ref1 (APEX1) as well as post-translational modification. Activated p53 also plays as a transcription factor that regulates its down stream genes including Gadd45a known to regulate nucleotide excision repair (NER). Recently, the evidence has provided that functional p53 status is dependent on the base excision repair (BER). Gadd45a-deficient cells exhibited slow BER after treatment with MMS, a pure base-damaging agent. In addition, Gadd45a-deficient cells showed the significant sensitivity to base-damaging therapeutic agent Thio-TEPA. Our data suggest that p53-regulated genes including Gadd45a contribute to the BER response. In other hand, we investigated whether the expression of APEX1 was regulated by Gadd45a, real-time PRC (RT-PCR) was performed. Our data showed the alteration of APEX1 in Gadd45a-deficient cells suggesting that Gadd45a might also regulate p53 pathway by regulating the expression of APEX1. Gadd45a may be a key component gene of the p53 pathway involved in protection from carcinogenic base damage as well as a potential therapeutic target for eliminating p53-mutant cancer cells.

Keyword : GADD45, P53, Cancer, DNA repair