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Editorial Comment

Beyond the Role of p53 in Prognostic Biomarker and Therapeutic Target: Modulator of Anti-Tumor Immunity

The primary role of p53 is known as tumor suppressor in various types of cancers. Gain-of-function p53 mutations occur commonly in cancer and lead to loss of p53 tumor suppressor function and acquisition of aggressive malignant phenotype. In cancers without mutation of p53, the function of p53 pathway is often suppressed via mechanisms that impair its stability as well as activity. For example, the overexpression of MDM2. MDM2 (or human ortholog HDM2), is an E3 ubiquitin ligase negatively regulating p53 through ubiquitination and subsequent proteasomal degradation.¹ Growing evidence demonstrates a role for p53 in immune modulation via induction of immunogenic cell death,² antigen processing and immune checkpoint regulation. It has been reported that MDM2 inhibition triggers adaptive immunity and augments the efficacy of immune checkpoint inhibitor blocking PD-1/PD-L1 pathway in wild-type p53 tumors.³ Taken together, p53 may have the roles not only for prognostic biomarker and therapeutic target, but also for modulator of anti-tumor immunity. Thus, the development of p53 modulators for cancer treatment may have greater significance beyond the direct anti-tumor activity.

Babao Dan is a traditional Chinese medicine formula with composition of herbs. It has been demonstrated capable of arresting the cell cycle at transition of G1/S boundary in gastric cancer cells by activating p53 pathway.⁴ Babao Dan up-regulated protein expression of phosphorylated p53, p21 level and down-regulated the expression of survivin, PCNA, Cyclin D1 and CDK4 which is correlated with the G1/S phase checkpoint.

The mechanism by which p53 affects immune function in the tumor microenvironment remains not well understood. The emerging evidence shows that immunogenic cell death, defined by the chronic exposure of damage-associated molecular patterns (DAMPs)

to the immune system, may promote immune-mediated elimination in the tumor microenvironment. Activation of p53 pathway could trigger immunogenic cell death.⁵ Whether modulators such as Babao Dan can induce immunogenic cell death along with promoting immunotherapeutic efficacy need further investigation. Combining the companion test of p53 expression status and its pharmacological role would be a promising task in development of novel category of anti-cancer therapeutics.

References

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