APR-246 INDUCES AN INCREASE IN TUMOR IMMUNOGENICITY IN A P53 INDEPENDENT MANNER

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Background Immunotherapy has made a significant impact in treating cancer, yet more than 40% of the patients remain unresponsive or have a short-lived response to therapy. Rationally designed combinations of targeted therapies with immune modulators have the potential to enhance therapeutic efficacy[1, 2]. As p53 is also well known to differentially modulate the immune system[3], it is an attractive target to be used in combination with immunotherapy. Thus, we evaluated the immunogenic potential of APR-246, a targeted therapy that activates p53[4]. In addition, APR-246 can also elicit p53-independent effects mainly through the induction of endoplasmic reticulum stress and oxidative stress in several preclinical tumor models[5]. As these cellular stressors as well as p53 are capable of enhancing the immunogenicity of tumor cells[6, 7], we hypothesized that agents that stabilize p53 such as APR-246 may also increase the tumor antigenicity.

Methods We designed a set of in vitro and in vivo assays to evaluate the ability of targeted therapies to elicit an immunogenic response in tumor cells. Here, we use the preclinical melanoma cell line B16-F10 as a model since it is highly metastatic and responds poorly to immunotherapy alone[8, 9].

Results When we treated B16-F10 cells with APR-246 either in culture in vitro or implanted as a tumor in C57BL/6j mice in vivo, we observed an increase in MHC expression. Further, when mice were immunized with APR-246-treated B16-F10 cells and then implanted with healthy untreated melanoma cells, they had prolonged tumor free survival. Additionally, in our in vitro co-culture assays, APR-246 treatment enabled tumor cells to activate antigen-specific cytotoxic T cells when mediated by antigen presenting cells. Therefore, we hypothesized that APR-246 has the potential to mechanically combine with immune modulation owing to its immunogenic potential. Thus, we rationally designed a treatment regimen to further enhance the tumor immunogenic effects elicited by APR-246. When APR-246 treatment was combined with the TLR4 agonist, Monophosphoryl lipid A (MPL) and a CD40 agonist antibody, we observed significant delay in the growth of B16 tumor in mice. Importantly, using CRISPR generated B16 p53 KO cells, we have identified that these immunogenic effects of APR-246 are observed independently of p53, albeit slightly reduced.

Conclusions Based on our findings, we propose that the combination of APR-246 with immunomodulatory agents may be effective in treating cancers irrespective of their p53 mutation status.

Note: D.V. and J.M contributed equally to this work.

REFERENCES

Ethics Approval All mice were maintained and treated in accordance with the NIH and American Association of Laboratory Animal Care regulations. All murine treatments and procedures were approved by the MSKCC Institutional Animal Care and Use Committee (IACUC).

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