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"Ivermectin synergizes with interferon-gamma to overcome resistance in renal cancer"

Background: Renal cell carcinoma (RCC) treatment challenges mostly due to tumor heterogeneity and resistance to immune-based therapies. Previous work done in Dr. Zea's lab has shown that some RCC tumors respond to interferon gamma (IFN-γ) treatment, while others remain unresponsive. He has also shown that a combined treatment with IFN-γ plus lipopolysaccharide (LPS) increased tumor killing, mostly mediated by the increased production of nitric oxide (NO). However, a subset of tumors continued to remain resistant to this combination therapy. IFN-γ has been shown by Dr. Zea to induce tumor cell death and cause growth arrest. On the other hand, Ivermectin (IVM), initially introduced in the 1970s, is an FDA approved antiparasitic drug that has been recently studied for its potential anti-cancer properties. IVM could also have immunomodulatory properties both in the tumor microenvironment and the immune system. Therefore, IFN-γ is an anti-tumor agent and IVM could overcome tumor resistance, and their combination could conceivably enhance the effectiveness of immunotherapy. The objective of this study is to investigate the potential anti-tumor activity of IVM alone or in combination with IFN-γ to overcome tumor resistance mediated by IFN-γ. The effect of NO production and its association with anti-tumor activity will be also assessed. We hypothesize that ivermectin can reduce tumor cell proliferation and enhance the therapeutic effects of IFN-γ in resistant renal cell carcinoma (RCC) cell lines.

Methods: Four different murine RCC cell lines (R0, R1, R2 and CL19) with different responses to IFN-γ were used. 40,000 cells from each cell line were plated in 24 well plates, in RPMI plus 10% fetal bovine serum. The cells were stimulated with 10 and 100 U/μL of IFN-γ and with increasing concentrations of IVM at 2.5, 5, 10, 15, and 20 μM alone or in combination. Unstimulated cells were used as controls. The cells were incubated for 24, 48, and 72 hours after stimulation. At each time-point, supernatants were collected to measure NO (Greiss Assay) and IFN-γ levels, whereas cell growth was measured by MTT assay. All experiments were repeated twice.

Results: At base line, R2 and CL19 cells grew faster than R0 and R1 ($p=0.043$) at 48hrs. Nitrite production was more abundant in CL19 (6-fold) compared to the other cell lines. We observed that R1, R2, and CL19 were sensitive to IFN-γ stimulation, proven by an increased production of nitrates, and inhibition of cell growth. The R0 cell line was resistant to IFN-γ treatment. Concentrations higher than 15 μM IVM were toxic to all cell lines. Whereas concentrations between 5 and 10 μM inhibit cell growth in R1, R2 and CL19, but not respectively, R0. The combination of IVM plus IFN-γ shows a synergistic effect on the resistant R0 cell line diminishing its growth by 25% in just 48 hours as compared to the individual treatments.

Conclusion: These results suggest that ivermectin may serve as a promising therapeutic agent for reversing resistance to immunotherapy in kidney cancer, particularly in contexts where IFN-γ contributes to anti-tumor activity. The combination of IVM with IFN-γ could enhance the effectiveness of existing treatments. However, more research is needed to understand the IVM mechanisms involved in overcoming resistance.