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Integrated immune ratio associated with tumor growth and prognosis in pancreatic cancer

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Background & Aim: The prognosis of Pancreatic Ductal Adenocarcinoma (PDAC) remains poor due to the difficulty of disease diagnosis and therapy. Immunotherapy has had robust performance against several malignancies, including PDAC. In this study, we aim to analyze the expression of CD8 and FoxP3 on T cell lymphocytes in tumor tissues and analyze the possible clinical significance of these findings in order to find a novel effective immunotherapy target in PDAC using a murine model.

Methods: A tissue microarray using patient PDAC and matched non-tumorous samples was stained and analyzed for associations with clinicopathological characteristics. A preclinical murine model administrated with various immunotherapies was analyzed with growth inhibitor, flow cytometry, enzyme-linked immune-sorbent assay and immunohistochemistry.

Results: Infiltrating $FoxP3^+$ regulatory T cells (Tregs) levels in tumor tissues were associated with survival, while $CD8^+$ infiltrating T cells (TILs) were not. Considering the drawbacks of these measures alone, the number of $CD8^+$ and $FoxP3^+$ T cells were combined to create a new estimated value Integrated Immune Ratio (IIR), which showed excellent validity in survival risk stratification. IIR was further verified as an independent prognostic factor according to multivariate analysis. In our preclinical murine model, CD25 and TGF-β combination blockade had a higher tumor growth inhibitor value. This combination therapy significantly depleted periphery and intratumor $FoxP3^+$ Tregs while increasing intratumor $CD8^+$ T cell levels compared to controls or anti-TGF-β monotherapy ($p<0.05$). Anti-CD25 monotherapy alone also had the ability to deplete periphery and intratumor Tregs ($p<0.05$). Intratumor IL-10, TGF-β was notably lower associated with higher IFN-γ excretion in this combination immunotherapy. Such combination immunotherapy was further confirmed to synergize with anti-PD-1 monotherapy to improve tumor growth inhibition and Japan cure rates.

Conclusion: The combination of CD25, TGF-β and PD-1 blockade plays a potentially effective role in inhibiting tumor formation and progression. Our results also provide a strong rational for use of IIR in future immunotherapy clinical trials.

Biography

Russell Miller is a Motivated health development professional seeking new long-term opportunity in the Life Science and Healthcare industries in Japan. Experience in laboratory, biotech and science communication fields both in Japan and US. He completed his Master of International Health from The University of Tokyo.

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