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A histological data-driven analysis of the hypoxic microenvironment of preclinical murine bladder tumors

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Abstract (2,000 CHARACTERS (not including spaces))

INTRODUCTION: Hypoxia is common in many solid tumors, including bladder cancer (BC). Preclinical murine models that mimic relevant molecular and phenotypical characteristics of clinical BC were used to assess the immune cell composition within the tumor, and mathematical modeling was used to analyze these data within the reconstructed hypoxic tumor microenvironment.

METHODS: We analyzed 18 murine BC tissues from a treatment protocol that included the intravesical installment of MB49-OVA tumor cells on day 0, gemcitabine treatment on day 10, and/or intravesical transfer of OT-I T cells on day 14, in addition to untreated controls and normal bladder tissues. The collected tissues were sliced, and consecutive sections were stained for vasculature (CD31), tumor (H&E), immune cells (CD8, CD4), and myeloid-derived suppressor cells (MDSCs, Ly6G). Histology images were co-registered, segmented, and preprocessed. A multi-cell off-lattice hybrid agent-based model that combines discrete cells and vasculature with continuous oxygen kinetics was developed to recreate oxygenation in the tumor microenvironment.

RESULTS: In all tissues, the hypoxic microenvironment was more prevalent in the tumor vs. nontumor regions due to differences between the irregular tumor vasculature vs. normal vasculature. The T cell and MDSC infiltration increased in the tumors treated with gemcitabine (as mono- or combination therapy). Despite the significant hypoxia level in these tumors, only small proportions of CD8+s and CD4+s were hypoxic, as the majority resided in the well-oxygenated portions of the tumor. High infiltration of CD8+ cells was observed in tumors treated with OT-I cells compared to the controls. However, only a small proportion were hypoxic, and most CD8+s and MDSCs were well-oxygenated. Hypoxic native CD8+s in untreated tissues were observed inside the tumors, and most well-oxygenated CD8+s were near the tumor borders. The CD8+s also resided in the well-oxygenated regions in the normal tissues.

CONCLUSION: Our computationally-reconstructed tissue oxygenation based on histology images revealed that the hypoxic tumor microenvironment hinders T cell accumulation in treated and untreated tumors. Such quantitative analyses may encourage designing more effective hypoxia-mediated therapies.