110 DEEP LEARNING MODELS IDENTIFY KEY TUMOR MICROENVIRONMENT FEATURES ASSOCIATED WITH GENETIC SIGNATURES OF UV MUTAGENESIS AND ALKYLATING AGENT TREATMENT IN MELANOMA

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Background Melanoma is the most aggressive type of skin cancer and often exhibits therapeutic resistance.[1 2] Different types of mutagenesis, for example UV exposure,[3 4] have been shown to result in distinct genetic signatures; however, their impact on histological features of the tumor microenvironment (TME) and response to treatment remains unknown. Alkylating agents are one of the most commonly used chemo-therapeutics for melanoma[5]; however, the impact of alkylating agents on the melanoma TME is also poorly understood. In this work, we quantified the TME in melanoma using machine learning and investigated TME feature associations with 1) increased UV mutagenesis, and 2) alkylating agent-induced mutations.

Methods PathExplore convolutional neural network-based models using hematoxylin and eosin (H&E)-stained whole slide images (WSI) were trained to classify histologic substances in the TME (table 1). We quantified model performance using nested pairwise comparisons with pathologist annotation.[6] We deployed PathExplore Melanoma along with a separately trained stromal subtyping model[7] to extract human-interpretable features (HIFs) that quantify the TME across each WSI in the TCGA (SKCM, N=363) cohort. We identified mutational signatures indicative of UV and alkylating agents using the deconstructSigs R package.[8] We utilized primary (N=71) and lymph node metastasis (N=255) slides for UV exposure analysis, and only primary slides for alkylating agent analysis. We quantified associations between HIFs and mutational signatures using univariate logistic regressions. P-values were corrected using Benjamini-Hochberg. Multivariable Cox models were used for survival analysis.

Results We found a positive association between tumor-infiltrating lymphocyte (TIL) abundance (p=0.01), as well as the area proportion of densely inflamed stromal regions (p=0.015), with UV exposure. Features quantifying neutrophil abundance were associated with alkylating agent treatment, most notably neutrophil-to-lymphocyte ratio (NLR; p=0.013). Higher NLR was associated with worse overall survival in general, but this effect was attenuated in patients previously treated with alkylating agents.

Conclusions We found that TIL abundance was associated with UV exposure, likely due to increased tumor mutational burden, which may have implications for immunotherapy. Additionally, NLR has previously been associated with poor prognosis in melanoma.[9 10] Our results indicate that the effect of NLR on prognosis is also mediated by prior treatment, pointing to a complex causal web between TME, treatment, and patient outcomes. Broadly, these results suggest that machine learning can extract meaningful information regarding underlying mutation-driven or treatment-induced changes in the TME.

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Abstract 110 Table 1 Cell and tissue substances in PathExplore Melanoma.

Class Category	Values
All tissue regions detected	Cancer, Cancer-associated stroma, Necrosis, Normal tissue
Predicted cells	Cancer cells, Fibroblasts, Lymphocytes, Macrophages, Plasma cells, Neutrophils, Eosinophils, Other cells

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