TMEInsight: Elucidating Patient-Specific Immune-Pathway Crosstalk via Deep Learning to Foreshadow Tumor Progression

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In the US, 1 in 3 individuals develops cancer in their lifetime. Yet, drug failure rates remain near 90%. Deciphering immune-cancer interactions within the tumor microenvironment (TME) is imperative for developing effective cancer treatments. Current research, like transcriptomic signatures and linear modeling, cannot fully manage tumor heterogeneity or TME crosstalk, leaving these interactions unelucidated. TMEInsight implements a novel artificial neural network (ANN) framework for patient-specific modeling of tumor-immune interactions across six cancer types. The multilayer architecture allows the model to consider non-linear TME crosstalk, foreshadowing tumor progression for early personalized intervention. Utilizing 3,500+ pan-cancer samples from the TCGA database, the ANN was trained on 73,710 immune predictors and 105,300 cancer pathway responses. The ANN was optimized via hyperparameter tuning and 5-fold cross-validation. For ANN interpretability, SHAP was utilized to elucidate heterogeneous relationships between 21 immune cell types and 30 signaling pathways. The ANN and SHAP were integrated into a web application, allowing for real-time prediction of Reactome signaling pathway enrichment based on patient-specific immune infiltration. TMEInsight achieved a mean squared error of 0.11 and an R-squared of 0.92, explaining 92% of the variation in cancer signaling activity. TMEInsight also outperformed linear regression (R-squared = 0.20) and Random Forest (R-squared = 0.52). Overall, TMEInsight provides a robust framework for tailoring therapies to the TME, enabling early intervention and revealing promising avenues for finding therapeutic targets. TMEInsight shows that cancer pathway activity can be predicted at earlier stages than previously possible.

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