Decoding Neural Networks: Novel Computational Methods to Discover Anti-Tumor B Cell Receptor Binding Motifs

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Studying B cell receptor (BCR) binding is crucial for understanding how the human adaptive immune system attacks cancer cells – information that can translate into targeted and more efficacious cancer therapies. My research focused on decoding a deep neural network model that was trained on 3 million BCR samples from patients of 13 cancer types. Currently, deep neural networks remain a black box, limiting our ability to apply them to their fullest potential and extract additional biological relevance. Since the model achieved 0.8 AUC accuracy in predicting cancer types based on BCR sequences, I hypothesized that the model learned motifs (recurring protein sequence patterns) from the training data that were used in its prediction. To uncover this key motif information, I developed a novel computational pipeline with multiple stages: generating random input sequences, running the model to rank them, visualizing top sequences to distinguish binding patterns, and clustering to identify motifs. Using my pipeline, I discovered 65 BCR binding motifs for 13 cancer types and identified the 12 most significant motifs overall. The robustness of the motifs was validated through a synthetic data simulation and extensive correlation analyses. Last, the versatility of my pipeline was demonstrated through applications to both antigen-specific and full-length sequences. My research is the first to reveal and validate anti-tumor BCR binding motifs for multiple cancer types, a crucial discovery that can inform synthesis of new motif-based antibody drugs and more precise cancer immunotherapy treatments. The versatile pipeline that I propose can be reused to decode a wide range of deep learning models and ultimately lead to more transparent and understandable AI.

Awards Won:
Third Award of $1,000