The Mutagenesis of the PD-L1 Inhibitory Ligand to Identify the Binding Site of the Novel PD-L1/B7-1 Pathway

Klee, Alyssa

Harnessing the immune system to attack cancer is a novel treatment called immunotherapy. It uses antibodies to block signaling pathways that deactivate T cells. These inhibitory pathways exist between cancer cells and T cells and clinical trials are successful in blocking them. Although the treatment works, it may result in autoimmune side effects when inhibitory pathways are blocked, since this activates T cells which can attack healthy cells. Usually it is negligible, but to prevent side effects in weaker patients, blocking one pathway is an option. An inhibitory pathway used in treatments goes from PD-1 (receptor on T cells) to PD-L1 (protein on cancer cells). A newer pathway connects PD-L1 to B7-1 (a protein found on T cells). The binding site of B7-1 on PD-L1 overlaps with PD-1 on PD-L1, but the binding site of PD-L1/B7-1 is unknown. The knowledge of the binding site location would let pharma companies make antibodies that block just one pathway, decreasing the side effects. In this study, my goal was to locate the binding site of B7-1 on PD-L1 by making mutations in PD-L1. I hypothesized that one or few of seven amino acids on PD-L1 are part of the binding site. I found a way to correlate the binding rates of the mutants with the location of the mutation relative to the binding site. A mutation on the binding site decreases the binding rate, since the mutation prevents the two proteins from binding. I tested for binding of the mutated proteins on COS cells (monkey cells) to determine which mutations directly affect binding to B7-1. I found that the amino acids M115, K124, D49, and R113 are contact points between B7-1 and PD-L1. This new information gives insight to pharma companies attempting to create an antibody blocking only B7-1, and not PD-1.

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