4.1 Identification of tumor antigens for cancer immunotherapy

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The recent successes and challenges of cancer immunotherapy have motivated intense investigation of the molecular and cellular determinants of therapeutic response. The generation of broad computational and analytic tools to directly probe human samples has led to the emergence of systematic approaches to meet this challenge. At the heart of productive anti-tumor immune responses is the interaction of the T cell and the antigen presenting cell, with recognition of antigen by the T cell receptor (TCR); these interactions are further impacted by heterogeneous immune cell populations within the tumor microenvironment. While the search for immunogenic tumor antigens has been the subject of decades-long studies, multiple lines of evidence have convincingly demonstrated tumor neoantigens as an important class of immunogenic tumor antigens. Neoantigens arise from amino acid changes encoded by somatic mutations in the tumor cell and have the potential to bind to and be presented by personal HLA molecules. Using next-generation sequencing approaches, we can now systematically identify mutations leading to amino acid changes that can be potentially recognized immunologically through the implementation of neoantigen discovery pipelines. In recent studies, we have demonstrated that neoantigen load is associated with clinical outcome to immune-based therapies, and neoantigens can be safely and feasibly targeted to generate customized cancer vaccines. We have been undertaking pilot clinical trials to develop personal cancer vaccines in melanoma and glioblastoma that utilize synthetic long peptides as delivery approach for this therapy. Recent results and new directions will be discussed.

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4.2 Deciphering the highly complex cancer immunopeptidome

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Immunotherapy has sparked new hope for oncology in recent years, due to its remarkable ability to induce long-term tumor regression of metastatic cancer. Accumulating evidence suggest that tumor regression observed with immunotherapy are driven by targeted elimination of antigen-bearing tumor cells that are explicitly recognized by T-lymphocytes. Our systematic analysis of melanoma tumors for HLA-presented peptides using HLA peptidomics has allowed us to identify cancer/melanoma antigens, neo-antigens, intracellular microbial antigens and aberrant peptides. Our studies reveal that the landscape of melanoma-presented HLA-peptides is highly complex. We will discuss relevant mechanisms, effects on immune recognition and therapeutic implications.

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