癌症免疫治療之生物標記

Biomarkers in Cancer Immunotherapy

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Since anti-CTLA-4 antibody, ipilimumab demonstrated a 21% long-term survival rate for patients with metastatic melanoma in 2011, novel immune checkpoint inhibitor immunotherapy has continued to evolutionize treatment of almost very kind of cancer. Immunotherapy was nominated “Breakthrough of the year 2013” in *Science*. Several FDA–approved agents, anti-PD1 and anti-PD-L1 antibodies, are available for an increasing number of cancers, including melanoma, renal cell carcinoma, lung cancer, urothelial carcinoma, head & neck cancer, esophageal cancer, gastric cancer, hepatoma, lymphoma, Merkle cell carcinoma and MSI-high cancers. By activating the immune system to eliminate cancer cells, immunotherapy offers the possibility of durable response. However, objective responses among patients treated with single-agent regimens are seen in around 20% patients treated. Combination of these novel immunotherapy increases efficacy but also increases toxicity and cost. Thus, to optimize selection of appropriate patients for immunotherapy and avoid unnecessary toxicity and health care costs, there is a clear need to identify truly predictive, and not simply prognostic, biomarkers of response.

The mechanisms of action of specific immunotherapies make it difficult to identify an appropriate marker for different classes of drugs. There may be host, tumor, and immune factors that can be used for biomarker development. Although PD-L1 expression level has been reported to be associated with better outcomes in some anti-PD1 and anti-PD-L1 antibodies studies, the results are still inconsistent. The number of tumor mutation load is usually increased in treatment responders. CD-8 T cells infiltration to the tumor microenvironment is believed to be essential to induce a tumor rejection. However, these TILs are sometimes exhausted and immunosuppressed. A number of T cell markers are

being studied. The biomarkers development is usually challenged by the fact that immunotherapy targets are often inducible and dynamic over time and location. The tumor microenvironment involves complicated interactions between several types of infiltrating immune cells such as monocytes, neutrophils, dendritic cells, T and B cells, eosinophils, basophils, mast cells, and natural killer (NK) cells, as well as the heterogeneous tumor cells themselves and their companion stromal cells, including tumor-associated macrophages, fibroblasts, adipocytes, and endothelial and other cells.

Some serum factors, including IL-6, CRP, VEGF, LDH and peripheral cells, such as lymphocyte counts, leucocyte counts, eosinophils, MDSCs, CD4 T cells are explored to develop the biomarkers. However, none of them can be applied to clinical setting. MSI/MMR abnormality can lead to high mutation burden and is associated with tumor response to checkpoint inhibitors. As a result, FDA approved anti-PD-L1 antibody for the treatment of MMR-deficient cancers, including colon cancer.

Finally, the presence of immune-mediated adverse events has long been hypothesized to predict clinical benefit from immunotherapy. Vitiligo has been consistently reported to be associated with better outcome in metastatic melanoma. Recently immune-mediated hypothyroidism has been demonstrated to be associated with better outcome in patients treated with checkpoint inhibitors. The observation of the association between adverse events and treatment outcome are mainly retrospective. The occurrence of severe adverse events usually hinders further administration of the immunotherapy. These results cannot be used as biomarkers. Further understanding of the relation between host, tumor and the microenvironment can lead to better biomarkers development in the future.