Editorial

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Immuno-Genomics and Score: Stepping Stone for Immune Design

Immunogenomics is referred as identification of prognostic and predictive neoantigens for immunotherapeutic interventions with recent high-throughput sequencing technologies and bioinformatics data analysis. In cancer cells, neoantigens are generated by non-synonymous somatic gene mutations, presented on the surface of cells, remained bound to human leukocyte antigen (HLA) molecules, and in response to that T cell immunity might be provoked. Therefore, immunogenic neoantigens identification are of utmost importance for improvement of efficacy of cancer immunotherapy.

Identification of Neo-antigen

Neoantigens may have diverse sources, viral and mutated proteins. In cancers with virus associated etiology such as Merkel cell carcinoma, adult T cell Leukemia and HPV associated cancers, viral associated antigens have been considered as tumor specific antigens. On the other hand, mutated protein generate as a result of single nucleotide variants (SNV) resulting in non-synonymous substitutions, frame-shift derived mutations due to insertion or deletion of nucleotides, chromosomal translocation from break-point mutations and post-translational modifications such as phosphorylation and deamidation. Identification of neoantigens can be carried out using high-throughput genomics techniques viz whole-exome sequencing, whole-genome sequencing and more recent technique HLA peptidomics.[1] After introduction of immune checkpoint modulating antibodies such as anti-CTLA4 and anti-PD1 and its association with mutation burden response, neoantigens have become potential biomarkers for immunotherapies.

Immune Check Point Molecules

Immune Check Point molecules includes stimulatory molecules and inhibitory molecules, regulate immune activation and maintain immune homeostasis. The neo-antigens can be potentially recognized by specific T cells and mount T cell specific immune response. Inhibitory check point molecules like Cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), programmed death-1 (PD-1), PD-1 ligand-1 (PD-L1), and lymphocyte activation gene 3 (LAG-3), suppress T-cell mediated immune response.CTLA-4 may be expressed on tumor cells, tumor infiltrating T regulatory cells or exhausted conventional T cells. The prognostic value of CTLA-4 expression of tumor cells has been described by few studies and have shown association with decreased survival in nasopharyngeal cancer and increased survival in non-small cell lung cancer. The ligand PD-L1 for PD-1 receptor is commonly over expressed on tumor cells or on non-transformed cells in the tumor microenvironment. PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T cells, which leads to the inhibition of the cytotoxic T cells in the tumor microenvironment. Further PD-1 and PD-L1 expression when correlated with patient's survival, dissimilar findings were noted in several studies. The higher expression of PD-1 and PD-L1 expression associated with decreased survival in melanoma, renal cell cancer, esophageal cancer, gastric cancer and ovarian cancer, and improved survival in angiosarcoma.[2] The immune checkpoint modulating antibodies such as anti-CTLA4 and anti-PD1 suppress host immune response against cancer cells and then allow activation of host immune system resulting in eradication of cancer cells.Anti-CTLA-4 and anti-PD-1 antibodies are shown effective in immunogenic tumors prior to treatment having T cell infiltration and high mutation rates. A meta-analysis have shown a benefit of immune checkpoint inhibitors only in a subset of patients; no or minimum clinical benefit in majority of patients and severe immune-related adverse reactions in some patients. This study highlighted identification of predictive biomarker(s) that can be used to select patients who are more likely to expect clinical benefit with minimal risk of autoimmune adverse events, contributing to reduction of unnecessary medical costs.

Tumor Infiltrating Lymphocytes (TIL)

To understand relationship between immune system and tumor, evaluation of TIL is an important component because it reflects host antitumor response.[3] TIL are evaluated by immuno-

histochemical staining of CD3 and CD8 in two core regions of the tumor and the invasive margin defined as immunoscore. An international consortium of 14 centres in 13 countries includes our institute GCRI the only centre of India, which was led by society of immunotherapy of cancer (SITC) recommended to evaluate immunoscore in routine pathological diagnosis because it is valid and cost-effective.[4] High immunoscore predicts better overall survival and response to neoadjuvant and adjuvant therapy. Immunoscore has recently been established as a new cancer prognosticator for survival in spinal chordoma, colon, lung, bladder and liver cancer.[4,5,6,7] Patients with high immunoscore exhibited significantly higher PDL-1 expression of tumor cells and immune cells than low immunoscore, however, survival did not differ significantly with respect to PDL-1 expression in high and low immunoscore groups in colorectal cancer.[8] In another study on gastric cancer, a significant association of tumor-PD-L1 (+) and immune cells-PD-L1 (+) with a high immunoscore was observed. Further, PD-L1 expression of tumor and immune cells alone was not significantly correlated with the overall survival of patients. But in combination PD-L1 (+)/immunoscore Low group showed the poorer overall survival and the PD-L1 (+)/immunoscoreHigh group showed the better overall survival.[9] In addition to immunoscore, recently immunophenoscore which is insilico constructed transcriptome sequencing based score having clinically robust 32 gene panel has been proposed as a possible predictor of immune check point inhibitors for immunogenic tumors.[10]

In nutshell, identification of prognostic and predictive neoantigens by immunogenomics are expected to generate new insights for development of neoantigen-formulated vaccines. Further, immunoscore and pan-cancer immunophenoscore evaluation prior to treatment help to overcome therapeutic resistance to immunotherapy.

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