Theme of the Quarter: Genes Relevant to Immuno-oncology

Greetings CKB CORE™ users! We are excited to announce this quarter we are highlighting **genes relevant to immuno-oncology**. Of the 50 available genes in CKB CORE™ this next quarter, you will find 20 relevant to immuno-oncology (Fig. 1).

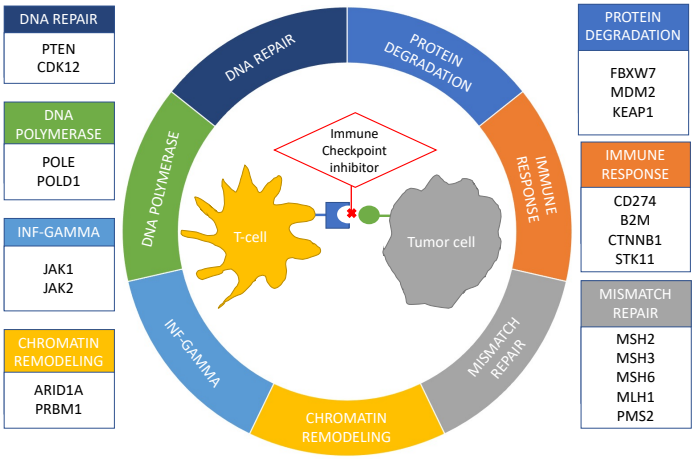

Figure 1. Twenty genes relevant to immunotherapy response grouped by roles.

The ongoing development and implementation of targeted therapies in the oncology field has resulted in significant breakthroughs and continues to lead to improved survival and quality of life in cancer patients. More recently added to the list of treatment options is immunotherapies, an approach that exploits the abilities of the immune system to treat cancer.[1] Cancer cells develop innate mechanisms to evade the immune system including dysregulation of checkpoint protein expression, which subsequently prevents T cells from detecting and eliminating cancer cells.[2,3] In other words, cancer cells utilize this mechanism to "turn off" immune cells. Some of the more commonly known inhibitory checkpoint receptors include CTLA-4, PD-1, and PD-L1, and the class of immunotherapies called immune checkpoint inhibitors (ICIs) can be used to target them. They are designed to induce a T cell-mediated immune response by preventing the cancer cells from turning off the immune cells. There are now several ICIs that are FDA approved for multiple tumor types. The first approved ICI was Ipilimumab in 2011, which targets CTLA-4, followed by PD-1-targeting therapies, Nivolumab and Pembrolizumab, in 2014. In 2016, the PD-L1 inhibitor, Atezolizumab was approved. And in 2017, two more PD-L1 inhibitors, Avelumab and Durvalumab, were approved, and then PD-1 inhibitor, Cemiplimab, in 2018.[4] Since PD-L1 (CD274) is widely expressed on cancer cells, its expression is a fairly well-adopted biomarker in the clinic. However, its predictive value is also debatable considering there are studies that have shown patients who are negative for PD-L1 expression also respond to ICIs.[5] Therefore, while these immunotherapies have resulted in dramatic responses in some patients, approximately 13%[6], the search to identify other predictive biomarkers for immunotherapy response continues to move forward.

Other frequently used biomarkers now include tumor mutational burden (TMB) and microsatellite instability (MSI). TMB measures the total number of mutations per coding area of the tumor genome and a "high" TMB (usually defined as >10 mut/Mb) has been shown to predict response to immunotherapies.[7] MSI is a measure of the change in the number of short, repeated sequences of DNA, referred to as "microsatellites or short tandem repeats", and is often a result of defects in the mismatch repair (MMR) genes (i.e. MSH2, MSH3, MSH6, MLH1, MLH2, PMS2), which are responsible for correcting any DNA mismatches that occur during replication. Studies have suggested tumors that are identified as MSI-high may have an upregulation of immune checkpoint proteins such as PD-1 and PD-L1, and therefore, can predict response to immunotherapy.[8]

In addition to the immune-related biomarkers, TMB and MSI, efforts to identify other predictors of response have led to exploring the effects of gene alterations in the context of immunotherapies (Fig. 2). Besides MSI, MMR defects can also lead to mutations in the DNA polymerase genes that are responsible for proofreading in DNA replication, POLE and POLD1, potentially leading to increased mutational burden and immunotherapy response

prediction.[9] Furthermore, studies have shown that changes to genes involved in cellular signaling pathways could affect immunotherapy response. For example, mutations in genes involved in the interferon-gamma pathway such as JAK1 and JAK2 may confer resistan ce to ICIs while mutations in ARID1A, a chromatin remodeling complex gene, may act as a predictor of response.[10,11] In a recent study, KRAS-mutant lung cancer patients were shown to have reduced response to ICIs if they harbored concurrent STK11 and/or KEAP1 mutations.[12] Both genes have been found to potentially play a role in ICI response in other studies as well but whether it is a true predictor remains controversial.[13] Lastly, amplification of MDM2, a negative regulator of TP53, has been demonstrated to act as a negative predictor of ICI response.[14]

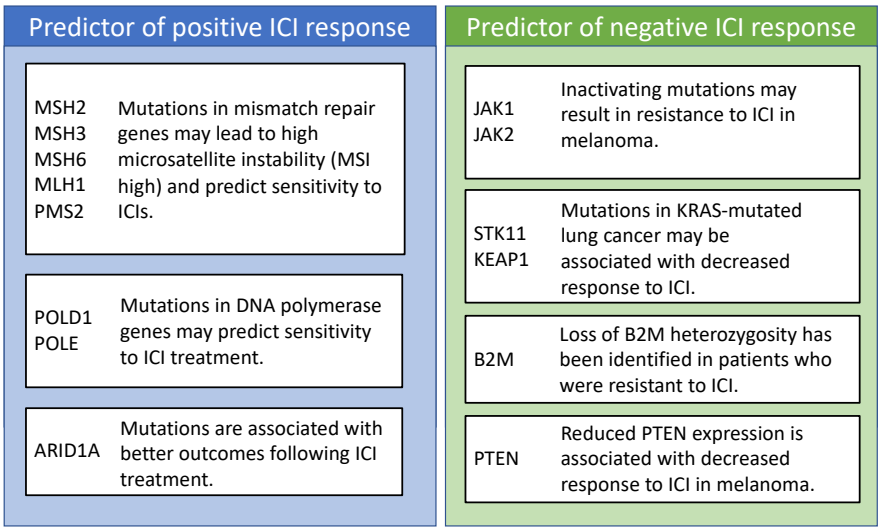

Figure 2. Select genes and their potential role as predictors of response to ICIs.

Although these data represent only a handful of genes that appear to play some type of role when altered, there are several other studies as well, clearly bringing to light the complexity involved in the interactions between the immune system and tumor cells. Furthermore, factors within the tumor microenvironment may also contribute to response. Regardless of the many unknowns that still exist, there is great promise in current and future research, which will hopefully lead to better predictors of immunotherapy response and outcome.

Summary

In this quarterly release, CKB-CORE™ includes 20 genes relevant to immuno-oncology (Fig. 1). Users have access to nearly 3,000 gene variants for interpretation, and many lines of preclinical and high level clinical efficacy evidence to help guide treatment decisions. We hope this updated version of CKB CORE™ continues to serve as a valuable resource for your variant interpretation needs, and if you have any questions or comments, please feel free to contact us at ckbsupport@jax.org.

Resources

https://www.fda.gov/drugs

References

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