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Guest Editorial

Pairing Cancer Biomarkers to Biomedicine

On May 23, 2017, the US Food and Drug Administration (FDA) approved pembrolizumab for the treatment of any solid tumors with certain specific genetic features or biomarkers, namely microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This was the first time that the FDA approved a cancer treatment based on a common biomarker, rather than the organ site or histology. Pembrolizumab binds to the programmed death 1 (PD-1) protein, preventing its ligands from binding. The PD-1/ligand interaction causes immune suppression, thus blocking this interaction helps restore the body's immune response against the cancer. Pembrolizumab was previously approved by the FDA for treatment of certain cancer types including metastatic melanoma, metastatic non-small cell lung cancer (NSCLC) and refractory classical Hodgkin lymphoma. It was approved for this new biomarker based indication using the Accelerated Approval pathway, under which the FDA can approve drugs for serious conditions where there is unmet medical need and a drug has certain effects that are reasonably likely to predict a clinical benefit to patients.

Simple genetic tests that allow clinicians to prescribe tailored treatments to cancer patients that take into account their genetic background, are becoming a reality. Theoretically this could allow clinicians to maximize therapeutic efficacy, while minimizing adverse effects. Precision oncology thus holds great promise for cancer research. Important biomarkers for many types of cancer have already been identified, allowing patients to benefit from analysis of their genetic traits. For example, the mutational status of the gene *Kras*, can help predict the efficacy of treatments for metastatic colorectal cancer patients with epidermal growth factor receptor (EGFR) inhibitors. Patients with colorectal tumors expressing wild type *Kras* benefit from cetuximab, an anti-EGFR antibody, while patients with colorectal tumors with mutated *Kras* exhibit resistance to EGFR inhibitors. Likewise, *Braf* mutants are also reported to confer resistance to EGFR inhibitor treatment in colon cancer patients. Checking the mutational status of specific, pertinent genes in patients, could thus help in choosing more effective treatments for individual patients in the clinic.

In most cases, however, the criteria that can predict drug responses are complicated. Finding appropriate and effective biomarkers for treatment is not easy. In cancer immunotherapy, for example, the expression level of programmed death-ligand 1 (PD-L1) is critical for determining the efficacy of treatments with the PD-1 inhibitors like pembrolizumab and nivolumab. A randomized controlled trial published in April 2016 in *The Lancet* showed that pembrolizumab prolonged overall survival in NSCLC patients where at least 50% of tumor cells expressed PD-L1, as determined by immunohistochemistry. However, another randomized clinical trial published in June 2017 in the *New England Journal of Medicine*, found that nivolumab was not associated with longer progression-free survival for late stage or recurrent NSCLC patients with a PD-L1 expression level of 5% or higher. Despite these discrepancies, the FDA recently approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors with certain biomarkers, regardless of tumor site/histology. This decision was based on the observation that the expression level of PD-L1 is correlated with the efficacy of PD-1 inhibitors, and importantly, the levels of PD-1 and PD-L1 are upregulated in the infiltrating lymphocytes of MSI-H-solid tumors.

In a research article published in this issue of *EBioMedicine*, Shin *et al.* observed very different treatment responses to β-catenin inhibitors in patient-derived xenograft (PDX) models of colon cancer. Crucially, the expression levels of β-catenin in individual PDX models seemed to play a role in these differing responses. β-Catenin plays essential roles in the Wnt pathway by interacting with T-cell factor 4 (TCF4) to transcribe oncogenes. A small molecule called HI-B1 was identified as a direct β-catenin inhibitor, and was tested *in vitro* and *in vivo*. Interestingly, a PDX tumor with higher levels of β-catenin expression was more sensitive to HI-B1 treatment, compared to the other tumor with lower expression levels of β-catenin. Although these are preliminary findings, it is hoped that some colon cancer patients may eventually benefit from treatments that specifically inhibit the Wnt/β-catenin pathway, and that β-catenin expression levels could provide an important biomarker that could help determine the therapeutic efficiency of Wnt/β-catenin inhibitors.

Two important questions in the field are, firstly, whether Wnt/β-catenin pathway inhibitors can be effective treatment options against cancer, and secondly, whether we can identify patients mostly likely to benefit from this treatment option. To address the first question, several Wnt inhibitors are being assessed in clinical trials. These include LGK974 (a porcupine inhibitor), OMP131R10 (an anti-R-spondin3 antibody), and Foxy-5 (a Wnt5a mimetic), which are in Phase I clinical trials. The Phase I trial of ipafricept (OMP-54F28), a decoy receptor for Wnt ligands, recently reported promising results and has now moved on to Phase II. To address the second question, retrospective cohort studies analyzing the genetic features of patients and their clinical outcomes will be carried out. At the same time, basic research will continue to elucidate molecular details of the Wnt/β-catenin pathway, as it relates to cancer heterogeneity, and could provide clues for identifying effective drug candidates that could be tested on future patients. Also, improvements in essential diagnostic tools such as liquid biopsies can help assess the genetic backgrounds of patients in a non-invasive manner. Clinically relevant models such as PDX models can also be utilized for preclinical analysis and assessment of potential drug candidates, to advance precision oncology treatment options.

Elucidating different cancers at a molecular level, by studying the myriad of pathways involved, is an expensive and time-consuming

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enterprise. However, this endeavor could provide rich rewards by allowing us to treat individual cancers more precisely. *EBioMedicine* will serve the cancer research community as an important platform for sharing important findings, pairing crucial biomarkers with current and promising treatment options, and to move the field of precision oncology forward.

Disclosure

The β-catenin inhibitor (HI-B1) described in the study was synthesized at The Hormel Institute, University of Minnesota and the author's name (ZD) is on the patent.

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