Editorial

EBV and further emerging directions towards increased precision in gastric cancer treatment

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The treatment of cancer has faced continuous improvement brought by new surgical approaches, as well as by new drugs and therapies, which are leading to unforeseen increments in the overall survival, disease-free intervals, as well the quality of life of patients diagnosed with distinct tumor types. A relatively recent innovation was the development of checkpoint blockage inhibition immunotherapies, a set of powerful approaches used to enhance the immune response, making it capable of recognizing and destroy neoplastic cells (1). However, whereas some patients show exceptionally good and durable responses after the treatment with immune checkpoint inhibitors (ICIs), a significant fraction of subjects have no benefits from these revolutionary, and still expensive therapies (2). In an effort to discriminate ICI-responders from non-responders, scientists have been investigating the complex interplay between host immune system activation, PD-L1 expression, tumor subtypes and other elements such as tumor mutation burden, neoantigen expression, and microsatellite instability, not to mention the immune regulation by the microbiota, pursuing the identification of reliable predictive biomarkers to ICI-response (2,3). However, all these are still insufficient to explain the heterogeneity of response rates seen across distinct tumor sites. The 'a priori' definition patients that may benefit from ICI treatment is still a daunting task.

In this regard, the search for a more precise interventional medicine, where genetic alterations characteristic of each individual are combined with other, extra-host elements, has the potential to be transformative. In most circumstances, the identification of patients that may have a better prognosis, or could benefit from specific therapies, is still a challenge.

According to molecular features, gastric cancer (GC), which is the third cause of cancer-related death worldwide, was classified in 2014 by the TCGA, into four molecular subtypes (4). One of these, the Epstein-Barr virus associated gastric cancer (EBVaGC), appear to determine a better prognosis, although the precise mechanisms still remain elusive (5).

In a previous issue of *Translational Cancer Research*, Xu *et al.* evaluated the potential of transcripts that appear to be induced after EBV-infection, which when evaluated together could be used as a classifier to discriminate GC-patients that would benefit from anti-PD1 immunotherapy (6). The work by Xu *et al.* involved 340 subjects from 3 cohorts, including a total of 96 EBV-positive (EBV^+) cases. The first cohort, from STAD-TCGA was used to determine a set of differentially expressed genes (DEGs) according to EBV status, including 21 EBV^+ and 207 EBV-negative (EBV^-) cases. From this same cohort a larger set of DEGs consisting of 144 immune regulatory genes was selected, including 11 genes with a central role as immune regulator hubs, as determined by in silico analysis of protein-protein interaction networks: *CD8A*,

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CXCL10, *CCR5*, *IFNG*, *CXCL9*, *GZMA*, *GZMB*, *KLRK1*, *TBX21*, *CCL5*, and *CD38*. The second cohort consisted of patients recruited by the authors, including 70 EBV^+ and 70 EBV^- GC samples and allowed the confirmation of the increased expression of these 11 hub genes in EBV^+ cases. However, this finding was only marginally related to patient's better prognosis. Finally, the authors demonstrated in a cohort of 45 GC subjects treated with anti-PD1, including 5 EBV^+ patients, that this 11-genes panel could be used as a classifier to determine individuals more likely to benefit from anti-PD-1 treatment. This finding reinforces previous reports of higher success rates of anti-PD-1 treatment in EBV^+ GC patients (7-10) and further demonstrates the role of EBV-induced alterations that regulate molecules relevant in ICI-therapies. These include diverse elements, varying from EBV-encoded miRNAs that modulate PD-L1 expression and allow immune-evasion (11,12), to increased mutation burden caused by the off-target effects of EBV-induced APOBEC activity (13).

Whereas the indication of a panel of 11 genes represents an important contribution to the field—that still requires further validation in larger and multi-ethnical populations—some questions still linger. For instance, are all these 11 genes necessary for predicting response to ICI? Would other clinical scenarios, including infections with other viruses or microbiome components active in GC subjects, be capable of stimulating the expression of these genes, independently of EBV infections? Could these 11 hub genes be induced after other stimuli, including specific mutation signatures and the subsequent presentation of neoantigens caused by off target effects of EBV-induced APOBEC activation? Would these 11 genes be valuable to discriminate cancer subjects receiving other immunotherapies?

The development of new treatment approaches will continue to improve the survival and the better quality of life of patients and to increase cancer cure rates. Nevertheless, a major challenge to fulfill the expectations of an effective and less aggressive cancer treatment will require the definition of treatment-response biomarkers that, in order to be implemented, will need to be validated in clinical trials comprehending multiple populations that include subjects from diverse ethnical/cultural backgrounds and admixed cohorts. Summing up, the microbiota, including viruses such as EBV and others, must be considered in the management of diverse tumor types, including GC.

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