Viral Therapy Gets Personal: A Potential Gene Signature to Predict Susceptibility to Measles Virus Oncolyis

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Are oncolytic viruses ready for the clinic in glioblastomas (GBMs)? Perhaps this idea, begun by Dr. R. Martuza (1) more than 25 years ago, is on the verge of clinical application (2). In this issue of the Journal, Kurokawa et al. (3) describe, for the first time, a gene signature in patients that might predict tumor susceptibility to measles virus (MV) infection and, on the basis of this signature, a clinically available drug that turns resistant GBMs into susceptible ones.

This study shows the potential power of patient-derived xenografts (PDXs), gene expression analysis, tumor specimens from GBM patients treated with MV, and state of the art biostatistical tools. They derived a 22-gene signature that allowed for pre hoc classification of tumors, and the predictions were experimentally validated using a different cohort. For the experimental validation, the authors used both PDXs and a uniquely available set of surgically resected tumors from glioma patients who received intraslesional injections of MV as part of a phase I clinical trial. Of note, the predictive value of this signature was also tested in ovarian tumors, with promising results, suggesting that this signature captures an underlying biological mechanism that is not confined to GBMs or a specific brain microenvironment, but may be generalizable to many tumor types.

The findings reported by Kurokawa et al. (3) are provocative and interesting for several reasons. First, they generate a tool that may help predict whether an oncolytic virus might benefit an individual patient based on a signature from their own tumor. Second, their analysis provides insight into the biological processes that render tumor cells susceptible to viral infection and oncolysis. Finally, they identify actionable targets such as JAK1, for which inhibitors are clinically available. These inhibitors might ultimately be used clinically to render resistant tumor cells permissive to MV replication and tumor cell death.

The identification of a gene signature predicting susceptibility is an important accomplishment as there are no other reliable biomarkers of response to virotherapy. As the authors describe, determinants of viral entry, such as expression of cellular receptors for MV, do not seem to be a good predictor of viral replication. Assuming that viral replication correlates with superior therapeutic outcomes, this tool has the potential to select patients who are likely to benefit from virotherapy, while sparing other patients futile treatments. To date, the only virotherapy agent approved by the US Food and Drug Administration (FDA) is talimogene laherparepvec (4). This is a genetically modified herpes simplex virus modified to produce Granulocyte Macrophage-Colony Stimulating Factor in infected cells. When administered as a single agent in melanoma patients, talimogene laherparepvec can induce responses in up to 26% of the patients. Moreover, response rates are higher when virotherapy is administered in combination with immunotherapy (reviewed in [5]). It is interesting that there is no signature available to predict which patients might benefit from talimogene laherparepvec.

One salient aspect of this study that is worth emphasizing is the analysis of human tumors that received oncolytic measles virotherapy in vivo as part of a clinical trial. This is the ultimate “experimental model,” which captures the full complexity of human disease in the setting of an immunocompetent organism. As a follow-up to this study, it would be necessary to determine whether increased viral replication translates into superior antitumor efficacy. In other words, does increased intratumoral viral replication lead to a better life or longer survival in these patients? This will undoubtedly be answered in a prospective cohort study from this same group. Validation by an independent group would also be ideal, though there are few other centers investigating MV as an oncolytic agent. The delayed effects of MV oncolytic therapy on the immunological...
properties of treated tumors should also be determined. In particular, a direct assessment of the presence of the components of adaptive immunity, such as T lymphocytes, would help evaluate to what extent a virus-induced antitumor immune response is important for the clinical outcome of virotherapy. A recently published study pointed to an immune-related mechanism as the key factor for the regression of gliomas in a clinical trial of an oncolytic adenovirus (2,6). The authors showed that following intralesional injection, viral replication was detected for a certain period of time but was self-limited. After clearance of the virus, infiltration of immune cells was observed, and clinical responses occurred somewhat later in a pattern that resembled pseudoprogression, which follows some immunotherapies (2). Whether such immune involvement is required for the therapeutic success of MV-based virotherapies remains to be determined. But the results reported by Kurokawa and collaborators (2) highlight the potential delicate interplay between viral replication and the patient’s immune system.

Kurokawa et al. (3) make a case for the tumor cell interferon response as a conditioning factor for viral replication. This notion is supported by other studies (7–9) and would suggest that certain aspects of the immune system may be detrimental to the success of virotherapy. On the other hand, it has been proposed that oncolytic virotherapy can enhance immunotherapy (10–12) and vice versa: immunotherapy can boost the efficacy of oncolytic virotherapy (13–16). One such study shed light on this apparent contradiction: using a preclinical model of oncolytic virotherapy, Fend and collaborators showed that immune checkpoint blockade, IFN-α blockade, and chemotherapy-induced immunogenic cell death potentiated the therapeutic efficacy of vaccinia virus (17). This suggests that very precise interventions on the immune system will be required to boost viral replication without jeopardizing the potential contribution of an antitumor immune response.

An important result of Kurokawa et al.’s study (3) is the identification of an FDA-approved agent (ruxolitinib) that inhibits JAK pathways that may enhance the efficacy of oncolytic MV. They showed that ruxolitinib can reverse the phenotype of tumors that are naturally not permissive to MV replication and proposed that these findings may provide the scientific rationale for combinatorial approaches for tumors that are resistant to MV infection. Further studies will also be required to determine if the effects of ruxolitinib are dependent on inhibition of JAK1, JAK2, off-target effects, or a combination thereof. Considering the central role of the JAK/STAT pathway in the transduction of signals initiated by cytokines, a careful analysis of the effects of ruxolitinib on the performance of cytotoxic T cells will likely be necessary to move forward with multimodal therapy.

This is a promising study that highlights the importance of combinatorial analytics that can be used to select patients who may benefit from an oncolytic virus, and to enhance MV’s effectiveness in less susceptible patients. Is this method ready for the clinic? Not yet. More work is needed to validate the signature and determine its characteristics. However, this study suggests that we could fulfill the promise of personalized oncology using oncolytic viruses in the near future.

Notes

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DAD is an inventor in two provisional patent applications related to Chimeric Antigen Receptors (CARs).

References