DNA-damaging cancer cells to improve virotherapy

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In the current issue of MTO, an interesting work by Koch and colleagues reveals that perturbing the DNA damage response (DDR) signaling pathway enhances the cytotoxic effect of local treatment with CAN-2409, a first-generation adenoviral vector encoding the suicide gene herpes simplex virus thymidine kinase (HSV-tk), which in the presence of ganciclovir causes DNA damage, and immunogenic cell death and that is already in clinical trials in high-grade gliomas.1–3 The authors evaluate the efficacy of ATR/ATM inhibitors in combination with the virus in vitro and in vivo in immunocompetent mouse models to decipher its effect in tumor immune microenvironment using state-of-the-art technologies such as cytometry by time of flight (CyTOF). Gliomas are malignant brain tumors that up to date remain incurable,4 so any advances in the therapeutic management of these tumors are of the utmost importance.

Unfortunately, as 2022 goes by, malignant gliomas are still an unmet clinical need. In the last decades, clinical trials utilizing a plethora of drugs ranging from small molecules to immunotherapies and cell therapies have tried to change the course of this devastating disease. Virotherapy, a class of biotechnology that encircled cytotoxic and immune triggering strategies, has gained momentum in recent years. Specifically, due to the grim prognosis of many types of brain tumors, virotherapy has been evaluated in several clinical trials for these diseases showing that it is safe and displays a degree of efficacy, but the potency of these agents should be improved.

CAN-2409 is a non-replicative adenoviral vector encoding the HSV-tk that will mediate DNA damage in infected cells by conversion of the anti-herpetic pro-drug ganciclovir (GCV) into the genotoxic nucleoside GCV triphosphate. As a result, CAN-2409 plus GCV offers a dual effect stimulating the immune system on one hand and inducing cytotoxicity, on the other hand, with the potential to trigger antitumor mechanisms such as immunogenic cell death.

The use of adenoviruses (Ad) as anti-glioma gene therapy vectors has been widely explored in the past, for instance, to restore the expression of tumor suppressor genes like retinoblastoma (Rb) in malignant cells. However, most attempts failed to achieve long-lasting responses because it is impossible to reach every single tumor cell to obtain a complete response due to the non-replicative nature of these vectors. This is of particular relevance for such infiltrative tumors as malignant gliomas. In addition, the immunogenicity of the adenoviral backbone and leaky expression of viral proteins lead to the destruction of adenovirus-infected cells a few weeks after injection. Therefore, a successful gene therapy strategy must focus beyond the infected tumor cell. In this matter, CAN-2409 represents an interesting approach because of its potential to enhance the antitumor immune response. This virus has already been clinically evaluated as a first-line treatment for malignant glioma followed by the standard of care (SoC) demonstrating an expanded, but not enough, survival compared with SoC alone.

In the current paper, Koch et al. claim and demonstrate that the combination of CAN-2409 with certain DDR blocking agents increases DNA double-strand breaks and prolonged survival in mice bearing high-grade glioma. Interestingly, only ATR inhibition with AZD6738 showed synergy with the virus, while ATM blockade (AZD1390) seems to be counter-productive. The authors do not explore whether these differences are drug or target specific, and more studies are needed.

Figure 1. Increasing virotherapy efficacy by inhibiting the DNA damage response

ATR inhibition results in amplification of adenovirus CAN-2409 efficacy. However, the immune response was dampened with this strategy.
are mandatory to understand and exploit the interaction between adenovirus and DDR inhibition.

The authors nicely showed that by combining this vector with an inhibitor of ATR (AZD6738), the cytotoxic part of the treatment was significantly enhanced. However and somehow unexpected, the immune-boosting properties of the virus were decreased. Previously, treatment of glioma murine models with this virus alone showed a potent immune stimulation accompanying the antitumor effect. In fact, although originally the rationale underlying the implementation of oncolytic viruses was the capability to replicate in and kill cancer cells, the field understood that the immune-activating capabilities of this biotherapeutic was of the utmost importance to achieve antitumor responses in clinical trials. After infecting the cells the viruses activate pathogen and danger recognition signals that trigger inflammation and induce innate and adaptive immune responses. Therefore, combinations that hamper this virus induced-inflammation could be detrimental in the context of efficacy in a clinical trial. Thus, this study underscores the need to conduct preclinical studies in relevant disease models to further understand the implications of this combination and others. This knowledge, in turn, could aid in designing protocols that not only increase the intrinsic cell killing potential of the virus but that positively reinforce the capacity of virotherapy to enhance the antitumor immune effect providing long-lasting and tumor-protective effects.

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