Live vaccines—a short-cut to cancer viro-immunotherapy

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Tumour immunotherapies have been a breakthrough in clinical oncology but only a few patients benefit from this progress. Additional interventions that sensitize immunologically cold tumours for the administration of checkpoint modifiers are urgently needed. In this issue of *EMBO Molecular Medicine*, Aznar et al present the already approved yellow fever vaccine 17D as an oncolytic agent for tumour immunomodulation. In tumour-bearing mice, they demonstrated a convincing synergy of the vaccine with CD137 agonistic antibodies resulting in significantly improved survival.

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See also: MA Aznar et al (January 2020)

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TLA-4 and PD-1/PD-L1 checkpoint immunotherapy has significantly improved long-term survival in metastatic melanoma, and clinical responses have been observed across a broad range of tumour entities. The experience that novel agents are indeed capable of facilitating durable tumour responses in advanced cancers has been paradigm-shifting and fuelled new phantasy for the future of cancer therapy. However, from a more rational perspective, these clinical studies unequivocally demonstrated that only a small subset of patients responds in this spectacular manner, whereas the vast majority does not benefit.

Some characteristics have been linked to tumour sensitivity to checkpoint immunotherapy. For example, PD-L1 expression in tumours indicating immune activity, or a high mutational burden as a source of neoantigens, increases the probability that a tumour will respond to therapy. However, regarding the enormous genetic diversity of tumours and the complex array of mechanisms a tumour can employ to keep the host’s immune defence in check, it is much more difficult to understand why tumours do not respond.

Critical steps to establish antitumour immunity include the release of tumour antigen, antigen presentation and T-cell priming. Furthermore, migration to the tumour and infiltration of tumour tissue are required that T cells recognize and kill tumour cells again to restart the cancer immunity cycle. Tumours can be classified according to essential stages where this cycle might be dysfunctional (Chen & Mellman, 2017). While “inflamed” (or “hot”) tumours show signs of immune activity and have highest probability to respond to checkpoint inhibitors, immune-inactive (“cold”) tumours are either “immune-excluded” due to defects in trafficking and tumour infiltration or “immune-desert” with dysfunctional antigen presentation and T-cell priming. The PD-1/PD-L1 axis is therefore not unique in restraining the antitumour response. In these cold tumours, other critical dysfunctions need to be addressed to keep the cancer immunity cycle going. Consequently, there is an intense search for interventions or agents that provide essential help to convert cold tumours into hot ones and enable effective checkpoint immunotherapy.

Oncolytic viruses that preferentially replicate in and lyse tumour cells are promising tools in this regard. A mutant herpesvirus, T-Vec, has been approved in 2015 following positive clinical trial data (Andtbacka et al, 2015). In general, viral oncolysis leads to effective release of tumour antigen and T-cell priming. Virus-induced tumour inflammation allows for T-cell infiltration and further killing of cancer cells. Since these functions positively affect the cancer immunity cycle at critical stages, oncolytic viruses are assumed to be ideally suited to initiate and to propel the cycle. In experimental models, oncolytic viruses synergize with systemic CTLA-4 or PD-1 blockade to achieve effective antitumoural immunity (Zamarin et al, 2014; Woller et al, 2015). Clinical studies using T-Vec and the PD-1 inhibitor pembrolizumab are ongoing (Ribas et al, 2017).

However, regarding all needed basic research investigations, preclinical development, toxicology studies and regulatory affairs, it is a tedious process to carry an oncolytic virus from the hypothesis to clinical trials, which can easily consume half of the professional lifetime of a researcher. Therefore, a smart idea is to exploit already approved live virus vaccines, which can exert critical functions of a bona fide oncolytic virus (Fig 1).

In the current issue of *EMBO Molecular Medicine*, Aznar et al (2019) have repurposed the established yellow fever vaccine 17D for tumour immunotherapy. The live, attenuated virus strain 17D is used as a prophylactic vaccine that provides potent protection against the wild-type virus. Aznar et al demonstrated that 17D replicates in and kills a broad range of human and mouse tumour cells thus qualifying the vaccine as an oncolytic agent. Furthermore, they showed in syngeneic murine models bearing subcutaneous tumours that intratumoural application of the vaccine did not only delay the growth of treated
tumours but also yielded an abscopal effect on contralateral, untreated tumours in a CD8 T-cell-dependent manner. This observation demonstrated that the vaccine induced antitumour CD8 T cells, an essential step for long-term responses and for the success of immune checkpoint modifiers. Accordingly, the authors investigated a possible synergy triggered by these interventions. Whereas a rather modest enhancement of PD-1 checkpoint therapy was observed, the synergy with an agonistic CD137 antibody was striking and led to dramatically improved survival. These results confirm that 17D can be successfully used to prepare a tumour for administration of immune checkpoint modifiers. The findings are consistent with previous results showing that a genetically engineered oncolytic vaccinia virus in combination with a CD137 antibody was more effective in mice with preexisting immunity. The underlying mechanisms of these counterintuitive findings remain enigmatic and deserve further investigations.

In summary, Aznar et al showed that the 17D vaccine is a promising “ready-to-use” oncolytic agent that would strengthen the effect of checkpoint modifiers and may significantly accelerate the establishment of viro-immunotherapy.

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