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Press information

A Vaccine to Overcome Immunotherapy Resistance

For patients with metastatic cancers such as those of the lung or bladder, or melanoma, immunotherapy represents a genuine therapeutic revolution. Unfortunately, it is only effective in 10 to 25% of those eligible to receive it. Researchers from the Cancer Research Center of Lyon (CRCL - Inserm / CNRS / Université Claude Bernard Lyon 1 / Léon Bérard cancer center) and the Léon Bérard and Gustave Roussy cancer centers have shown that a commercially-available vaccine can overcome resistance to immunotherapy. Their study, published in *Science Translational Medicine*, shows that not only can gastroenteritis vaccines induce the immunogenic death of cancer cells *in vitro*, but also that combining them with immunotherapy triggers a potent anti-tumor immune response *in vivo* – where immunotherapy alone had failed.

How can we overcome resistance to immunotherapies, so that as many patients as possible can benefit from these innovations? A team of researchers led by Aurélien Marabelle (Gustave Roussy and Léon Bérard cancer centers), Christophe Caux (Inserm U1052) and Sandrine Valsesia-Wittmann (Léon Bérard cancer center - Inserm UA8) has studied this question. Their idea was to use vaccines to render immunotherapy effective in those cancers in which it has been unsuccessful so far. Then, the aim was to increase the number of patients who could benefit from such therapy in cancers where it has already been shown to be effective.

"In this study, our research team looked at pediatric tumors such as neuroblastomas, which are aggressive cancers that do not respond to existing immunotherapies such as anti-PD(L)1 and anti-CTLA4. In our aim to transform how they respond to immunotherapy, we used various vaccines as sources of pro-inflammatory elements because pathogens such as viruses are able to directly stimulate innate immune receptors" explains Marabelle.

Gastroenteritis vaccines

To start with, the researchers tested 14 commercially available vaccines (BCG, Cervarix, TicoVac, etc.) *in vitro* for their ability to stimulate these innate immune receptors. Out of the vaccines tested, those used against rotavirus (Rotarix, Rotateq), the virus responsible for gastroenteritis, were identified as having strong pro-inflammatory properties. Unexpectedly, they observed that these vaccines have an oncolytic action – namely the ability to preferentially infect and kill cancer cells in relation to normal cells and induce what is known as immunogenic death.

Vaccine plus immunotherapy – a potent combination

The researchers also conducted *in vivo* testing of the most pro-inflammatory vaccines using models of neuroblastoma in which the anti-PD(L)1 and anti-CTLA4 immunotherapies are ineffective in humans. This involved injecting these vaccines either systemically or intratumorally (directly into the tumors).

They observed that when the rotavirus vaccines were injected intratumorally, some of the tumors disappeared. When they then administered the vaccine in combination with anti-PD(L)1 or CTLA4 immunotherapies, all of the tumors disappeared.

While the tumors usually do not respond well to either of these treatments used alone, combining them generates a strong systemic antitumor immune response capable of eradicating both injected and non-injected tumors. "*Our findings show that the rotavirus strains contained in gastroenteritis vaccines can make usually naturally-resistant tumors sensitive to immunotherapy*", highlights Caux.

The researchers also sought to explain how the rotaviruses exert a stimulant effect on the immune system. They showed that the activation of an innate immune receptor known as RIG-I (*retinoic acid induced gene 1*) was essential for the synergistic effect of the intratumoral rotaviruses with the immunotherapies. "*The findings of this study provide a strong scientific rationale in favor of the development of intratumor immunization strategies for immunotherapy-refractory cancers, particularly in pediatric oncology but also in adults*," concludes Valsesia-Wittmann.

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Sources

Repurposing Rotavirus Vaccines for Intratumoral Immunotherapy can overcome Resistance to Immune Checkpoint Blockade

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<https://stm.sciencemag.org/content/11/515/eaat5025>

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