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Cover Story

Combined therapy of imatinib and an anti-CTLA4 immune-checkpoint inhibitor

Cancer immunotherapy that triggers the immune system to eradicate tumors has garnered great attention in recent years. Various immune-checkpoint inhibitors, such as antibodies against programmed death protein 1 (anti-PD1) and cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA4), have been developed to achieve a more active antitumor immune response. The presence of regulatory T (Treg) cells, specifically in the tumor microenvironment, greatly impedes the efficacy of cytotoxic T lymphocyte (CTL)-induced antitumor effect, and thus, is a predictor of poor prognosis and reduced survival [1]. Hence, targeting the Treg cells in the tumor microenvironment and inhibiting their suppressive effects on CTLs have great potential in activating antitumor immunotherapy.

In this issue, Professor Jong Oh Kim and his team have described the development of Treg cell-targeted, imatinib-loaded nanoparticles which, in combination with an anti-CTLA4 immune-checkpoint inhibitor, hinder the suppressive function of Treg cells and help enhance the $CD8^+$ T cell-induced antitumor effect. They utilized a truncated sequence of LyP1 (tLyp1)-modified hybrid nanoparticles (tLyp1-hNPs) to encapsulate imatinib, a drug that could impair the suppressive function of Treg cells at a lower dose, into PLGA nanoparticles. LyP1 is a peptide that specifically binds to tumor and endothelial cells of tumor lymphatics in certain tumors [2]. The tLyp1-hNPs deliver imatinib to Treg cells via the neuropilin-1 (Nrp1) receptor that is highly expressed on Treg cells [3]. Moreover, an *in vivo* antitumor study has shown that the anti-CTLA4 antibody further inhibits the suppressive function of Treg cells and achieves a synergistic antitumor effect in combination with tLyp1-hNPs. Unlike other cancer immunotherapies that rely on delivering imatinib to tumor cells, the strategy adopted by the Kim group focuses on specific immune cells in the tumor microenvironment to remove the barriers for CTL expansion. The group has demonstrated that tLyp1-hNPs serves as a good carrier for Treg cell targeting, and that the release of imatinib from tLyp1-hNPs is capable of inhibiting Treg cells. The *in vivo* study has shown that tLyp1-hNPs decrease the number of intratumoral Treg cells, which consequently boosts the activation of antitumor $CD8^+$ T cells, contributing to tumor inhibition. The Kim group's findings indicate that modulating Treg cell function in the tumor microenvironment by imatinib-loaded, Treg cell-targeting nanoparticles plus an immune-checkpoint inhibitor (anti-CTLA4) is an effective strategy for cancer immunotherapy.

Although the strategy of initiating antitumor immunotherapy by regulating the effects of intratumoral Treg cells in a mouse model is promising, more studies are needed before initiating a clinical study. For example, Treg cell accumulations were quite different in different types of cancers and in different patients. More data should be collected on Treg cell numbers before designing a precise individual therapy. The *in vivo* antitumor study demonstrates the potential of the Kim group's strategy to slow down tumor growth, i.e., the tumor volume decreased most by administration of both hNPs and an antibody. Such results, however, have been obtained by numerous other nanoparticle formulations over the last few decades with no clinical relevance, and thus, it is difficult to conclude that the results in the study by the Kim group would make a difference in clinical studies. The approach described by the Kim group, however, is a step forward in developing effective anti-tumor formulations. Many different approaches need to be tested until an effective one is found. For a disease as difficult to treat as cancer, the best way to find an effective treatment is to test as many different approaches as possible. The Kim group's approach of combining imatinib and an anti-CTLA4 immune-checkpoint inhibitor can be expanded to include other therapeutic methods, such as surgery or radiation therapy. Even if the efficacy may not be improved over the existing treatment methods, it would be worthwhile, if the safety is increased. The Kim group's approach certainly increases the safety, as the nanoparticle formulation enhanced the delivery of imatinib to the tumor while reducing the distribution to other organs in the body.

References

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