Leveling cancer with IL-15

By Kai-Jye Lou, Senior Writer

Initial excitement about using IL-15 as a therapeutic in cancer has been tempered by substantial delivery and efficacy issues. Now, data from an **Institut National de la Santé et de la Recherche Médicale**—led team showing that IL-15 stimulates T cell proliferation inside tumors suggests that the cytokine could help boost the potency of checkpoint inhibitors and other immunotherapies that harness T cells to attack cancer cells.¹

The data also highlight IL-15 as a potential prognostic biomarker for predicting patient outcomes in colorectal cancer and other malignancies.

IL-15 is an immunostimulatory cytokine that promotes the proliferation of various immune cell populations by activating a dimeric receptor complex on immune cells composed of subunits shared with the IL-2 receptor.

According to Peter Rhode, VP of R&D at cancer company **Altor BioScience Corp.**, interest in developing IL-15 as an immunotherapy for cancer was first sparked over five years ago, when the cytokine was viewed as a potential successor to IL-2-based immunotherapies.

Although both cytokines activate similar downstream pathways because of the shared receptor subunits, IL-15 was perceived as a safer alternative to IL-2 based on animal data suggesting decreased toxicity.²

However, according to Thomas Waldmann, chief of the metabolism branch at the **National Cancer Institute** and co-discoverer of IL-15, concerns related to translation of animal data to humans and delivery difficulties hampered its clinical development. His group and other groups are still working to resolve those problems.

One approach has been to engineer molecules that combine IL-15 and the IL-15 receptor α -chain (IL-15RA) to increase the potency of the immune response.

One of Altor's lead compounds, ALT-803, is an IL-15-mutant agonist complexed to an Fc fusion protein of IL-15RA. The product is in Phase I/II trials for metastatic melanoma and hematologic malignancies.

Now, a large-scale association study of colorectal cancer tumors led by Jérôme Galon at the Institut National de la Santé et de la Recherche Médicale (INSERM) has provided patient data highlighting the importance of IL-15 to patient outcomes and the proliferation of various immune cell populations in tumors.

Galon is a research director at INSERM and head of the institute's Laboratory of Integrative Cancer Immunology.

Galon's aim was to unravel the complex roles of cytokines in regulating the immune response inside tumors that helps control their growth.

His team had previously shown that the number of infiltrating cytotoxic and memory T cells in tumors could predict patient outcomes with greater accuracy than conventional tumor-staging approaches.³⁻⁶

Higher densities of those immune cells at the centers and invasive margins of tumors correlated with better disease outcomes and increased survival, especially in colorectal cancer.

However, the underlying biological factors influencing the levels of these infiltrating immune cell populations in tumors were poorly understood. Several genomic and expression changes in cytokines had been linked to colorectal cancer tumor progression and recurrence, whereas other cytokines showed no association.

That led Galon and colleagues to design a comprehensive analysis of cytokines in a large number of colorectal cancer tumors to identify which cytokines might be altered and what role they play in the intratumoral immune reaction.

The researchers assessed expression of 59 cytokines or their receptors in samples from multiple cohorts of patients with colorectal cancer. They found that patients with tumors containing an *IL-15* gene deletion had lower levels of B and T cell proliferation in the tumor microenvironment than patients without the deletion.

In samples from patients with high *IL-15* expression, increased densities of proliferating T and B cells were seen in both the invasive margins and center of the tumor compared with those in samples from patients with low *IL-15* expression.

Overall, patients with low IL-15 levels—including those without an *IL-15* deletion in the tumor—had increased risk of tumor recurrence and decreased survival compared with patients with high IL-15 levels.

The researchers also showed that in colorectal cancer tissue samples, incubation with IL-15 induced proliferation of T cell populations.

Mechanistically, the results suggest that IL-15 stimulates T cells and thus confirm the cytokine's role as a key mediator of the immune response in the tumor microenvironment. Practically, the data position IL-15 as a robust predictor of patient outcomes in colorectal cancer.

Results were published in *Science Translational Medicine*.

“The results suggest that IL-15-based therapies could be effective in providing antitumor activity, at least for those patients who have reduced IL-15 expression at the tumor site.”

—Peter Rhode,
Altor BioScience Corp.

“Our work provides one mechanism explaining the difference in T cell levels we see in patient tumors that translate into differences in clinical outcomes.”

—Jérôme Galon,
Institut National de la Santé et de la Recherche Médicale

Figure 1. Bolstering cancer immunotherapy with IL-15. (I) IL-15 is an immunostimulatory cytokine that typically is found pre-bound to the IL-15 receptor α -chain (IL-15RA) on antigen-presenting cells (APCs) such as dendritic cells. These APCs display IL-15 to a heterodimeric receptor complex on T and NK cells to induce their proliferation.

The receptor complex is composed of the IL-2 receptor β -chain (CD122; IL2RB) and IL-2 receptor γ -chain (CD132; IL2RG). IL-15 also inhibits apoptosis pathways in the various leukocyte populations, resulting in more persistent immune cells.

Candidate therapies that stimulate IL-15 activity can potentially bolster the efficacy of cancer immunotherapies.

One potential combination is with checkpoint inhibitors such as the anti-programmed cell death 1 (PDCD1; PD-1; CD279) mAbs, which block the interaction between PD-1 and programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1). The combination could yield a larger and more persistent pool of immune cells available to attack cancer cells and thus could result in a more robust antitumor response.

(II) Without IL-15 stimulation, fewer immune cells are around to attack cancer cells after treatment with a checkpoint inhibitor.

Beyond prognostics

Although Galon's study establishes IL-15 as a prognostic biomarker in colorectal and other cancers, it also provides new arguments to further develop the therapeutic potential of the cytokine.

According to Galon, the study suggests that IL-15 might be the missing mechanistic link for correlations seen in the clinic between T cell levels and patient outcomes.

"Our work provides one mechanism explaining the difference in T cell levels we see in patient tumors that translate into differences in clinical outcomes," he said.

Galon added that the results could help identify potential patient populations that would respond to IL-15-based immunotherapies. These could include patients with tumors containing a defect in IL-15 or those who have lower-than-average numbers of infiltrating T cells, he said.

Rhode agreed that the findings could support an IL-15-targeted therapy for specific patient populations.

"The results suggest that IL-15-based therapies could be effective in providing antitumor activity, at least for those patients who have reduced IL-15 expression at the tumor site," he said.

In addition, the results further strengthen IL-15's position relative to IL-2.

"Both cytokines seem to act through the same receptor but trigger a different response, with IL-15 inducing a stronger proliferative response than IL-2," Rhode told *SciBX*.

Novartis AG markets Proleukin aldesleukin IL-2 for metastatic melanoma and renal cell carcinoma (RCC). **Eisai Co. Ltd.** markets Ontak denileukin diftiox for cutaneous T cell lymphoma (CTCL). Proleukin and Ontak both carry black box warnings for serious adverse effects such as capillary leak syndrome.

Moreover, according to both Galon and Rhode, the cytokine's ability to stimulate T cell proliferation suggests that IL-15 immunotherapies might work synergistically with various cancer immunotherapies, such as those that block immune checkpoint proteins (see Figure 1, "Bolstering cancer immunotherapy with IL-15").

Immune checkpoint proteins, such as CTLA-4 (CD152) and programmed cell death 1 (PDCD1; PD-1; CD279), act as regulatory controls to dampen excessive T cell activation and prevent autoimmunity. However, tumor cells are known to express checkpoint proteins to evade the host immune system.

“Checkpoint inhibitor therapies initiate a T cell attack against cancer cells. Adding IL-15 can help boost the proliferation of these T cells,” said Galon.

Bristol-Myers Squibb Co. markets the anti-CTLA4 mAb Yervoy ipilimumab for metastatic melanoma. Yervoy is the first checkpoint inhibitor to reach the market.

The two most advanced anti-PD1 mAbs are nivolumab from Bristol-Myers and partner **Ono Pharmaceutical Co. Ltd.** and MK-3475 from **Merck & Co. Inc.**

Nivolumab is in Phase III testing for metastatic melanoma, non-small cell lung cancer (NSCLC) and RCC. Ono submitted an NDA in Japan for nivolumab to treat melanoma last December.

MK-3475 is in Phase III trials for advanced melanoma, for which it has breakthrough therapy designation from the FDA. It is in Phase II/III testing for NSCLC and Phase I/II trials for RCC. Merck began submission of a rolling BLA for MK-3475 to treat advanced melanoma in January.

Galon told *SciBX* that his group plans to develop mouse models to evaluate how manipulating IL-15 signaling affects tumor growth. He said that some of these studies will include evaluation of IL-15 in combination with checkpoint inhibitors.

INSERM has filed a patent covering an immune gene signature

for predicting prognosis of patients with cancer and for tumor classification. The signature includes IL-15.

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COMPANIES AND INSTITUTIONS MENTIONED

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