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NEWS AND COMMENTARY

**Boosting the power of cytotoxic lymphocytes**

# Cancer-killing, decoy-resistant interleukin-18

Kyohei Nakamura, Tobias Bald & Mark J Smyth

QIMR Berghofer Medical Research Institute, Herston, QLD 4006, Australia

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Cytokine therapies for advanced cancer have a long history of modest effects and dose-limiting toxicity. Interleukin-18 (IL-18) is a cytokine with tumor-suppressing and tumor-promoting functions depending on the immune cell context. A limitation to the impact of IL-18 on cytotoxic T-cell and natural killer (NK) cell effector function is its high-affinity decoy receptor IL-18-binding protein (IL-18BP) that is upregulated in diverse cancers. In a recent issue of *Nature*, Zhou *et al.*[1] engineered a decoy-resistant IL-18 (termed DRIL-18) that maintains IL-18 function, evading tumor-derived IL-18BP, expanding stem-like precursor T cells in tumors and exhibiting potent antitumor T-cell activity. This work indicates just how much IL-18BP-mediated negative regulation acts as tumor barrier.

Immune checkpoint blockade and adoptive T-cell therapies are now well-established cancer treatments, but the latter had its genesis in conjunction with the very earliest cytokine-based cancer immunotherapy more than 35 years ago.[2,3] Despite significant efforts being made to harness antitumor immunity by cytokines, only recombinant IL-2 (rIL-2) and interferon-alpha (IFNα) have received Food and Drug Administration approval as cancer therapies.[4] Insufficient single-agent activities and dose-limiting toxicities have acted as major barriers for clinical translation of cytokine therapies. However, in the era of new immunotherapies with advanced structural analysis and high-throughput genetic engineering, the adjuvant effects of cytokines have been re-evaluated, and various new approaches are actively being developed. These include tumor-targeted delivery of immunocytokines (antibody–cytokine fusion proteins),[5] a mutant IL-2 preferentially activating cytotoxic lymphocytes[6] and cytokine-secreting chimeric antigen receptor T cells.[7]

IL-18 was originally identified as an IFNγ-inducing factor. Indeed, IL-18 stimulates IFNγ production from NK cells and T helper type 1 cells, in particular in remarkable synergy with the highly potent and toxic cytokine IL-12.[8] IL-18 is a member of the IL-1 superfamily of cytokines, and its release is regulated by caspase-1 or caspase-8.[8] Upon binding of IL-18 to the IL-18 receptor complex composed of α-chain (IL-18Rα) and IL-18 receptor complex composed of β-chain, cytoplasmic Toll/IL-1 receptor domains interact with myeloid differentiation primary response 88, leading to a downstream signaling cascade. While IL-18R–myeloid differentiation primary response 88 proinflammatory signaling has various tumor-promoting functions including angiogenesis, tumor invasiveness and immunosuppression under physiological concentrations of IL-18,[9,10] therapeutic high doses of rIL-18 have shown strong antitumor activities in preclinical models by stimulating cytotoxic lymphocytes to enhance IFNγ secretion, granule-mediated cytotoxicity and Fas ligand expression.[11,12] However, clinical trials assessing rIL-18 have shown negligible clinical benefits as monotherapy in patients with advanced cancers, despite good tolerability.[12]

Physiological regulation of IL-18 activity is primarily mediated by high-affinity neutralizing protein, called IL-18BP.[8] To overcome the negative regulation by IL-18BP, Zhou *et al.*[1] performed yeast display screening of IL-18 variants, and identified a mutant form of IL-18 with binding activity to IL-18Rα, but not to IL-18BP. Indeed, this DRIL-18 showed superior antitumor efficacies as both monotherapy and in combination with anti-PD-1, compared with conventional rIL-18. Consistent with the fact that $CD8^+$ T cells and NK cells express high levels of IL-18Rα, both cell types were implicated in DRIL-18-mediated antitumor immunity. Mechanistically, DRIL-18 treatment induced high infiltration of polyfunctional $CD8^+$ T cells and $TCF1^+$ stem-like CD8 T cells with reduced frequencies of $TOX\text{-}1^+$-exhausted CD8 T cells. Moreover, DRIL-18 monotherapy showed excellent preclinical efficacy against major histocompatibility complex class

**Correspondence** Mark J Smyth, QIMR Berghofer Medical Research Institute, 300 Herston Road, Herston, QLD 4006, Australia. E-mail: mark.smyth@qimrberghofer.edu.au

I-deficient tumors that were refractory to the combination therapy of anti-PD1 and anti-CTLA-4.[1] DRIL-18 treatment also triggered high infiltration of poly-functional NK cells, with increased expression of IFNγ and cytotoxic granules. Collectively, DRIL-18 demonstrated remarkable preclinical antitumor efficacies by dramatically improving the effector functions of cytotoxic lymphocytes, which cannot be achieved by conventional rIL-18 treatment (Figure 1).

It is well-appreciated that NK cells critically contribute to control of metastasis by elimination of disseminated tumor cells,[13] but growing body of evidence suggests that NK cells also play an important role in immune checkpoint blockade therapy.[14] Although anti-PD-1 blockade predominantly targets T cells, high infiltration of NK cells is associated with good responsiveness to anti-PD-1 blockade in patients with melanoma, which is explained by NK cell-mediated stimulation of dendritic cells.[15] In addition, missing-self recognition by NK cells might play a crucial role for controlling tumor cells, given that loss of major histocompatibility complex class I in tumor cells remains a major barrier for T-cell-based immunotherapy.[16] In this context, potent impacts of DRIL-18 on both CD8 T cell and NK cell activities might have important implications for immunotherapies including, but not limited to, anti-PD-1 blockade. It will be intriguing to know whether the DRIL-18 can augment therapeutic blockade of NK-cell checkpoint molecules such as the CD94/NK group 2 member A and killer inhibitory receptor, both of which are actively being tested in clinical trials.[14] More recently, anti-CD19 chimeric antigen receptor-NK cell therapy has shown promising clinical responses with a good safety profile in patients with B-cell malignancies.[17] DRIL-18 might be able to improve the effectiveness of chimeric antigen receptor-NK cell therapy. Of note, IL-18BP is not the only negative regulator for IL-18 activities. IL-1 receptor 8 was recently identified as an inhibitory orphan receptor that is clustered with IL-18Rα on NK cells.[18] Indeed, IL-1 receptor 8-deficient NK cells display prolonged activation in response to IL-18,[18] suggesting that IL-18 activity is regulated by two processes: neutralization by IL-18BP and negative signaling by IL-1 receptor 8. It is possible that co-targeting two regulators (i.e. the combination of DRIL-18 and anti-IL-1 receptor 8 blockade) might maximize antitumor immune responses by NK and T cells. Overall, the remarkable immuno-stimulatory effects of DRIL-18 have broad translational implications, and further studies are warranted to determine the best combination approaches.

For clinical translation of DRIL-18, immune-related adverse events remain a concern to be addressed. As observed in IL-18-transgenic mice, Fas/Fas ligand-mediated hepatitis may be a possible DRIL-18-related toxicity.[19] Elevated levels of free IL-18 (IL-18BP-unbound IL-18) are frequently observed in patients with adult-onset Still's disease, a rare systemic inflammatory disease which shares the similar pathophysiology with cytokine release syndrome and macrophage activation syndrome. Recently, Girard-Guyonvarc'h et al.[20] demonstrated that mice deficient for IL-18BP show hyperinflammatory phenotypes upon Toll-like receptor-9 stimulation, leading to the

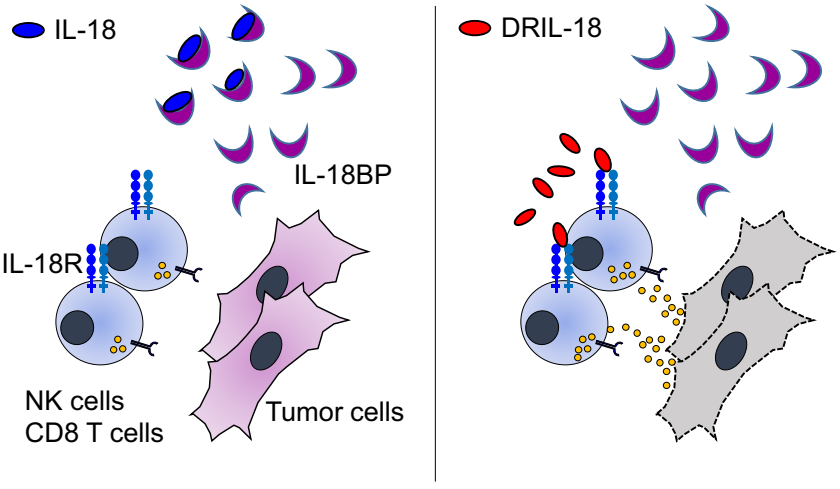


**Figure 1.** Decoy-resistant interleukin-18 (DRIL-18) augments antitumor immunity. IL-18-binding protein (IL-18BP) is abundantly released in the tumor microenvironment. IL-18BP critically impedes therapeutic benefits of conventional recombinant IL-18 (left), but DRIL-18 can potently stimulate antitumor immunity by cytotoxic lymphocytes (right). IL-18R, interleukin-18 receptor; NK, natural killer.

development of severe macrophage activation syndrome in an IL-18- and IFNγ-dependent manner. Compared with chimeric antigen receptor-T-cell therapies and bispecific T-cell engagers, it is not common to observe cytokine release syndrome/macrophage activation syndrome in patients treated with immune checkpoint blocking antibodies, but the risk might be increased by prolonged DRIL-18 treatment. Thus, careful optimization of scheduling and dosage is warranted. Alternatively, targeted delivery of DRIL-18 into tumor tissues might diminish systemic off-target effects. Further, as seen for other pro-inflammatory cytokines, IL-18 has both protumor roles and antitumor roles depending on the context.[9,10] Thus, it is critical to carefully select tumor types to test the efficacy of DRIL-18 in the clinic. This work clearly highlights that IL-18BP acts as a soluble checkpoint regulating IL-18 activity on cytotoxic lymphocytes, and that DRIL-18 is a promising therapeutic agent to boost cancer immunotherapy.

## CONFLICT OF INTEREST

MJS has research agreements with Bristol Myers Squibb and Tizona Therapeutics and is a member of the Scientific Advisory Board (SAB) for Tizona Therapeutics and Compass Therapeutics.

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