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Editorials

Are we Able to Harness the Immunomodulatory Power of Cytokines for Novel Autoimmune Disease Treatments?

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Since the end of the 1970s, interleukin 2 (IL-2) has been known as a key player in T cell expansion/activation (Watson *et al*., 1980). In the late 1980s, some groups used IL-2 to stimulate the immune systems of tumour patients (Jacobs *et al*., 1986). The idea seemed brilliant and several attempts were made, but the results were disappointing (Lim *et al*., 1992; Procopio *et al*., 2011). Nowadays, is difficult to find IL-2 as a first-line tumour treatment.

The reason for the disappointing results came to light some years ago. IL-2 is crucial, not only for the expansion of effector T cells (Teff), but also for the expansion of regulatory T cells (Tregs), lymphocytes that are able to inhibit the activation/expansion of Teff (Boyman and Sprent, 2012; Liao *et al*., 2013; Waldmann, 2006). Indeed, more recent studies attempted to use IL-2 to repress the immune response in patients with autoimmune disorders and graft-versus-host disease (von Spee-Mayer *et al*., 2015; Hartemann *et al*., 2013; Matsuoka *et al*., 2013). However, IL-2's paradoxical effects on immune cell homeostasis have limited its clinical utility. Delivery of the cytokine can either ameliorate or exacerbate the disease depending on several factors including genetics and epigenetics, immune system maturation, disease activity and drug dosage and administration schedule. In this context, a key question is if it is possible to decouple the immunostimulatory and immunosuppressive effects of IL-2.

In the last 10 years, some members of the Tumour Necrosis Factor (TNF) super family have been demonstrated as co-stimulatory molecules. In particular, triggering OX40 (CD134, TNFRSF4), 4-1BB (CD137, TNFRSF9) and glucocorticoid-induced TNFR-related protein (GITR; CD357, TNFRSF18) together with T Cell Receptor (TCR) favours $CD4^+$ and $CD8^+$ T cell proliferation (Kober *et al*., 2008; Croft, 2014; Watts, 2005; Nocentini *et al*., 2012; Ronchetti *et al*., 2007). Furthermore, triggering OX-40 and GITR on Tregs inhibits their activity (Voo *et al*., 2013; Bianchini *et al*., 2011; Ronchetti *et al*., 2004) and GITR has pro-inflammatory activity in several murine models (Nocentini and Riccardi, 2009; Galuppo *et al*., 2011; Ronchetti *et al*., 2011). GITR-mediated immune system stimulation in tumours can lead to their clearance in murine models and is under phase I study in patients with melanoma (Nocentini *et al*., 2012; 2015). However, the long-term effects of GITR triggering by anti-GITR Ab are unknown.

Like IL-2, GITR triggering also favours Treg expansion with immunosuppressive effects in transgenic murine models (van Olffen *et al*., 2009; Carrier *et al*., 2012). Once again the question is: Is it possible to decouple GITR's immunostimulatory and immunosuppressive effects with smart drugs?

The stakes are high. Currently used immunosuppressive treatments are able to control autoimmune disease in many cases, with attenuated inflammation and symptom improvements. However, disease progresses during treatment in a high percentage of patients, even more so when drug treatment is halted (e.g., due to adverse effects). If new treatments could stably expand the Treg population in these patients, it could lead to long-term or even permanent remission.

In the last 10 years, encouraging results in mouse models seem to indicate that we may be able to control the kind of the effect. Studies using IL-2 complexed with two antibodies (Abs) demonstrated that IL-2's effects could be directed towards one cell type. In particular, IL-2 conjugated with JES6-1 Ab preferentially induces Treg cell proliferation whereas IL-2 conjugated with S4B6 Ab preferentially induces Teff proliferation (Boyman *et al*., 2006). Spangler *et al*. (2015) recently characterized IL-2/JES6-1 and IL-2/S4B6 complexes and demonstrated that JES6-1 Ab blocks the interaction between IL-2/IL-2Rβ and IL-2/IL-2Rγ and lowers the affinity of IL-2 for IL-2Rα. Therefore, only those cells that express high levels of IL-2Rα (i.e., Tregs) are activated by the IL-2/JES6-1 complex. Conversely, IL-2/S4B6 complex favours IL-2/IL-2Rβ interaction, stimulating cells that express high levels of IL-2Rβ (i.e., Teff). Although studies with JES6-1 and S4B6 have been performed in mice, they reveal the possibility of using a similar strategy in humans.

Studies on murine GITR have demonstrated that different antibodies can preferentially stimulate Teff or Treg expansion/activation so that the former can favour tumour rejection (Nishioka *et al*., 2008). The rationale for the unique activities of these antibodies is not clear, but data demonstrate that GITR triggering by different molecules can preferentially co-stimulate either Teff or Tregs (Petrillo *et al*., 2015). Moreover, patients with autoimmune diseases show a milder phenotype when $GITR^+$ Tregs are expanded, suggesting that GITR is crucial in Treg expansion, which can counteract autoimmune disease progression (Alunno *et al*., 2013; Nocentini *et al*., 2014; Ronchetti *et al*., 2015; Gerli *et al*., 2009).

Conclusion

We firmly believe that in the near future it will be possible to treat patients with autoimmune diseases in a way that specifically facilitates Treg expansion and allows long-term disease remission. The last mile must be urgently walked.

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Ethics

The authors declare they do not have any conflict of interest concerning the matter of the Editorial.

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