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The rise of IL-2 therapy — a picture beyond T_{reg} cells

Zhanguo Li, Jing He and Di Yu

We thank Dr Jens Y. Humrich and Dr Gabriela Riemekasten for their interest in our study[1], which they discussed in a News & Views commentary (Humrich, J. Y. & Riemekasten, G. The rise of IL-2 therapy — a novel biologic treatment for SLE. *Nat. Rev. Rheumatol.* **12**, 695-696; 2016)[2]. We are particularly excited that more clinical and basic scientists are working to understand the mechanisms of action underpinning the promising 'experimental medicine' observations of low-dose IL-2 therapy in systemic lupus erythematosus (SLE). After reading the commentary, however, we noted that there was a misunderstanding of the research design of our study. We hereby provide further clarification.

The inspiration for this study of low-dose IL-2 therapy in autoimmune diseases came from our previous publication showing that hyperactivation of follicular helper T (T_{FH}) cells correlated with disease activity in patients with SLE and rheumatoid arthritis[3]; this is a different focus from the studies of low-dose IL-2 therapy, which centred on regulatory T (T_{reg}) cells[4–6]. Although IL-2 had been shown to suppress T_{FH} and type 17 T helper (T_H17) cells in mouse models[7,8], its effects in human cells were unknown. We started our study in 2013, with clinical responses as the primary end point and an emphasis on immunological responses, including changes in T_{FH}, T_H17 and T_{reg} cells, as secondary end points[9]. For the first time, we demonstrated that low-dose IL-2 therapy could suppress T_{FH} and T_H17 cells in humans[1]. In addition, using a mouse model, we revealed that suppression of T_{FH} and T_H17 cells was as sensitive to low-dose IL-2 as the promotion of T_{reg} cells. During the peer review process, we were asked to exclude the possibility that the increase in T_{reg} cells and decreases in T_{FH} and T_H17 cells accompanying low-dose IL-2 administration were a consequence of significantly lowered disease activity. Therefore, we analysed the immunological phenotype in another, separate cohort of patients who underwent a comparable response under conventional immunosuppressive treatments, and found no such changes in T_{reg}, T_{FH} and T_H17 cells. This separate cohort was not a placebo-control group and we agree with the proposal of Drs Humrich and Riemekasten that a parallel study would be ideal.

Our study characterized T_{reg} cells based on a $CD4^+CD25^{high}CD127^{low}$ phenotype, a method reported in 2006 (REFS 10,11) and cited in thousands of publications. Drs Humrich and Riemekasten suggest $CD4^+FOXP3^+CD127^{low}$, a less well-characterized phenotype, could be better. Notably, their own study indicated a substantial proportion of $CD4^+FOXP3^+CD127^{low}$ cells did not express CD25 but secreted effector cytokines such as IFNγ, suggesting possible contamination with conventional effector T cells[12]. This agrees with the results of many studies on human samples showing that FOXP3 is expressed in activated effector $CD4^+$ T cells in addition to T_{reg} cells[13]. Owing to the limitations of the available phenotypical markers used to characterise T_{reg} cells, we also performed a standard suppressive assay showing that low-dose IL-2 treatment in mice and humans promoted the suppressive function of T_{reg} cells[1].

SLE is a very complex and poorly treated disease. As low-dose IL-2 emerges as a new therapy for this disease, we agree that more studies, including well-controlled randomized trials, will be needed to understand the underlying mechanisms, optimise treatment regimens and select the most suitable patients. These important follow-up studies are currently underway.

Zhanguo Li and Jing He are at the Department of Rheumatology and Immunology, Peking University People's Hospital, 11 Xizhimen South Street, 100044, Beijing, China.

Di Yu is at the Department of Immunology and Infectious Disease, John Curtin School of Medical Research, Australian National University, Canberra, ACT 0200, Australia.

Correspondence to Z.L. and D.Y.
li99@bjmu.edu.cn; di.yu@anu.edu.au

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Competing interests statement
The authors declare no competing interests.