Letter to the Editor

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FK506 Enhances IL-13 Production by T Cells Activated through CD3/CD28

F.J.

Francis J.

Dumont

Department of Immunology, Merck Research Laboratories, Rahway, N.J., USA

Correspondence to: Dr. Francis J. Dumont, Department of Immunology, Room RY80W107, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065 (USA), Tel +1 (908) 594 7516, Fax +1 (908) 594 7516, e.mail: francis-dumont@merck.com

Dear Sir,

Kawamura et al. [1] recently reported on an infant with X-linked autoimmune entero-pathy who was successfully treated with FK506 (tacrolimus), but developed extremely high levels of serum IgE. We speculate that this paradoxical effect of FK506 on IgE may be related to an increased production of IL-13 which, like IL-4, is known to promote IgE synthesis [2, 3]. We found that under certain conditions, FK506 upregulates IL-13 secretion by T cells in vitro. In our experiments, peripheral blood T cells from normal donors were purified by Ficoll centrifugation followed by E-rosetting and cultured (5×10^3

RPMI-1640 medium +10% fetal calf serum) in flat-bottom microtest plates in the presence of anti-CD3 (0.4 μ g/ml) and anti-CD28 (0.4 μ g/ml) monoclonal antibodies (Research Diagnostics, Flanders, N. J., USA), without or with FK506 at various concentrations. Supernatants were collected for analysis of IL-13 content by sandwich ELISA (Research Diagnostics). Figure 1a shows that the IL-13 level in control cultures rose with time and that FK506 (12.5 nM) increased this level at all three time points examined. On day 3, the enhancement of IL-13 production occurred with an EC₅₀ of 0.25 nM (fig. 1b) and an average of 6.4 ± 1.4 -fold (mean $\pm$ SEM of 9 donors) in the presence of 12.5 nM FK506. As expected [4], FK506 inhibited the production of IL-2 and IL-4, measured in similar cultures on day 1, by 80% (EC₅₀ = 0.12 nM) and 62% (EC₅₀ = 0.07 nM), respectively (not shown). These data extend the previous observation [5] that cyclosporin A also enhances IL-13 production by T cells. Since both FK506 and cyclosporin A inhibit calcineurin during T cell activation [4], this suggests that calci-

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FK506 [nM]

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Fig.1. Levels of IL-13 in supernatants from human T cells activated with anti-CD3+ anti-CD28 monoclonal antibodies in the absence or presence of FK506. a Supernatants were analyzed at different days of culture. $\square$ = No FK506; $\blacksquare$ = 12.5 nM FK506. Values are mean $\pm$ SEM from 6 separate experiments with different individuals, b Effect of various concentrations of FK506 ($\bullet$) on IL-13 production measured on day 3 of culture. The control level in cultures without FK506 is also shown (O). Values are mean $\pm$ SEM of 4 separate experiments with different individuals.

of immune dysfunction associated with au-toimmunity. Moreover, glucocorticoid (beta-methasone) cotreatment might potentiate IL-13-induced IgE synthesis [6]. It would therefore be interesting to examine T cell IL-13 production and its modulation by FK506 in the patient studied by Kawamura et al. [1]. Note that increased IL-13 production in this case might be beneficial, since IL-13 suppresses proinflammatory macrophage functions [2]. Finally, enhanced IL-13 secretion [5] might also account for the earlier finding that cyclosporin A bolsters IgE antibody responses in animal models [7].

neurin has a negative effect on IL-13 induction, a notion further supported by our finding that L-685,818, an antagonist FK506 analog which does not inhibit calcineurin [4] , failed to enhance IL-13 production, but blocked the enhancement caused by FK.506 (not shown). The artificial mode of T cell activation employed here may not accurately reflect the in vivo situation. It is nevertheless tempting to postulate that FK506 treatment might favor IL-13 production by T cells, perhaps in certain lymphoid tissue microenvironments, thereby driving IgE synthesis. Such an effect of FK506 might be exacerbated in the context

KAHGER

E-Mail karger@karger.ch

Fax +41 61 306 12 34 <http://www.karger.ch>

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