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Response to Shawn G. Kwatra

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TO THE EDITOR

We are pleased at the interest that Kwatra (2011) has shown in our article ''Malignant cutaneous T-cell lymphoma cells express IL-17 utilizing the Jak3/Stat3 signaling pathway'' (Krejsgaard *et al.*, 2011) and welcome the opportunity to discuss the conclusions drawn from the study.

Kwatra (2011) argues that because only the two IL-2 receptor β chain (IL-2Rβ) cytokines, IL-2 and IL-15, but not the other Jak3-activating cytokines utilizing the common cytokine receptor γ chain (γ_c) increase the expression of IL-17, it is misleading to conclude that the Jak3/signal transducer and activator of transcription 3 (Stat3) pathway promotes the malignant expression of IL-17 in cutaneous T-cell lymphoma (CTCL). Instead, he suggests that the conclusion that can be drawn from the study is that IL-2 and IL-15 mediate IL-17 expression through Jak3 signaling. Of notice, this is in agreement with our statement in this article, namely that ''Our results show that the IL-2Rβ cytokine-induced expression of IL-17 is mediated through a Jak3/Stat3-dependent mechanism''. Thus, the question is, can Jak3 also promote the expression of IL-17 in the absence of IL-2Rβ cytokines?

First of all, the malignant T cells spontaneously produced low amounts of IL-17 after cytokine starvation, indicating that IL-17 is not exclusively regulated by IL-2 and IL-15. Second, although the activity of Jak3 is greatly increased after stimulation with IL-2Rβ cytokines, it exhibits constitutive activity in the malignant CTCL cells even after cytokine starvation (Krejsgaard *et al.*, 2006). This is possibly through a cytokine-independent mechanism involving loss of regulatory control by the protein tyrosine phosphatases and/or suppressors of cytokine signaling (Zhang *et al.*, 2000; Brender *et al.*, 2005). Third, Jak3 knockdown by small interfering RNA inhibited the spontaneous IL-17 production. Therefore, we do not think that it is misleading to conclude that our results *indicate* Jak3 promotes the expression of IL-17 by the malignant T cells.

As Kwatra (2011) points out, we are aware that WHI-P154 inhibits Jak2 and Jak3 at comparable concentrations and that recent data have indicated that CP-690,550 inhibits Jak1 and Jak2 with similar affinities as Jak3 (Carbonnelle *et al.*, 2009; Meyer *et al.*, 2010). However, because we substantiated the results obtained using the Jak3 inhibitors by the Jak3-directed small interfering RNA, we think that it justifiable to conclude that Jak3 is involved in promoting the expression of IL-17. That said, these data do not exclude that the expression of IL-17 can also be modulated with other members of the Jak family.

In the study, we primarily focused on the role of IL-2Rβ cytokines in the malignant secretion of IL-17 and concur that further studies are needed to fully establish if other members of the γ_c family can modulate the expression of IL-17 by the malignant T cells. Nevertheless, our data show that relatively high concentrations of IL-4, IL-7, IL-9, and IL-21 do not significantly increase their secretion of IL-17 *in vitro*. Of notice, we have confirmed that IL-21 activates the Jak3/Stat3 pathway in the malignant T cells with minimal influence on the expression of IL-17 (data not shown). In addition, we found that some patients were IL-17 negative even though the malignant T cells exhibited constitutive activation of Stat3. Accordingly, as discussed in the article, the capacity of the Jak3/Stat3 pathway to promote IL-17 expression seems to be regulated by additional factors. It is possible that some cytokines, like IL-21, not only activate the Jak3/Stat3 pathway but also activate other pathways that modulate the Jak3-dependent IL-17 expression. Moreover, it seems likely that the expression of IL-17 is also modulated by other signaling pathways and transcription factors that are often known to be aberrantly regulated in CTCL (Sors *et al.*, 2006; Krejsgaard *et al.*, 2009; Kopp *et al.*, 2010). In our opinion, the present data suggest that Jak3 promotes the expression of IL-17 by the malignant CTCL cells both in the presence and in the absence of IL-2 and IL-15. Therefore, we conclude in the article that Jak3 promotes the expression of IL-17, but we also clearly highlight that this is regulated by other factors.

Abbreviations: CTCL, cutaneous T-cell lymphoma; IL-2Rβ, IL-2 receptor β chain; Stat3, signal transducer and activator of transcription 3; γ_c, common cytokine receptor γ chain

CONFLICT OF INTEREST

The authors state no conflict of interest.

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