

Correspondence

CD203c in patients with cystic fibrosis and allergy to *Aspergillus fumigatus*

To the Editor:

The recent article by Mirković et al.¹ showed that the CD203c marker on basophils from patients with cystic fibrosis (CF) could identify allergic sensitization to *Aspergillus fumigatus* in a homemade basophil activation test (BAT).¹ Interestingly, despite previous evidence, the BAT did not include CD63 evaluation,^{1,2} and yet the authors did not report any possible explanation for this exclusion.¹ Use of a single activation marker in the BAT might generate bias, although this approach is less expensive and time-consuming.

Some authors have shown that patients with CF and allergic bronchopulmonary aspergillosis (CF-ABPA) exhibited an increase in membrane expression of basophil CD203c when compared with that in patients with only CF or CF with inhaled *A. fumigatus* or after a 30-minute *ex vivo* challenge with *A. fumigatus* extract or recombinant allergens.² These authors reported that the baseline level of CD203c in basophils from patients with CF-ABPA was higher than in patients with CF and those with CF with stable *A. fumigatus* colonization, suggesting the existence of a priming mechanism in membrane upregulation of the marker.²

The question of whether primed basophils with baseline CD203c upregulation are reliable tools to diagnose *A. fumigatus* allergy in patients with CF might yet be raised. During activation with *A. fumigatus* allergens in patients with CF-ABPA, CD123, which is notoriously known as the α -chain of the IL-3 receptor, was moderately downregulated,² probably a consequence of the IL-3-mediated receptor recycling and downregulation. An autocrine priming mechanism involving IL-3 occurs at a low level of IgE/Fc ϵ RI cross-linking and has been described during sample handling.^{3,4} In this context the role of autocrine IL-3 in basophils appears critical at the level of Fc ϵ RI activity; that is, the role of IL-3 in increasing CD203c baseline expression might generate bias in the interpretation of BAT results, even to the level of Fc ϵ RI, because it might depend on the IgE receptor binding affinity and regulation and could increase false-negative results. Moreover, according to some authors, protocols to phenotype basophils and hence to electronically capture them in a flow cytometric assay might be influenced by the action of IL-3 on the basophil transcriptome.⁵ Furthermore, the effect of IL-3 on the regulation of Fc γ RIIB (CD32b), which regulates IgE/Fc ϵ RI cross-linking and activity,⁶ might be upregulated (3- to 12-fold) by autocrine IL-3.⁷

In the article by Mirković et al.,¹ the cohort characterization of recruited patients included 48 patients with CF-ABPA,¹ who should have high baseline CD203c levels, a fact that might suggest that basophils were primed for CD203c, even during their sampling collection,² because primed basophils upregulate

membrane CD203c, particularly when optimal preanalytic issues are not addressed.³ In basophils priming is caused by IL-3, the enhanced expression of which initially downregulates its membrane receptor.^{2,3} Primed basophils constitutively express CD203c in a bright form, then causing a reduced increase in expression of this membrane marker after non-IgE- or IgE-mediated stimulation.¹ If primed basophils are IL-3 regulated, then the action of this cytokine in the reliability of the BAT should be addressed. In the article by Mirković et al.,¹ patients with CF-ABPA had higher values of membrane CD203c than *A. fumigatus*-sensitized patients with CF but without ABPA, a possible effect of the reported priming mechanism, rather than an increase in BAT analytic performance.^{1,2} The same authors showed that for *A. fumigatus*-sensitized patients with CF but without ABPA, serum specific IgE levels rather than BAT results are more suitable markers to diagnose allergy from *Aspergillus* species in CF-affected subjects.¹ In this context a good suggestion is to test basophils with IFN- α (to dampen IL-3-mediated priming) or introduce a further marker to CD203c to optimize BAT performance and diagnostic predictivity.⁸

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Disclosure of potential conflict of interest: S. Chirumbolo declares no relevant conflicts of interest.

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<http://dx.doi.org/10.1016/j.jaci.2015.11.014>