

Correspondence

IL-18 binding protein reverses the life-threatening hyperinflammation of a baby with the NLRC4 mutation

To the Editor:

We read with excitement the article titled “Life-threatening NLRC4-associated hyperinflammation successfully treated with Interleukin-18 inhibition” by Canna et al.¹ We congratulate the authors for this outstanding diagnostic and therapeutic triumph. This article also represents translation from the bench of a unique protein, the IL-18 binding protein (IL-18BP),² into a targeted therapy drug that saved the life of this child. IL-18BP was an unexpected discovery and we believe that a short description of its unique features^{3,4} is useful to scientists and essential to clinicians and therefore should have been included in the publication of Canna et al. For example, IL-18BP has an exceptionally high affinity for IL-18 and the K_{off} rate is unusually low; that is, IL-18BP dissociates from the complex with its ligand at a very slow rate,³ thus serving as a potent decoy protein.² The authors allude to these therapeutically relevant properties when they write “Free IL-18 fell slightly with immunosuppression, but quickly fell to normal with rhIL-18BP.”

In addition, the IL-18BP deviates from the canonical definition of soluble receptors, that is, does not correspond to the extracellular ligand-binding domain of the IL-18 receptor.⁴ Naturally occurring soluble cytokine receptors and binding proteins are potent reagents for neutralization of cytokines because they ideally fulfill the requirement of highly specific drugs, combining high-affinity binding with low immunogenicity. Because the natural soluble receptors have a short half-life *in vivo*, genetically modified molecules have been generated, which decrease their clearance time. IL-18BP fulfills these prerequisites with no modifications required.

The authors correctly refer to the concept that free IL-18 is what counts in pathological situations but provide no reference to this concept, which can be found in our article published in 2001.⁵ The authors refer to a newly developed ELISA for the actual measurement of free IL-18 but this ELISA is presently not available to most. However, what is available and found in our publication from 2001 is the method to calculate free cytokine in general and IL-18 in particular.⁵

We agree with the authors about the clinical situation of macrophage activation syndrome (MAS) in the context of treating with IL-18BP and our 2005 report provides the first data that MAS can be treated with IL-18BP to quench the high circulating levels of free IL-18.⁶ In a more recent study,⁷ Put et al refer to a cytokine storm that often develops in MAS in a subgroup of children with

systemic juvenile idiopathic arthritis (sJIA). In that study, the calculated free IL-18 level was higher in active patients with sJIA ($n = 7$) than in those who developed MAS ($n = 3$) probably due to high enough levels of IL-18BP in the patients with MAS as reported. In a study from 2010, Shimizu et al⁸ conclude that serum IL-18 concentration may be a promising indicator of disease activity in patients with MAS who have sJIA. In another study from 2015, Shimizu et al⁹ showed that extremely high levels of total IL-18 predict MAS in patients with sJIA. Both in Shimizu studies and in most studies on circulating IL-18 levels, the investigators do not measure IL-18BP and therefore the level of free IL-18 remains unclear regarding any relation to disease severity.

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