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EDITORIAL

Sébastien Gibot
Frederic Massin

Soluble form of the triggering receptor expressed on myeloid cells 1: An anti-inflammatory mediator?

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S. Gibot (✉)
Hôpital Central et Laboratoire de Physiologie expérimentale (groupe Choc), Service de Réanimation Médicale,
29 avenue du Maréchal de Lattre de Tassigny, 54035 Nancy Cedex, France
e-mail: s.gibot@chu-nancy.fr
Tel.: +33-3-83852970
Fax: +33-3-83858511

F. Massin
Faculté de Médecine, Laboratoire d'Immunologie,
Nancy, France

Although the quality of the immediate innate immune response is a determinant in the fight against invasive pathogens, its exaggerated amplification may be deleterious and lead to septic shock. One of the pathways leading to such an intensification of the initial and appropriate inflammatory response involves the triggering receptor expressed on myeloid cells (TREM) 1. TREM-1 belongs to a family related to natural killer cell receptors and is present on the surface of neutrophils and mature monocytes [1]. Its expression is upregulated during infection but not during inflammation of noninfectious origin [2]. Upon stimulation by its as yet unknown ligand TREM-1 activates a downstream signal with the help of an accessory protein called DAP12 (or KARAP) leading to cytoskeleton rearrangement, calcium mobilization, and the activation of several transcriptional factors. Indeed, TREM-1 synergizes the effects of the Toll-like receptor ligands 2, 3, and 4 and amplifies the synthesis of many proinflammatory cytokines and chemokines [1]. TREM-1 also promotes an immediate neutrophilic degranulation and the phagocytic respiratory burst [3]. In addition to its presence as a membrane bound form, TREM-1 can also be found as a soluble protein, probably released from the membrane by proteolytic cleavage [4]. The role of this soluble TREM-1 (sTREM-1) as an "anti-inflammatory" agent is becoming understood.

In the *Intensive Care Medicine* Giamarellos-Bourboulis et al. [5] now report the results of their investigation of the level of sTREM-1 relative to those of other cytokines (TNF-α, IL-6, IL-8, and IL-10) in a homogeneous cohort of 90 patients suffering from a ventilator-associated pneumonia (VAP). The authors found a good correlation between the ratios IL-10/TNF-α and sTREM-1/TNF-α, IL-10/IL-6 and sTREM-1/IL-6, and IL-10/IL-8 and sTREM-1/IL-8, and therefore the expression pattern of sTREM-1 seems to follow that of IL-10. The authors thus conclude that sTREM-1 behaves as an anti-inflammatory product. Moreover, the ratio sTREM-1/TNF-α was higher in septic shock patients than in those suffering from severe sepsis or sepsis possibly indicating an imbalance of the immune response towards an exaggerated systemic anti-inflammatory state, as demonstrated for the IL-10/TNF-α ratio [6].

The role of sTREM-1 as an anti-inflammatory mediator is further supported by experimental studies. By using a chimeric protein TREM-1/IgG1 (equivalent to the extracellular domain of TREM-1), Bouchon et al. [2] demonstrated a protective effect on outcome of its administration both during endotoxemia and peritonitis in C57BL/6 mice. We obtained the same beneficial effect, along with a reduction in the inflammatory response, by administering a short fragment of the sTREM-1 into BALB/c mice [7]. Interestingly, the survival advantage conferred by this short peptide was still evident when it was injected as late as 24 h after the onset of sepsis.

The mechanism by which sTREM-1 modulates the inflammatory response is not clear but may be linked to

protection of the membrane-bound TREM-1 by preventing engagement with its endogenous ligand. This form of counterinflammatory mechanism has been described for the TNF-α/soluble receptor of the TNF-α complex and is crucial to the appropriate regulation of the immune system [8]. An illustration of the necessity of such a tight regulation is highlighted during the tumor necrosis factor receptor (tnfr) associated periodic syndrome (TRAPS) which is an autosomal dominant, multisystemic, autoinflammatory disorder caused by mutations in the *tnfr1* gene (*tnfrsf1a*). The pathogenesis of the hyperinflammatory state in TRAPS has been attributed to a shedding defect of TNFRSF1a from the cell surface resulting in increased TNF inflammatory signaling [9].

Another mechanism by which sTREM-1 may exert its anti-inflammatory action has recently been suggested by Hamerman et al. [10]. These authors demonstrated that DAP12 (the accessory protein that mediates the TREM-1 signaling) deficient macrophages produce higher levels of inflammatory cytokines in response to diverse microbial stimuli. Moreover, DAP12-deficient mice were more susceptible to endotoxemia and had enhanced resistance to infection by *Listeria monocytogenes*. These data suggest the existence of DAP12-pairing receptor(s) that negatively regulate the TLR-mediated signaling. One of these could be a specific receptor for sTREM-1, since many DAP12-paired receptors have a related inhibitory receptor [11].

In addition to these questions, another interesting finding in the Giamarellos-Bourboulis et al. [5] study is the differential course of sTREM-1 concentrations in survivors and nonsurvivors: those patients who finally died showed constant elevation in sTREM-1 levels. Even more interesting was that the patients who did not manage to clear their VAP exhibited a constant elevation and even a constant increase in sTREM-1 as compared to those with VAP resolution [12]. Was the resolution of VAP impaired by high levels of sTREM-1 (decreasing the phagocytosis competency?), or did sTREM-1 remain elevated because of an ongoing infectious process? Whichever the mechanism, these findings are in line with some of our data which reveal a progressive decrease in sTREM-1 concentrations in septic shock survivors, whereas those patients who ultimately died displayed persistent elevation in the level of this protein [13, 14]. These findings add to the growing body of evidence supporting the usefulness of the measurement of sTREM-1 concentration during the follow-up of the septic process. A progressive decrease in sTREM-1 level may comfort the clinician with the appropriateness of his treatment. Conversely, persistently elevated sTREM-1 level should lead to a prompt reevaluation of the therapy.

TREM-1 seems to be a crucial player during the immensely complex process of the innate immune response to infection. Whether it is one mediator among hundreds of others or it is *the* mediator remains to be elucidated. One way to better understand its behavior is to conduct studies within as homogeneous a population as possible, such as that presented here [5], and for which the authors must be congratulated.

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