CRITICAL CARE

COMMENTARY

GAS6 in systemic inflammatory diseases: with and without infection

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See related research by Ekman *et al.*, http://ccforum.com/content/14/4/R158

Abstract

Vitamin K-dependent proteins are not only essential regulators of blood coagulation. A recent paper in *Critical Care* describes the levels of the vitamin K-dependent GAS6 and the soluble form of its receptor Axl in plasma from patients with sepsis of systemic inflammation. The results confirm that GAS6 is elevated during septicemia, but the fact that inflammatory conditions without infection produce a similar effect suggests it is inflammation that induces the synthesis of GAS6, rather than the interactions with bacteria or other infectious agents. The soluble form of the GAS6 receptor Axl was induced less compared with the effect observed in GAS6. This is important as the two proteins form an inactive complex in plasma, suggesting that a functional GAS6 form could be synthesized under these conditions. GAS6 has been proposed as a broad regulator of the innate immune response. GAS6 synthesis is therefore likely to be a regulatory mechanism during systemic inflammation. Recent advances provide the necessary tools for further research, including genetic screenings of the components of this system.

Since its discovery in 1929 as the 'Koagulations-Vitamin' by Henrik Dam, the main role assigned to vitamin K has been linked to maintaining hemostasis. Vitamin K inhibitors have been used in the clinic as anticoagulants since the 1950s. Vitamin K is an essential cofactor in the post-transcriptional modification of glutamic residues of a small number of proteins in the human genome. Although the majority of these vitamin K-dependent proteins are part of the coagulation cascade or its regulators, others are involved in different processes. The view of vitamin K function is therefore now broader, and recent research has demonstrated a wide range of functions associated with vitamin K-dependent proteins; for instance, their implication in calcium homeostasis in the bone and other tissues. Furthermore, vitamin K-dependent proteins are present in invertebrates and other species lacking a coagulation cascade.

A later addition to these functions has been produced by studies on GAS6, the subject of the recent report by Ekman and colleagues [1]. GAS6 and the highly similar anticoagulant protein S were discovered to be ligands of a family of formerly orphan receptor protein tyrosine kinases, the TAM family [2,3]. The function of this family of receptors was soon recognized to be important in mechanisms of defense against injuries, especially through their action as regulators of inflammation, apoptotic cell clearance and platelet–endothelial activation [4-7].

Owing to the low concentration of GAS6 in plasma and its similarity to protein S, which is 1,000-fold more concentrated, creating a reliable test to detect its concentration under different disease conditions has been a challenge. Despite these difficulties, several groups have reported that GAS6 acts as an acute-phase reactant, increasing its concentration during sepsis [8,9]. The present study by Ekman and colleagues provides detailed evidence of this increase by comparing at the same time patients with different diagnoses related to septicemia – including severe sepsis, sepsis, systemic inflammatory response syndrome without infection, and verified infection – blood donors, systemic inflammatory response syndrome patients with infections, and patients without systemic inflammatory response syndrome as controls. Furthermore, the study determines the concentration of soluble Axl, a processed form of the receptor that is present in plasma at molar excess compared with GAS6 and that seems to capture most of the GAS6, forming a stable complex [10]. Previous studies have clearly established that GAS6 is increased in septic patients, and its concentration correlates with disease severity [8,9].

In the present study, the authors show that plasma GAS6 increased in all conditions studied, irrespective of

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the presence of infection. Other conditions with an important activation of inflammation, such as pancreatitis, also show increased levels of GAS6 [11]. Taken together, these data suggest that GAS6 would be a general marker of inflammatory conditions rather than a specific marker for sepsis. This hypothesis would fit well with the view of the TAM receptor system as a brake for the innate immunity [12]. GAS6 itself shows anti-inflammatory properties in certain cells, reducing cytokine synthesis [13], but could also orchestrate the course of inflammation by favoring platelet and leukocyte interactions with the endothelium [7].

The study of the role of GAS6 and its TAM receptors in human pathology has just begun. Recent developments include assays to test the genetic variability of the GAS6 gene [14] and to test the TAM receptors in the human genome [15]. These assays would allow correlating plasma parameters with the genetic background, leading to a deeper understanding of the possible role of the GAS6–TAM system in sepsis.

Competing interests

The authors declare that they have no competing interests.

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