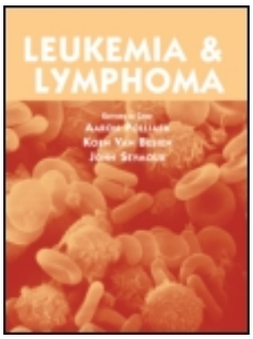

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COMMENTARY

High-mobility group box 1 protein and hematologic malignancies with severe inflammation: therapeutic intervention with recombinant thrombomodulin

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High-mobility group box 1 protein (HMGB1), one of the best characterized damage-associated molecular pattern (DAMP) molecules, has pleiotropic effects both inside and outside the cell. In the cell nucleus, HMGB1 bends DNA, and promotes protein assembly on specific DNA targets. In the extracellular milieu, HMGB1 acts as a signal of tissue damage. HMGB1 is passively released from necrotic or damaged cells and actively secreted by inflammatory cells. Extracellular HMGB1 can bind to cell surface receptors – receptor for advanced glycation end products (RAGE) or toll-like receptors (TLR2, TLR4, and TLR9) – and promotes inflammation, immune responses and tissue regeneration [1,2]. HMGB1 has been implicated in various disease states, including sepsis, ischemia–reperfusion, arthritis, neurodegeneration and cancer. In addition, HMGB1, along with other intracellular factors released from tumor cells induced by chemotherapy (CT) or radiotherapy (RT), is a component of the tumor microenvironment [3].

In this issue of ***Leukemia and Lymphoma***, Inoue and colleagues used serum HMBG1 levels to demonstrate the efficacy of recombinant human thrombomodulin (rhTM) treatment in patients with hematologic malignancies complicated by systemic inflammatory response syndrome (SIRS) and disseminated intravascular coagulation (DIC). This pilot study included 54 patients, classified into three groups according to their disease status after CT (group 1: 13 patients, complete remission; group 2: 16 patients, no remission; group 3: 25 patients, no remission, SIRS during CT ± DIC). The results of the study demonstrated significantly elevated serum HMBG1 levels in group 3 compared to groups 1 and 2. In addition, 17 patients (group 3), complicated by DIC, received rhTM, and 12 of them showed clinical improvement and remarkable amelioration of serum HMBG1 levels. Although the study has limitations, the report by Inoue *et al*. provides new/additional information about the management of severe inflammation in patients with hematologic malignancies [4]. It is probably correct to consider that the increased serum HMBG1 levels were associated with severe inflammation, and consisted mainly of the active secretion from activated inflammatory cells and/or the accumulation of HMBG1 passively released from necrotic cells [2]. Furthermore, the clinical and laboratory responses to rhTM treatment in patients complicated by DIC suggest the efficacy of this anticoagulant agent. rhTM is a protein homologous to the extracellular domains of TM, with anti-inflammatory as well as anticoagulant properties, with fewer bleeding complications [5,6]. In addition, the lectin-like domain of TM sequesters HMGB1 protein [7]. TM also aids the proteolytic cleavage of HMGB1 by thrombin [8]. This finding underlines an additional anti-inflammatory role of TM, in which thrombin–TM complexes degrade HMGB1 to a less pro-inflammatory form, and may also explain the decrease of serum HMBG1 levels among patients treated with rhTM [8].

So far, very few clinical investigations on the effects of rhTM have been reported, and included patients with hematologic malignancies. Saito *et al*. used rhTM to perform a multicenter, randomized controlled trial in patients with DIC associated with hematological malignancy or infection. In this trial, 116 patients received rhTM, and the same number of patients received heparin. rhTM treatment resulted in a better DIC resolution than heparin (66.1% vs. 49.9%, respectively). The disappearance rates of bleeding symptoms were 35.2% for the rhTM group, and 20.9% for the heparin group. However, the overall mortality was similar between the two groups. Decreases of plasma thrombin–antithrombin complex and D-dimer levels were significantly greater in the rhTM group. Consequently, the results of the trial demonstrated that rhTM therapy was more effective and safer than heparin therapy [9].

Its is clear that further basic and clinical studies are needed to understand HMGB1 and its complex effects on the immune system, to confirm its important role in various clinical states and to develop novel therapeutic strategies.

In addition, further clinical investigations are necessary to evaluate the effect of rhTM on the pathophysiology of sepsis-induced DIC.

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Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

References

[1] Wang H, Bloom O, Zhang M, et al. HMG-1 as a late mediator of endotoxin lethality in mice. Science 1999;285:248–251.
[2] Huang W, Tang Y, Li L. HMGB1, a potent proinflammatory cytokine in sepsis. Cytokine 2010;51:119–126.
[3] Tang D, Kang R, Zeh HJ 3rd, et al. High-mobility group box 1 and cancer. Biochim Biophys Acta 2010;1799:131–140.
[4] Inoue Y, Saito T, Ogawa K, et al. Role of serum high mobility group box 1 in hematological malignancies complicated with systemic inflammatory response syndrome and effect of recombinant thrombomodulin. Leuk Lymphoma 2013;54:1953–1958.
[5] Suzuki K, Kusumoto H, Deyashiki Y, et al. Structure and expression of human thrombomodulin, a thrombin receptor on endothelium acting as a cofactor for protein C activation. EMBO J 1987;6: 1891–1897.
[6] Ito T, Maruyama I. Thrombomodulin: protectorate God of the vasculature in thrombosis and inflammation. J Thromb Haemost 2011;9(Suppl. 1):168–173.
[7] Abeyama K, Stern DM, Ito Y, et al. The N-terminal domain of thrombomodulin sequesters high-mobility group-B1 protein, a novel anti- inflammatory mechanism. J Clin Invest 2005;115:1267–1274.
[8] Ito T, Kawahara K, Okamoto K, et al. Proteolytic cleavage of high mobility group box 1 protein by thrombin-thrombomodulin complexes. Arterioscler Thromb Vasc Biol 2008;28:1825–1830.
[9] Saito H, Maruyama I, Shimazak S, et al. Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. J Thromb Haemost 2007;5: 31–41.