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Editorial

Thrombomodulin, a Novel Immune Regulator in Liver Inflammatory Injury?

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Thrombomodulin (TM) is a transmembrane glycoprotein expressed on the surface of endothelial cells and acts as a cofactor for thrombin. The human TM protein is composed of five domains (Figure 1) (1). Thrombin binding to TM activates protein C to initiate the anticoagulant pathway. Although previous studies revealed the anticoagulant effects of TM, recent studies have suggested that TM, especially its lectin-like domain (TMD1), seems to play an important role in anti-inflammatory activity.

TM appears to have an anti-inflammatory activity that is primarily mediated by inducing protein C activation and suppressing thrombin activity. Activated protein C binds to endothelial protein C receptor and activates protease-activated receptor 1 and its downstream sphingosine-1 phosphate receptor 1 signaling pathway, resulting in reduced inflammation-induced vascular leakage and proinflammatory cytokine release. Moreover, TM-thrombin binding reduces damage to endothelial cell junction and inhibits tumor necrosis factor-α (TNF-α), C-C motif chemokine ligand-2, intercellular adhesion molecule-1, and p-selectin production from the recruited monocytes (2). Recombinant TMD1 (rTMD1) reduces neutrophil accumulation within the endothelium and inhibits nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathway activation. The mechanism of the anti-inflammatory effect of TMD1 involves reducing the levels of high mobility group box 1 (HMGB1), a protein released from necrotic cells or secreted by activated monocytes and macrophages. HMGB1 binding to the endothelial cell surface receptor, receptor for advanced glycation end products (RAGE), triggers its downstream inflammatory signaling pathway and tissue damage. Disruption of HMGB1 protein by TM or TMD1 binding blocks the HMGB1-RAGE pathway, leading to reduced inflammation.

Recombinant human soluble thrombomodulin (rTM) is a new anticoagulant agent that has been approved and used as a standard treatment for disseminated intravascular coagulation (DIC) in Japan. A phase III clinical trial is currently under way in the United States to study the efficacy of TM for the treatment of sepsis with DIC complications. rTM has been shown to reduce mortality in animal models of severe sepsis (3). Clinical studies also demonstrate that rTM has significant benefits in patients with sepsis-induced DIC (4).

In this issue of the *American Journal of Transplantation,* Kadono et al (5) report the first rTM treatment to reduce ischemia/reperfusion (IR)–induced liver inflammation by regulating the TLR4-dependent signaling pathway. The authors found that rTM ameliorated IR-induced liver injury, suppressed proinflammatory cytokine and chemokine expression, and prevented hepatocellular apoptosis. Moreover, rTM inhibited intracellular HMGB1 release, Toll-like receptor 4 (TLR4) and NF-κB activation, and MAPK pathways in liver IR. These results suggest that rTM modulates the liver inflammatory response and may be involved in the HMGB1-TLR4 signaling pathway. To confirm this, the authors used the TLR4-deficient (KO) mice and found that TLR4 deficiency diminished liver injury and intracellular HMGB1 release. More interestingly, although rTM treatment improved IR-induced liver damage in wild-type (WT) mice, it did not show any protective effect or reduce serum or cytoplasmic HMGB1 levels in TLR4 KO mice after liver IR. Thus, this work demonstrates that TLR4 signaling is essential for rTM-mediated immune regulation in liver IR injury. Consistent with these results, the authors also demonstrate the anti-inflammatory effect of rTMD1 in IR-triggered liver inflammation.

Another important finding from Kadono et al (5) is that rTM mediated inhibition of HMGB1-induced inflammatory response via a TLR4-dependent manner. While recombinant HMGB1 treatment increased TNF-α production in macrophages from WT mice, the authors demonstrated that rTM suppressed the HMGB1-mediated induction of TNF-α. However, HMGB1-induced TNF-α production was not observed in TLR4-deficient macrophages after rTM treatment. Therefore, this effect may be dependent on the presence of TLR4. This work raises questions about the potential effect of rTM on the mechanism of the HMGB1-TLR4 axis. In liver IR, the

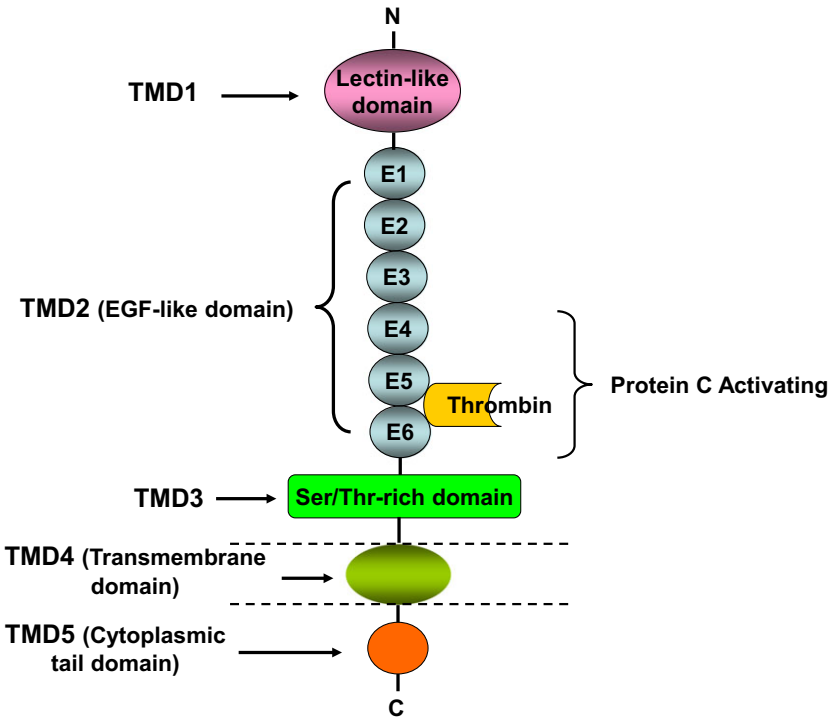

Figure 1: Structure of thrombomodulin (TM). The human TM protein is composed of five domains: N-terminal lectin-like domain (TMD1); six epidermal growth factor (EGF)-like domain (TMD2); serine/threonine-rich domain (TMD3); transmembrane domain (TMD4); and short cytoplasmic domain (TMD5).

interaction of HMGB1 and TLR4 may result in induction and accumulation of reactive oxygen species from stressed cells, leading to increased liver damage. With regard to this issue, the myeloid-specific HMGB1-deficient mice may be useful for revealing the mechanistic links between rTM and HMGB1-TLR4 signaling pathway in liver IR injury. Since HMGB1-TLR4 signaling plays an important role in the activation of NLR Family, Pyrin Domain-Containing 3 (NLRP3) inflammasome, the authors investigated the effect of rTM on NLRP3 signaling. They demonstrated that rTM reduced IR-induced hepatocellular apoptosis and pyroptosis by inhibiting the activation of caspase-3 and NLRP3/caspase-1, suggesting that rTM-mediated immune regulation may be involved in the activation of multiple signaling pathways. Therefore, these observations emphasize the crucial role of rTM in the regulation of immune response and provide a therapeutic potential to alleviate IR-induced liver inflammation.

Liver IR injury is a complex pathological process involving both the innate and adaptive immune responses. The current study has demonstrated the novel role of TM in regulating liver inflammatory response via the HMGB1-TLR4 signaling pathway. The use of rTM protein to treat IR-induced liver inflammation suggests that TM may be a promising new therapy for patients with liver IR followed by liver transplantation.

Disclosure

The author of this manuscript has no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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