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Editorial

Heparin Cofactor Ⅱ:

A Novel Plausible Link of Obesity and Diabetes with Thrombosis

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The global obesity pandemic is one of the major public health crises facing the world today. Obesity is not only a strong risk factor for the development of insulin resistance and type 2 diabetes (T2DM), but has also been implicated in the pathogenic processes underlying numerous metabolism-related disorders. Importantly, abundant clinical and epidemiological evidence has shown that central obesity is closely related to cardiovascular mortality, and is a significant risk factor for arterial thrombosis and venous thromboembolism with increased thrombin generation and platelet hyperactivity[1-3]. Therefore, identifying the molecules linking obesity with thrombosis may help us to better understand the pathogenesis of metabolism-related thrombosis.

Heparin cofactor Ⅱ (HCⅡ), a serine protease inhibitor (serpine) first identified in 1974[4], has structural similarities to antithrombin[5]. HCⅡ is mainly produced in the liver and secreted into the bloodstream. Physiologically, HCⅡ binds to dermatan sulphate, which is present on the surfaces of cells comprising the vascular endothelium and primarily acts as an anticoagulant[5] (**Fig. 1**). Via its inhibitory effects on thrombin action, HCⅡ has emerged as a novel vascular protective factor against vascular remodeling and atherosclerosis in humans and mice[6-8]. However, the role of HCⅡ in the regulation of obesity and diabetes has yet to be characterized.

In this issue of the Journal of Atherosclerosis and Thrombosis, Kurahashi *et al.*[9] demonstrated that plasma HCⅡ activity correlates inversely with glycosylated hemoglobin, fasting plasma glucose and HOMA-IR in elderly Japanese patients with lifestyle-related diseases. In addition, studies using high fat diet-fed HCⅡ+/- mice revealed that HCⅡ exerts a beneficial effect on glucose metabolism. Notably, selective blockade of thrombin action by HCⅡ was sufficient to reverse insulin resistance, which is reminiscent of the anti-inflammatory and insulin-sensitizing effects of HCⅡ. Although these data raise the possibility of HCⅡ-mediated coagulant responses playing roles in various aspects of the metabolic syndrome, many issues pertaining to HCⅡ remain to be elucidated, including identification of the main cellular and tissue targets and the physiological conditions (i.e. inflammation, hypofibrinolysis and hypercoagulation) involved in HCⅡ responses.

In conclusion, central obesity is accompanied by significant alterations in coagulable state. Additional important risk factors for thromboembolism in obese patients include inflammation, decreased fibrinolysis, increased thrombin generation and platelet hyperactivity. HCⅡ-targeted therapies may help to control the thrombotic process and minimize the risk of cardiovascular complications in patients with metabolic syndrome. HCⅡ and its related signaling could thus represent a potential therapeutic target for hypercoagulable states in patients with obesity, T2DM and especially thrombosis-related metabolic dysfunction.

Conflicts of Interest

None.

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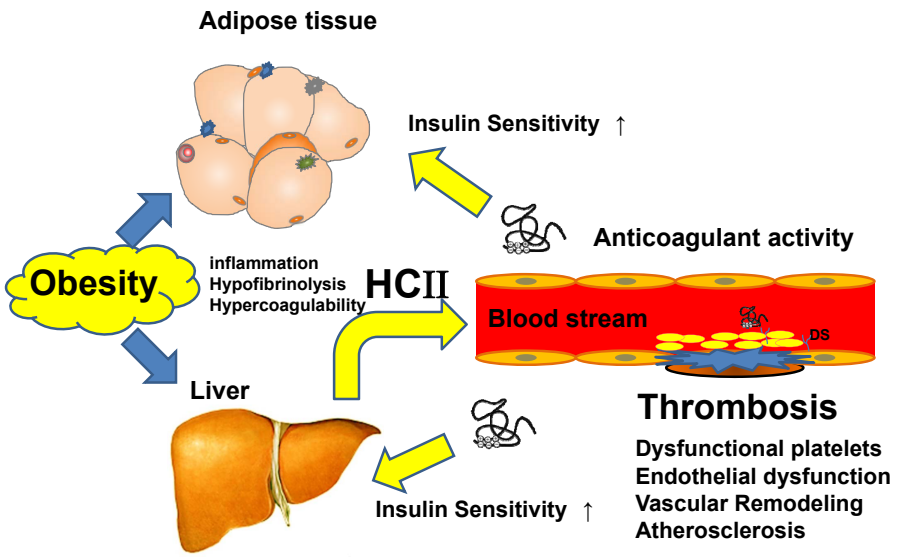

Fig. 1. Mechanistic action of heparin cofactor Ⅱ (HCⅡ) in obesity

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