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The NF-κB pathway: regulation of the instability of atherosclerotic plaques activated by Fg, Fb, and FDPs

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Abstract Recently, the molecular mechanism responsible for the instability of atherosclerotic plaques has gradually become a hot topic among researchers and clinicians. Matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) play an important role in the processes of formation and development of atherosclerosis. In this study, we established and employed the transwell co-culture system of rabbit aortic endothelial cells and smooth muscle cells to explore the relationship between fibrin (Fb), fibrinogen (Fg), and/or their degradation products (FDPs) in relation to the instability of atherosclerotic plaques; meanwhile, we observed the effects of Fg, Fb, and FDPs on the mRNA levels of MMPs and VEGF as well as on the activation of nuclear factor-kappa B (NF-κB). We concluded that Fb, Fg, and FDPs are involved in the progression of the instability of atherosclerotic plaques via increasing the expression of MMPs and VEGF. This effect might be mediated by the NF-κB pathway.

Keywords Fibrin(ogen) · Fibrinogen degradation products · Atherosclerosis · Matrix metalloproteinase · Vascular endothelial growth factor · Nuclear factor-kappa B

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Introduction

The instability of atherosclerotic plaques is an important factor leading to the rupture of plaques and the occurrence of stroke, and has been drawing increasing attention of researchers and clinicians. Epidemiological studies have demonstrated that hyperfibrinogenemia is an independent risk factor for stroke, as well as that fibrinogen (Fg), fibrin (Fb), and fibrinogen degradation products (FDPs) are involved in the formation and development of atherosclerosis (AS) [1, 2]. Fg is a 340 kD glycoprotein which is constitutively expressed exclusively in hepatocytes [3]. As a key plasma protein, Fg has a plasma half-life of 3–5 days and can be converted to Fb in the final step of the coagulation cascade [4]. FDPs are fragments (polypeptides) produced when either Fg or Fb is broken down by the enzyme plasmin [5].

Numerous studies have demonstrated that the plasma levels of Fg, Fb, and FDPs have close association with vascular diseases. People with high levels of Fg are more than twice as likely to die of a heart attack or stroke as people with normal Fg levels [6]. Wada et al. [7] found that the plasma level of Fb monomer in patients with disseminated intravascular coagulation (DIC) was significantly higher than that in patients with pre-DIC or in non-DIC patients. Gaffney et al. [8] reported that the levels of FDPs can rise after any thrombotic event, indicating it can be used to test for DIC. Despite the findings of these studies, however, the relationship between Fg, Fb, and FDPs and the instability of atherosclerotic plaques remains unclear. The aim of the current study was to explore the molecular mechanisms of Fg, Fb, and FDPs as they are involved in the instability of atherosclerotic plaques. We established and employed the transwell co-culture system of rabbit aortic endothelial cells (ECs) and smooth muscle cells