Aspects of Plasminogen Activator Inhibitor 1 in Metabolic Syndrome

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I Brogren H, Sihlbom C, Wallmark* K, Lönn M, Deinum J, Karlsson L, Jern S. Heterogeneous glycosylation patterns of human PAI-1 may reveal its cellular origin.
Thrombosis Research 2008;122:271-281.

II Mossberg KE, Nilsson J, Sihlbom C, Larson G, Jern S, Brogren H. Increased glycosylation of plasma Plasminogen Activator Inhibitor 1 in obesity.
In manuscript.

III Mossberg KE, Svensson PA, Gidlöf O, Erlinge D, Jern S, Brogren H. Normalization of qPCR in platelets – YWHAE a potential generic reference gene.
Platelets. 2016. DOI: 10.1080/09537104.2016.1180349. In press.

IV Mossberg KE, Olausson J, Fryk E, Jern S, Jansson PA, Brogren H. The role of the platelet pool of Plasminogen Activator Inhibitor 1 in type 2 diabetes.
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ABSTRACT

Plasminogen activator inhibitor 1 (PAI-1) is the main inhibitor of the fibrinolytic system and binds irreversibly to tissue-type plasminogen activator (t-PA), and thereby inhibits the protective action of t-PA against thrombus formation. Elevated levels of plasma PAI-1 is observed in subjects with type 2 diabetes (T2D) and the metabolic syndrome (MetS), which is a combination of metabolic features including obesity. PAI-1 has become recognized as a central molecule linking the MetS and thrombotic vascular events. However, the origin of plasma PAI-1 is not fully established in these conditions. The aim of this thesis was to investigate the role of platelet PAI-1 and source of plasma PAI-1 in T2D, obesity and healthy subjects.

Our group has previously shown that platelets can *de novo* synthesize PAI-1 and the amount synthesized *in vitro* in 24 hours is 35-fold higher than required to maintain normal plasma levels. Therefore we wanted to investigate if platelets are the cellular origin of plasma PAI-1. Tissue-specific glycosylation patterns on PAI-1 from different tissues were determined. The results indicate that platelets are the source of plasma PAI-1, since no glycans were detected on PAI-1 isolated from plasma or platelets from healthy lean subjects. PAI-1 isolated from the other tissues expressed heterogeneous glycosylation patterns.

In obese subjects plasma PAI-1 had a glycan composition similar to that of adipose tissue suggesting that obese subjects, with elevated PAI-1 levels, may have an additional contribution from adipose tissue. Since glycosylated PAI-1, in comparison to unglycosylated forms, exhibit a lower inactivation rate and a stronger inhibitory effect, we also studied the level of glycosylated plasma PAI-1 in obesity. This was increased in obese subjects by 54% compared to lean subjects and a weak but significant correlation between the level of glycosylation and BMI was observed. These results suggest that an elevated level of glycosylated plasma PAI-1 is an important contributor to the increased risk of cardiovascular events associated with increased plasma PAI-1 levels in obese subjects.

Diabetic platelets are known to be hyper-reactive and larger in size; however, whether these features affect their contribution to the elevated levels of plasma PAI-1 in T2D is unknown. To elucidate the role of platelet PAI-1 in T2D, we characterized the PAI-1 antigen content and the mRNA expression in platelets from T2D subjects compared to both obese and lean control subjects. In order to analyze the mRNA content in platelets, reference genes to normalize for qPCR were identified and YWHAE was the most stable transcript in platelets. Furthermore, there was no significant difference in PAI-1 mRNA expression or PAI-1 antigen in platelets comparing the three groups, but an elevated level of plasma PAI-1 was seen in both T2D and obese control subject, indicating an uneffected role of platelets.

In conclusion, in balanced physiological conditions, platelets may be the major source of plasma PAI-1, however, the platelet contribution seems less important for the increased plasma levels and hence the risk of cardiovascular events in MetS and T2D.

Keywords: PAI-1, metabolic syndrome, obesity, type 2 diabetes, cardiovascular disease, fibrinolysis, thrombi, plasma, platelets, adipose tissue, mRNA, qPCR, reference gene

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