The signaling lipid sphingosin-1-phophate (S1P) regulates expression and secretion of the plasminogen activator inhibitor-I (PAI-1) in differentiated fat cells

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Background: The versatile lipid signaling molecule sphingosin-1-phophate (S1P) is a regulator of immune functions such as utilization of immune cells and local inflammatory responses. It has also been suggested as a link between inflammation and coagulation as platelets generate and release large amounts of S1P upon activation. S1P can regulate expression of the protease-activated coagulation factor receptors (PARs) to enhance cellular response to thrombin in monocytes and has been implicated in mechanisms of platelet activation.

Aims: Since hyperlipidemia and obesity are typical risk factors for thrombosis, this study investigates possible effects of S1P on prothrombotic gene expression in adipocytes in vitro.

Methods: Murine 3T3-L1 fibroblasts were differentiated with MDI (methylisobutylxanthine, dexamethasone, insulin) induction medium. Gene expression of adiponectin, PAR1-4, the S1P receptors S1PR1-5 and PAI-1 were determined by RT-PCR. PAI-1 protein was measured by Western blotting and ELISA.

Results: MDI-induced differentiation resulted in characteristic phenotypical chances as well as a 600-fold increase in adiponectin expression. Cell viability was maintained and apoptosis not significantly elevated. Expression of the PARs and S1PRs was reduced in differentiated adipocytes which fitted with cellular senescence. Incubation of adipocytes with S1P (0.3 to 10 µM) resulted in a significant upregulation of PAR-1 (2.7-fold) and PAI-I (8-fold) mRNA. Conversely, thrombin (0.1 to 3.0 units/mL) induced expression of S1PR3, but not of the other S1P receptors. S1P also highly significantly induced PAI-I protein expression and secretion to the culture media (about 4-fold). This was attenuated by pharmacological inhibition of S1PR2 and -3, but not by a S1PR1 inhibitor.

Conclusions: S1P regulates expression and secretion of PAI-I in adipocytes in vitro. This mechanism may modulate the pathogenesis of thrombosis in individuals at risk such as in obesity or metabolic syndrome.

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