UKE Paper of the Month January 2013
Blood, January 2013, (PMID: 23315166)

Rapid activation of monocyte tissue factor by antithymocyte globulin is dependent on complement and protein disulfide isomerase

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ABSTRACT: Lymphocyte depletion with antithymocyte globulin (ATG) can be complicated by systemic coagulation activation. We found that ATG activated tissue factor procoagulant activity (TF PCA) on monocytic cells more potently than other stimuli that decrypt TF, including cell disruption, TFPI inhibition or calcium ionophore treatment. Induction of TF PCA by ATG was dependent on lipid raft integrity and complement activation. We showed that ATG-mediated TF activation required complement activation until assembly of the C5b-7 membrane insertion complex, but not lytic pore formation by the membrane attack complex C5b-9. Consistently, induction of TF PCA by ATG did not require maximal phosphatidylserine membrane exposure and was not correlated with the magnitude of complement-induced lytic cell injury. Blockade of free thiols, an inhibitory monoclonal antibody to protein disulfide isomerase (PDI) and the small-molecule PDI antagonist quercetin-3-rutinosid prevented ATG-mediated TF activation, and C5 complement activation resulted in oxidation of cell surface PDI. This rapid and potent mechanism of cellular TF activation represents a novel connection between the complement system and cell surface PDI-mediated thiol-disulfide exchange. The delineation of this clinically relevant mechanism of activation of the extrinsic coagulation pathway during immunosuppressive therapy with ATG may have broader implications for vascular thrombosis associated with inflammatory disorders.

STATEMENT: *Although TF has well established roles in the initiation of thrombosis, the mechanisms that activate this receptor on hematopoietic cells remain incompletely understood. Thiol-disulfide exchange has been implicated in TF activation, but up to date no clear evidence has been presented that cell surface PDI-mediated TF activation contributes to thromboembolism. Our report delineates the mechanism enabling monocytes to promote rapid coagulation activation when exposed to ATG, a potent and potentially thrombogenic immunosuppressive drug. We show that ATG triggers Fc-mediated complement- and PDI-dependent TF activation specifically on myelomonocytic cells. This report is thus the first to demonstrate PDI-dependent TF activation in a clinically relevant context. By revealing a novel crosstalk between inflammation and coagulation, our findings may also be of broader significance for other prothrombotic disorders characterized by deregulated complement activation.*

BACKGROUND: This work was conducted at the II. Medizinische Klinik und Poliklinik in the group Experimentelle Hämostaseologie led by the first author in collaboration with the Interdisziplinäre Klinik für Stammzelltransplantation and Prof. Ruf from The Scripps Research Institute in La Jolla, CA. The group of PD Dr. Langer has long-term interests in revealing the cellular and molecular events underlying coagulation activation and thrombus formation in various disease states, particularly in cancer and inflammation.