Inflammation, platelets and diabetes

Francesca Santilli, Paola Simeone, Rossella Liani

Department of Medicine and Aging, Center for Advanced Studies and Technology, University of Chieti, Italy

ABSTRACT

Type 2 diabetes is a key player in atherothrombosis. Inflammation participates in metabolic homeostasis interacting with adipose tissue-specific macrophages. Platelets appear as addresses and players carrying and transducing metabolic derangement into vascular injury. AGE-RAGE pathway is recognized as the driver of metabolic memory. Human platelets have insulin receptors that participate in the regulation of platelet function and platelets are potential sites of insulin resistance. The present mini-review addresses key pathophysiological aspects including i) the role of inflammation in the pathogenesis of diabetes; ii) platelets as inflammatory cells; iii) the involvement on inflammation in the interindividual variability in aspirin response. Taken together, these aspects may contribute to expand knowledge about the link between the extent of inflammation, platelet activation and turnover, and interindividual variability in the development of atherothrombosis and its prevention, in a view of precision medicine.

Correspondence: Francesca Santilli, Center for Advanced Studies and Technology (CAST), "G. d'Annunzio" University, Luigi Polacchi, 66013 Chieti, Italy.
Tel: +39.0871.541322 - Fax: +39.0871.541261.
E-mail: francesca.santilli@unich.it

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Inflammation in the pathogenesis of diabetes and its complications

Type 2 diabetes (T2DM) accounts for nearly 90% of the approximately 537 million cases of diabetes worldwide.[1] Observational studies provided the first evidence for the possible association between inflammation and diabetes.[1]

The hypothesis that inflammation plays a causal and potentially primordial role in the development and natural history of diabetes has been raised for many years.[1] Several organs have been reported to participate in the metabolic homeostasis and inflammatory state in T2DM, including the pancreas, adipose tissue, liver, gut, skeletal muscle.[1]

Inflammation can drive the development of diabetes through interacting with adipose tissue-specific macrophages, leading to an imbalance in adipokine production, ectopic fat deposition, and insulin resistance.[1]

Inflammation has been suggested to be a common driver of both atherothrombosis and diabetes, in part through activation of the NOD-like receptor protein 3 (NLRP3) inflammasome, and the production of interleukin (IL)-1β and IL-18, both potent proinflammatory cytokines.[1]

T2DM, as a typical metabolic inflammatory disease, is under the joint regulation of environmental factors and genetics, combining with a variety of epigenetic changes. The inflammation-related epigenetics is one of the core pathomechanisms leading to β-cell dysfunction and insulin resistance. Epigenetic modifications of immune cells can indirectly regulate the inflammatory state of the body and affect insulin resistance and insulin secretion dysfunction.[1]

A large body of evidence shows that high glucose-exposed cells or diabetic animals and patients continue to develop inflammation and vascular damage even after achieving glycemic control. The AGE-RAGE pathway (AGE, advanced glycation endproducts; RAGE, receptor for advanced glycation endproducts) and its role as amplifier of local inflammation and oxidant stress through irreversible glycation of the various proteins and lipids, is recognized as the main driver of metabolic memory.[2]

The RAGE, a member of the immunoglobulin superfamily of transmembrane cell surface molecules, engages various ligands

relevant to the pathogenesis of atherosclerosis and is highly over-expressed at sites of vascular pathology.[3] Blockade of AGE-RAGE interaction can be achieved by truncated soluble forms of the receptor, referred to as total soluble RAGE (sRAGE), including both an endogenous splice variant of RAGE lacking the transmembrane domain of the receptor (endogenous secretory receptor or esRAGE).

Our study showed for the first time that plasma sRAGE levels were lower in diabetic patients as compared to controls.[3] Glycated hemoglobin (HbA1c) and urinary 8-iso-Prostaglandin F2α (8-iso-PGF2α), were correlated inversely with sRAGE, suggesting that oxidative stress and up regulation of the ligand-RAGE axis are, at least in part, related to glycemic control.

Platelets as inflammatory cells

Platelet hyperactivity is typically observed in diabetes and plays a key role in thromboinflammation.[4] Hyperglycemia was shown to prime thromboinflammatory responses by increasing platelet activation/adhesion and by promoting the release of neutrophil- and platelet-derived microparticles in human and murine samples.[4]

Platelets of individuals with diabetes, compared with those of healthy controls, show dysregulation at both the receptor and the intracellular signal transduction levels, leading to hyperreactive adhesion, activation, degranulation, and aggregation.[4] Human platelets have insulin receptors that participate in the regulation of platelet functions;[5] thus, platelets are potential sites of insulin resistance, which translates into an impairment in the physiological antiaggregating and vasodilating effects exerted by insulin, mediated by nitric oxide.[5] Reduced insulin sensitivity also causes increased signaling of P2Y purinoceptor 12 (P2Y12 receptor), the main platelet receptor for adenosine diphosphate.[4] Platelet hyperreactivity in patients with T2DM is also associated with increased platelet production of thromboxane.[6]

The observation that biochemical evidence of thromboxane (TX)-dependent platelet activation may be detectable as early as within one year since the diagnosis of T2DM,[7] together with its correlation with glycemic control and reversal with its improvement, point-out to hyperglycemia, both fasting and postprandial, as the main trigger for platelet activation,[8] and suggests that TX biosynthesis is an early event in the natural history of the disease.[9]

Along these lines, TXA_2-dependent platelet activation was at least as high in patients with prediabetes (impaired glucose tolerance) as in patients with T2DM and further increased over time, especially in those who progressed to overt diabetes.[10] This latter observation raises the hypothesis of TX as a potential predictor of the occurrence of T2DM in preclinical states, and of a bidirectional link between platelet activation and beta cell dysfunction with platelets also contributing to a local inflammatory milieu fostering beta cell apoptosis.[11]

LIGHT is a protein primarily expressed on T-cells and dendritic cells, but has also been found in platelets, monocytes and granulocytes, being involved in innate and adaptive immunity as well as in the pathogenesis of atherosclerosis and vascular inflammation; we have shown that platelets from T2DM patients spontaneously release in the circulation higher levels of LIGHT than platelets from healthy controls. On inflammatory stimulation with a cytokine such as IL-1β, tumor necrosis factor, and IFN-γ, pancreatic islet produces LIGHT and its receptors. By immunofluorescence staining, LIGHT is shown to be co-localized in both alpha and beta cells. During high glucose exposure, LIGHT attenuates insulin release due to LIGHT-induced apoptosis of pancreatic islet cells, further contributing to hyperglycemia.[11]

Inflammation and interindividual variability in aspirin response

Finally, platelets from patients with diabetes show increased turnover, resulting in a higher number of reticulated platelets, and increased adhesion to endothelial cells.[4] Increased platelet turnover contributes to the hyperreactive status of T2DM platelets. In normal conditions, approximately 10% to 15% of circulating platelets are replaced every day. Diabetic patients have a greater number of large and hypersensitive younger platelets and a more abundant fraction of small, exhausted platelets compared to non-diabetics. Aspirin irreversibly acetylates and inactivates COX-1 in circulating platelets and has only a 20-minute half-life. Therefore, there is the theoretical possibility that a single daily dose could not be sufficient to exert a full inhibitory effect on the new platelets generated and released by the bone marrow during the course of the 24 hours after aspirin intake.[9,12]

An imbalance between platelet production and clearance, with accelerated megakaryopoiesis/platelet production and reduced clearance/prolonged survival, characterizes patients with poor aspirin response, as reflected by the accelerated recovery of platelet COX-1 activity, especially those with diabetes.[9,12] This imbalance translates into increased platelet count and enhanced TX-dependent platelet activation.

Specifically, by employing an integrated approach including biochemistry, proteomics, flow cytometry, cell biology, and a mechanism-based endpoint to monitor aspirin pharmacodynamics, we analyzed the platelet proteome, platelet turnover, as reflected by thrombopoietin (TPO) and glycocalicin (GC) circulating levels, galactose exposure and GPIbα ectodomain shedding, megakaryocyte (Mk) cell maturation and proplatelet formation in patients at high cardiovascular risk with or without T2DM stratified according to the kinetics of COX-1 recovery. We show that reduced platelet GPIbα shedding characterizes patients with accelerated COX-1 recovery and may contribute to higher TPO production and higher rates of newly formed platelets, escaping aspirin inhibition over 24 hours. The TPO/GC ratio, a relatively simple, mechanism-based biochemical tool, may identify with significant diagnostic accuracy aspirin-poor responders due to accelerated renewal of the drug target.[13] Myeloid-related protein (MRP)-8/14 is expressed in granulocytes during inflammatory conditions and secreted in response to tissue damage along with the release of pro-inflammatory cytokines together with leukocyte recruitment and activation.[14]

Hyperglycemia triggers thrombopoiesis by activating liver inflammation. Indeed, MRP-8/14 and esRAGE interactions trigger IL-6- mediated TPO production by liver cells in conditions of low-grade inflammation and hyperglycemia. In our study,[13] plasma levels of MRP-8/14 were higher, while esRAGE had a trend for lower levels in third *vs*. first tertile in patients with T2DM. TPO was directly related to MRP-8/14 circulating levels and inversely related to esRAGE levels.

Thus, liver inflammation drives accelerated thrombopoiesis

which shortens the duration of aspirin effect over 24-hours. We unraveled a clinical and molecular signature, including younger age, NAFLD, visceral obesity and high TPO/GC, identifying with high accuracy aspirin-poor responders, amenable for a twice daily dosing aspirin regimen.[13]

Conclusions

Inflammation at different sites fuels the development of diabetes and its complications. Hyperglycemia triggers thrombopoiesis by activating liver inflammation, which is central for platelet turnover. The extent of inflammation may drive the response to antiplatelet agents. Future studies should develop pathophysiology-based markers predicting the development of atherothrombosis and the response to antiplatelet therapies in patients with different stages of diabetes mellitus.

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