UPDATES IN THROMABASTHENIA INHERITED AND ACQUIRED DEFECTS

Essay

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SUMMARY

Most disorders of platelet function are acquired; heritable qualitative platelet disorders are rare. When critical pathways of platelet biochemistry are perturbed, bleeding typically occurs, but because of redundancy of biochemical and receptor pathways that mediate the function of platelets, other defects may be detectable only on laboratory testing and do not produce clinically significant bleeding. In most cases, transfusion of platelets or other therapies will (temporarily) augment hemostasis in a patient with a congenital or acquired qualitative platelet disorder who has bleeding or who is to undergo an invasive procedure.

Subendothelial molecules such as VWF, collagen, and fibronectin mediate adhesion of platelets to the exposed subendothelial matrix at sites of vessel wall compromise. In "high-shear" states such as arterioles, VWF is especially important, because it tethers the platelet to the endothelial surface via interaction with its receptor, platelet glycoprotein (GP) Ib (GPIb).

Subendothelial collagen activates platelets; thrombin, which has been generated locally in reactions following the interaction of factor VIIa and tissue factor (provided by the membranes of cells), also activates platelets by binding to receptors on the platelet surface and initiating a series of signal transduction events.

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INTRODUCTION

Platelets ordinarily circulate in the blood stream individually not interacting with other platelets or any other cell type. However when exposed to appropriate stimulus a scenario of platelet activation adhesion and aggregation is started.

In conjunction with the adhesion reaction the cells often encounter agonists in their microenvironment that trigger platelet secretion. Granule constituents include substances that can stimulate circulating platelet and make them acquire new adhesive properties.

Abnormalities in platelet adhesive reactions of either a genetic (e.g., Glanzmanns thrombasthenia or Bernard-Soulier syndrome) or an acquired origin can result in bleeding episodes. Thus, platelet adhesive reactions and secretion are central events in hemostasis ***(Hoffman hematology 3rd edition).***

Hereditary platelet disorders

Hereditary intrinsic platelet disorders are rare and produce lifelong bleeding tendencies. Diagnosis is confirmed by platelet aggregation tests. Platelet transfusion is necessary to control serious bleeding.

Glanzmann's disease is a rare autosomal recessive disorder producing a defect in the platelet glycoprotein IIb-IIIa complex platelets can not aggregate. Patients may experience severe mucosal bleeding the diagnosis is suggested by the finding of single platelets without aggregates on a peripheral blood smear obtained from a finger stick. It is confirmed by the finding that platelets fail to aggregate with epinephrine, collagen or even high levels of ADP but do aggregate transiently with ristocetin. Interestingly the severity of the clinical bleeding does not correlate well with the degree of deficiency of IIb\IIIa.

Allogenic HSCT has been used in the management of severe cases ***(Bethesda clinical hematology 2nd ed, 2010).***

Bernard – Soulier syndrome

Is another rare autosomal recessive disorder it imapairs platelet adhesion via defect in glycoprotein Ib-IX complex (the receptor for VWF). Bleeding may be severe, platelets are unusually large. They do not aggregate with ristocetin but aggregate normally with ADP, collagen and epinephrine.

The syndrome comprises a triad of large platelets moderate thrombocytopenia and a prolonged bleeding time. BSS is distinguished from VWD in that the reduced ristocetin induced platelet aggregation in BSS is corrected by addition of normal platelets, whereas in VWD, it is

corrected by addition of normal plasma the diagnosis can be confirmed by platelet flow cytometry ***(Bethesda clinical hematology 2nd ed, 2010).***

Acquired platelet dysfunction may result from aspirin, other NSAID or a systemic disorder

Acquired platelet dysfunction can be very common. aspirin and many other drugs may induce platelet dysfunction. Many clinical disorders (eg, myeloproliferative disorder, uremia, macroglobulinemia and multiple myeloma, cirrhosis, SLE) can impair platelet function as well. Acquired platelet dysfunction is suspected and diagnosed when an isolated prolongation of bleeding time is observed and other possible diagnoses have been eliminated. Platelet aggregation studies are unnecessary ***(Williams hematology 8th edition, 2005).***

AIM OF THE WORK

An essay aiming to review hereditary and acquired qualitative platelet disorders that result in clinically overt compromise of coagulation.

The essay aspires to a better and a more universal understanding of novelties in diagnosis and management of hypocoagulable states resulting from inherited and acquired platelet functional deficits.

PLATELET PHYSIOLOGY

Megakaryopoiesis

Each day the adult human produces approximately 1 x 10^{11} platelets, a number that can increase 10 to 20 folds in response to increased demand. Production of platelets depends on the proliferation and differentiation of hematopoietic stem and progenitor cells to a cell committed to the megakaryocyte lineage, its maturation to a large, polyploid megakaryocyte, and its final fragmentation into platelets. The external influences that impact megakaryo-poiesis and thrombopoiesis are a supportive marrow stroma consisting of endothelial and other cells, matrix glycosaminoglycans, and a family of protein hormones and cytokines, including thrombopoietin ***(Chagaraoui et al., 2011).***

Platelet turnover

Evidence indicates the transit time from megakaryocyte progenitor cell to release of platelets into the circulation ranges from 4 to 7 days, following platelet apheresis, the platelet count falls, recovers substantially by day 4, and completely recovers by day 7.

Platelet Formation

Platelets form by fragmentation of megakaryocyte membrane exvaginations termed *proplatelets*, in a process

that consumes nearly the entire cytoplasmic complement of membranes, organelles, granules, and soluble macromolecules. Each megakaryocyte is estimated to give rise to 1000 to 3000 platelets then the residual nuclear material is engulfed and eliminated by marrow macrophages.

One of the most characteristic features of megakaryocyte development is endomitosis, a unique form of mitosis in which the DNA is repeatedly replicated in the absence of nuclear or cytoplasmic division. The resultant cells are highly polyploid. Endomitosis begins in megakaryoblasts following the many standard cell divisions required to expand the number of megakaryocytic precursor cells and is completed by the end of stage II megakaryocyte development. During the endomitotic phase, each cycle of DNA synthesis produces an exact doubling of all the chromosomes, resulting in cells containing DNA content from eight to 128 times the normal chromosomal complement in a single, highly lobated nucleus. Endomitosis is not simply the absence of mitosis but rather consists of recurrent cycles of aborted mitoses. Cell cycle kinetics in endomitotic cells also are unusual, characterized by a short G_1 phase, a relatively normal DNA synthesis phase, a short G_2 phase, and a very short endomitosis phase. During the latter phase, megakaryocytic chromosomes condense, the nuclear membrane breaks down, and multiple (at advanced stages) mitotic spindles form upon which the replicated chromosomes assemble. However, following initial chromosomal separation, individual chromosomes fail to

complete their normal migration to opposite poles of the cell, the spindle dissociates, the nuclear membrane reforms around the entire chromosomal complement, and the cell once again enters G_1 phase.

The cytokines, hormones, and chemokines responsible for survival and proliferation of megakaryoblasts include thrombopoietin, interleukin (IL)-3, stem cell factor (also termed mast cell growth factor, steel factor, and *c-kit* ligand), and stromal cell-derived factor (SDF)-1 ***(Chagaraoui et al., 2011).***

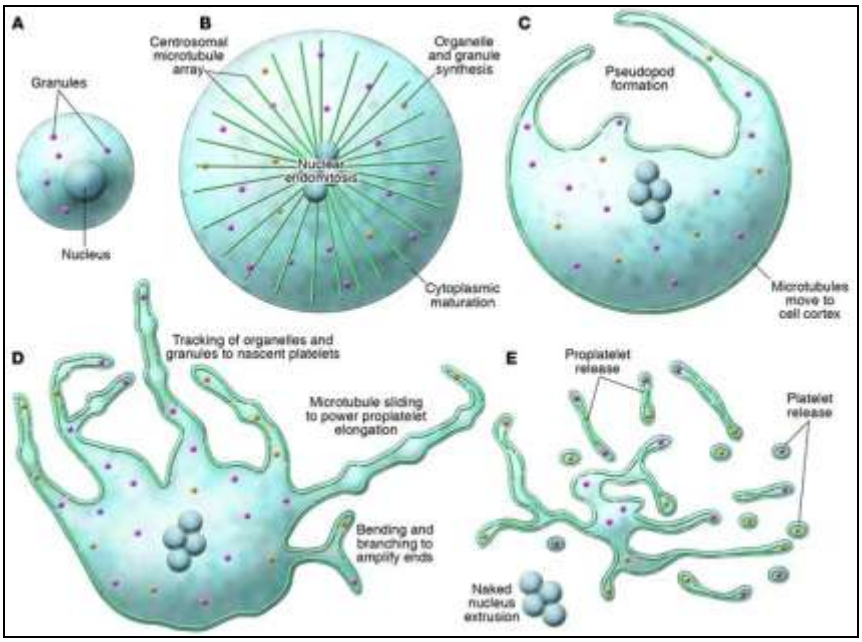

Figure (1): Megakaryopoiesis**.** ***J Clin Invest.*** **2005; 115(12)**

Platelet Morphology

The final product of megakaryopoiesis is a small 2-4 micron in diameter platelets which have a half life of 4

days. Between 60% and 70% of formed platelets are present in the circulation but the remainder are mostly in the spleen.

Platelets have ring of microtubules around their periphery and an extensively invaginated membrane with an intricate canalicular system in contact with the extra cellular fluid.

The platelet cytoplasm contains actin, mucin and two types of granules dense granules which contain nonprotein substances that are secretd in response to platelet activation including serotonin and ADP. And alpha granules which contain secreted proteins including clotting factors and platelet derived growth factor (PDGF) ***(Stankiewicz et al., 2009).***

Platelet functions

Introduction to platelet function

Primary hemostasis is the results of a complex series of cell–cell, cell–protein, and protein–protein reactions that involve platelets, leukocytes, subendothelial matrix, and plasma proteins, such as fibrinogen, von Willebrand factor (vWF), and other proteins.

Formation of platelet plugs at sites of vascular damage requires a co-ordinated, both in time and place, series of events leading to: i) platelet arrest onto the exposed subendothelium creating a monolayer of activated cells (initiation phase); ii) recruitment and activation of

additional platelets through the local release of major platelet agonists (extension phase); iii) stabilization of the platelet plug preventing premature disaggregation until wound healing occurs (stabilization phase).

Disruption of the endothelial cell lining of the vessel exposes constituents within the subendothelial matrix, including a variety of adhesive proteins that can support initial platelet attachment. After attachment, platelets may undergo a spreading reaction that permits formation of multiple and tight contacts between the cell surface and the matrix. These additional contacts may be critical in stabilizing the association of the platelets with the matrix in flowing blood. In conjunction with these adhesive reactions, the cells often encounter agonists in the microenvironment that can trigger platelet secretion. The secretory response results in the release of the contents of intracellular storage granules from within the platelet. Granule constituents include substances that can stimulate circulating platelets and cause them to acquire new adhesive properties. These stimulated platelets interact with one another, during platelet aggregation, to form an effective plug to seal the injured vessel wall and prevent excessive blood loss. This series of platelet responses attachment, spreading, secretion, and aggregations essential for the hemostatic function of platelets ***(Brewer, 2006).***