(PS2468) FC-GAMMA-RIIA-MEDIATED PROCOAGULANT PLATELETS ARE IMPORTANT DRIVERS OF IMMUNOTHROMBOSIS IN APS

Topic: 35. Thrombosis and vascular biology

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Background

Antiphospholipid syndrome (APS) is a prothrombotic autoimmune disease characterized by recurrent thrombosis and obstetrical complications. Autoantibodies (AAbs) that are targeting phospholipids and phospholipid-binding proteins are well characterized for being key drivers of the multicellular-driven prothrombotic condition in APS. Despite antithrombotic therapy is the mainstay in APS therapy, onset of thromboembolic events or anticoagulant-related bleeding can be frequently observed. Therefore, a better understanding of the exact pathomechanisms leading to the increased prothrombotic potential in APS is urgently needed.

Aims

To investigate the impact of APS AAbs on the formation of different PLT subpopulations and their potential relevance in thrombus formation ex vivo.

Methods

For the investigation of APS patient AAb-mediated PLT alterations, a flow cytometry (FC)-based procoagulant PLT assay was employed. To study the impact of APS AAb-mediated PLT changes on thrombus formation, a microfluidic ex vivo model of antibody-mediated immunothrombosis that utilizes tetra straining was used.

Results

82 sera from APS patients with a history of thrombosis were tested in this study. FC analysis revealed that a subgroup of 38/82 (46%) patient sera induced significant formation of (CD62p/phosphatidylserine [PS] double positive) procoagulant PLTs while such alterations were not observed in PLTs from healthy individuals upon incubation with controls. APS AAb-mediated procoagulant PLT formation was identified for being PLT Fc-gamma-RIIA (FcγRIIA)-dependent as specific FcγRIIA blockade via monoclonal Ab IV.3, intravenous immunoglobulin (IVIG) or inhibition of FcγRIIA-signaling downstream via spleen tyrosine kinase (SYK) inhibitor Lanraplenib resulted in a near complete abrogation of APS AAb-induced procoagulant PLT formation in vitro. Most importantly, via the utilization of an ex vivo model of antibody-mediated thrombosis APS AAb-induced procoagulant PLTs were identified for being critical mediators of immunothrombosis. Compared to control, spike in of APS patient serum or corresponding immunoglobulin G (IgG) isolates into healthy whole blood resulted in dramatic formation of immunothrombi that were characterized by high amounts of procoauglant PLTs and high numbers of leukocytes that were recruited into the growing thrombus. Importantly, and of potential therapeutic interest, APS AAb-induced procoagulant PLT as well as immunothrombosis were significantly abrogated in the presence of intravenous immunoglobulin (IVIG) or Lanraplenib.

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Summary/Conclusion

Our studies indicate that a subgroup of APS patient AAbs induce the formation of a procoagulant PLT phenotype with dramatic prothrombotic potential in a PLT FcγRIIA-dependent manner .The observation that the presence of IVIG or SYK inhibitor Lanraplenib rescued from APS AAb-mediated procoagulant PLT and increased thrombus formation directs towards a therapeutic potential of such Fc-gamma-receptor-targeting therapeutics to prevent the onset of thromboembolic events in APS.

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