LUPUS NEPHRITIS IS LINKED TO DYSBIOSIS, INCREASED LUPUS ICs in FcγRIIA

Methods To model IC-mediated response more accurately, as they occur in humans, transgenic FcγRIIA (FcγRIIA^TGN) mice expressing FcγRIIA on platelets and certain leukocytes, were used in this study. As acute model, we intravenously injected ICs in FcγRIIA^TGN and FcγRIIA^TGN mice and monitored mouse reaction and platelet activation. To model platelet response to chronic exposure to ICs, we backcrossed NZB mice with FcγRIIA^TGN mice, generating NZB::FcγRIIA^TGN mice and crossed the mice with NZW mice, thus generating NZB::NZW::FcγRIIA^TGN and NZB::NZW::FcγRIIA^null mice. Platelet activation was monitored through time in these mice.

Results Platelet activation by acute exposure to ICs through a mechanism requiring expression of platelet FcγRIIA resulted in the induction of systemic shock. IC-driven shock was dependent on release of serotonin from platelet dense granules secondary to platelet outside-in signaling by αIIbβ3 and its ligand fibrinogen. On FcγRIIA activation, platelets underwent sequestration, but surprisingly they returned in the blood circulation with emptied granules after activation. Strikingly, reminiscent observations were made in lupus NZB::NZW::FcγRIIA^TGN mice. We found significant platelet activation and circulating degranulated platelets, uniquely in mice expressing FcγRIIA.

Conclusions Platelet activation in IC-mediated pathogenesis is well recognized. In lupus patients, platelets are found activated in blood circulation, however, to what extend ICs and FcγRIIA contribute to platelet activation was unknown. Here, we showed that the expression of FcγRIIA is critical to adequately examine platelet role in lupus.

Acknowledgements This work was supported by a Foundation grant from the Canadian Institutes of Health Research (CIHR) to EB. PRF is recipient of a tier 1 Canada Research Chair on Systemic Autoimmune Rheumatic Diseases. NT and IM are recipient of fellowships from The Arthritis Society.