Profibrinolytic microparticles are not adequately produced to compensate their prothrombotic effect

We read with interest the report by Lacroix *et al.*[1] on the fibrinolytic potential of cell-derived microparticles (MPs), i.e. specifically endothelial- and leukocyte-derived microparticles, in a very well designed set of *in vitro* experiments. They have reported elevated levels of profibrinolytic MPs in different pathological situations (systemic lupus erythematosus, thrombotic thrombocytopenic purpura (TTP), atherosclerosis) compared with normal healthy controls. Authors have also suggested that these profibrinolytic MPs may be produced as a compensatory mechanism that may counterbalance the effect of procoagulant MPs and reduce the risk of thrombosis in these patients.

Increased MPs, especially of endothelial origin, have been reported in patients suffering from recurrent pregnancy loss (RPL) by several authors.[2-4] A study at our center involving 70 women suffering from recurrent miscarriages and 20 healthy control women showed that 40 of 70 (57.1%) had increased annexin labeled endothelial MPs ($P<0.05$). The samples were collected at least four months after the adverse event in women with RPL.

Various roles and functions have been attributed to MPs by different authors. However, the general perception is that MPs are highly thrombogenic as the majority of the MPs express phosphatidylserine (PS) or tissue factor on their surface that are prothrombotic in nature. The common finding in all these studies is that MPs are increased in women with RPL when compared to healthy controls and thus contribute to fetal loss by causing uteroplacental thrombosis. Also, the increase in the endothelial MPs a certain period of time after the adverse event suggests a continued chronic endothelial damage or activation. However, we have not looked into the expression of tissue plasminogen activator or urokinase type plasminogen activator on MPs and therefore cannot comment on the fibrinolytic capacity of these MPs. However, if these profibrinolytic MPs were sufficient to compensate the thrombotic effect of thrombogenic MPs, these patients would not suffer pregnancy losses. The effect of antithrombotic therapy[5,6] in women with unexplained fetal loss is irrefutable and is known to greatly increase the success rate of delivering a live child in such patients. This may only suggest that the increased fibrinolytic activity of MPs may not be sufficient to balance the thrombogenicity of the MPs.

The endothelial cell is a Janus faced cell. Depending on the *in vivo* condition and stimuli, it can support either the thrombotic arm or the fibrinolytic arm of the coagulation system. Normal endothelium secretes tissue plasminogen activator that activates the fibrinolysis system. Injury to endothelium is accompanied by loss of protective molecules and expression of adhesive molecules, and procoagulant activities leading to development of thrombosis. Exposure to TNFα, immune complexes (the fetus being one of the sources), increased homocysteine levels (folic acid deficiency in pregnancy, etc.) are all linked to an increased risk of thrombosis. Hence the condition in which endothelial MPs are produced may suggest which attribute (fibrinolytic or thrombogenic) it supports. Increase in MP levels are also seen in healthy pregnant women as the pregnancy advances.[7]

However, the euglobulin clot lysis test is usually prolonged in pregnancy[8] and confirms reduced fibrinolytic activity on this condition making pregnant women prone to thrombosis. This also suggests that the profibrinolytic activity of MPs is not sufficient to restore hemostatic balance. However, the study carried out by Lacroix et al. leads us to question the conventional wisdom of analyzing MPs at a distance in time from the adverse event in women suffering from RPL rather than studying MPs during their pregnancy. Also, the source of profibrinolytic MPs may not always be from the endothelium. In pregnancy, trophoblast cells also circulate in the mother's blood and may produce profibrinolytic MPs. Profibrinolytic MPs may also be derived from neutrophils, monocytes, platelets and other cells, depending on different pathological states and activated conditions. For example, in certain conditions, such as acute leukemia, prostate cancer, etc., which are complicated with increased fibrinolysis, increased levels of fibrinolytic MPs may be found.

It also remains to be seen in different clinical settings whether formation of profibrinolytic MPs *in vivo* is a cause (primary event) or the consequence (secondary reaction) for maintaining a balance in a given condition. The authors have rightly pointed out that further studies are needed to correlate prothrombotic *versus* fibrinolytic effects in different clinical settings and find which arm of the clotting system, i.e. thrombotic or fibrinolytic, dominates in causing the resultant thrombohemorrhagic imbalance.

Rucha Patil, Kanjaksha Ghosh, and Shrimati Shetty

National Institute of Immunohaematology (ICMR), KEM Hospital, Parel, Mumbai, India.

Correspondence: shrimatishetty@gmail.com.

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