Blood Dust as Active Circulating Cellular Representatives During Gestational Vascular Complications

Jean-Christophe Gris

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From the Department of Hematology, University Hospital, Nîmes, France; and Research Team EA2992, University of Montpellier, Nîmes, France.

Correspondence to Jean-Christophe Gris, Consultations et Laboratoire d’hémato-oncologie, Centre Hospitalier Universitaire, Groupe Hospitalo-Universitaire Carémeau, Place du Pr. Robert Debré, F-30029 Nîmes cedex 9, France. E-mail jean.christophe.gris@chu-nimes.fr

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Editorial Commentary

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History sometimes repeats itself. Alfred Donné was probably the first to recognize platelets in the blood in 1842, and Schultz associate the platelets to clotting later on in 1865, but actually, hemoconia (blood dust), devoid of a nucleus, was probably seen by earlier microscopists without any thought being given to their significance. In fact, looking closely at modern electronic microscopic pictures of blood, the background between platelets is filled with blood dust, whose significance has been ignored for a while. Minute particles in normal human plasma and serum were first described by Wolf, who found this material containing most of the platelet-related phosphatase molecules, were subsequently described to be associated with increasing gestational age in normal pregnant women and moreover in women with early-onset PE. Given that syncytiotrophoblasts constitutively express high levels of the main activator of the coagulation process, tissue factor, the analysis of the thrombogenicity of MPs during pregnancy showed a cellular switch: whereas most of tissue factor in healthy pregnant women was related to syncytiotrophoblast MPs, the majority of tissue factor-bearing MPs in women with gestational vascular complications (GVCs) were of the maternal cellular origin, with increased concentrations of circulating endothelial MPs. In women with GVCs, the same group also demonstrated the presence of MPs bearing non-negatively charged phospholipids, thus unable to support coagulation reactions and an increase in endothelial CD144+ MPs and CD31+/CD41− MPs, the latter being significantly reduced in low-molecular-weight heparin treated patients.

The study published by Shomer et al in this issue of Hypertension adds very original results in the field, providing accurate information on the functional heterogeneity of pregnancy-related MPs in women with GVCs (gestational hypertension and PE) compared with women with a normal pregnancy (NP). GVC patients harbored higher levels of endothelial and leukocyte MPs, containing higher concentrations of inflammatory and angiogenic proteins. Early-stage trophoblast cells isolated from second trimester placenta incorporated NP-platelet antigen bearing MPs. MPs apoptotic effect on trophoblasts depended on pregnancy stage: NP-MVs decreased early-stage trophoblast cells apoptosis whereas GVC-MVs had no effect; conversely, GVC-MVs increased cell apoptosis in term trophoblasts whereas NP-MVs did not. Only NP-MVs could induce early-stage trophoblast cells migration, which involved ERK2 (extracellular-regulated kinase 2)-signal transduction pathway. Focusing on cultured human umbilical vein endothelial cells, cell migration could be induced by NP-MVs and GVC-MVs but NP-MVs induced endothelial tube formation, which was inhibited by GVC-MVs. In summary, NP-MVs have an in vitro physiological effect on endothelial and trophoblast cells, favoring angiogenesis and early placentation, respectively, which can be counteracted by GVC-MPs, the latter exhibiting varying effects according to gestational age and target cell type, globally favoring trophoblasts and endothelial dysfunction.

These elegant in vitro results call for some comments and questions.

First, plasma samples and MPs issued from women with gestational hypertension and from women from PE demonstrated similar activities, whereas these are 2 distinct human...
medical entities, generating nonsimilar morbidities. The same remark applies for mild and severe PE. The relationship linking MVs, their particularities if any, to the various entities described under the term GVC have now to be described and explained.

Second, plasma samples were obtained because pregnant women developed a late pregnancy complication. We cannot appreciate whether the described functionally pejorative MVs are a consequence of acute diseases or whether they appear before and can thus announce the onset of the diseases. Prospective longitudinal studies in high-risk women are thus now mandatory.

Third, the molecular genesis leading to the generation of the 2 kinds of MVs has now to be elucidated, together with the principles controlling their cellular emission. What are the 2 kinds of MVs has now to be elucidated, together with the principles controlling their cellular emission. What are the links between the MVs and the placenta transcriptomes?

Fourth, the relative importance of these MVs in the whole pathophysiological process of PE has now to be weighted. Are these abnormal MVs a major precipitating event, thus prone to targeted therapeutic developments, or only an epiphenomenon, which can act for instance as an accessory amplification loop but with no major impact on clinically relevant issues, being more a Supporting Role than a Star?

Fifth, can these circulating abnormal MVs be a valuable biological marker, and is it time for a translational development paving the way for clinically relevant markers with strong negative or positive predictive values? Do we have robust exploratory tools able to detect and quantify the abnormal MVs by cheap standardized procedures, and can the performances of these tools be sufficiently independent from preanalytical variables? Can the dynamic analysis of the MVs content itself during pregnancy give some clear indications on individual prognosis?

Finally, can these abnormal MVs reprogram trophoblasts, for instance, through the targeted delivery of mRNA and of noncoding RNAs? Isn’t it time for a systematic screening of the transcriptome of the pre-eclamptic placentas to identify genes that could be involved in placental dysfunction,11 highlighting over-represented putative transcription factor binding sites in the promoters of consistently modified, up- or downregulated, genes in the pre-eclamptic placenta, these transcription factors being known to regulate specific biological pathways, such as cell response to inflammation, hypoxia, DNA damage, and proliferation.12 What are the links between the MVs and the placenta transcriptomes?

The results obtained by Shomer et al13 have given a new horizon and a new destination to the growing pathophysiological highway of MVs and MPs in medicine. They also generate a number of strong hypotheses and promises which now have to be systematically explored.

Disclosures

None.

References

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