Tissue Factor-triggered Procoagulant Activity of Murine/Human Mesenchymal Stem Cells

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Abstract

[Background] Mesenchymal stem cells (MSCs) have been highlighted in the field of regenerative medicine for their availability and multipotency. However, it has been reported that MSC may associate with cell-infusion-related events including thromboembolism after being administered intravenously. This study investigated the procoagulant property of MSCs.

[Methods] As a preliminary study, we administered 1.5 x 105 cells of murine adipose-derived MSC (ASCs) to wild-type mice via tail vein, and found that 11 out of 13 mice died within 24 h after injection. This fatal event was found to be associated with thromboembolism in the lung, heart, or liver. In order to investigate precise mechanism of this ASC-related event, we assessed ASCs-derived procoagulant properties with (1) citrated whole-blood using ROTEM and (2) citrated plasma using a coagulometer. We also performed the immunostaining and gene expression analysis of ASCs for mouse tissue factor (TF), and a clotting assay using normal plasma (NP) and factor VII-deficient plasma (F7DP).

[Results] ROTEM analysis demonstrated significant shortenings of CT and CFT, and increased a-angle in ASCs samples. Plasma clotting assay also showed the procoagulant property of ASCs in a cell-number dependent manner. We also found that ASCs expressed high TF mRNA, and TF was strongly expressed around the cell surface. ASCs also shortened the clotting time of NP, while the time of F7DP was unable to be shortened as clearly as that of NP. Further investigations were conducted using human ASCs and found that human ASCs also possess strong procoagulant activity triggered by TF.

[Conclusions] ASCs express TF around the cells, and TF may trigger the activation of extrinsic coagulation pathway, leading unexpected thromboembolism. An optimal inhibition for TF by some anti-coagulant agents is recommended for securing the clinical safety of systemic ASCs administration.