Platelet Mitochondria Determine Lung Microvascular Barrier Function In Acid-Induced Lung Injury

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Rationale. Although platelets contribute to acute lung injury (ALI), underlying mechanisms remain unclear. We considered the possibility that platelet mitochondria might determine platelet function in ALI. Mitochondria determine cellular bioenergetics, hence cell function. Loss of function of platelet mitochondria may lead to loss of critical aspects of platelet function that the maintenance of lung microvascular barrier properties. We tested this hypothesis in the mouse model of acid-induced ALI.

Methods. We exposed isolated mouse platelets to the inhibitor of the mitochondrial electron transport chain, rotenone (20 μM, 20 min) that inhibits mitochondrial ATP production. We perfused isolated mouse lungs (IPLs) with dextran-HEPES buffer alone, or dextran-HEPES buffer containing RBCs, leukocytes and rotenone-treated or untreated platelets. IPLs were maintained at constant pulmonary artery, pulmonary vein and airway pressures of 10, 3 and 5 cmH2O. To induce ALI, we gave HCl (pH 1.2, 1.5ml/kg) to the IPLs by airway instillation.

After 1 h, we determined the microvascular filtration coefficient (Kf) to quantify lung microvascular barrier properties.

Results. In IPLs perfused with dextran-HEPES buffer alone, Kf was 0.22±0.04 ml/(cmmH2O min.100g wet lung weight). Addition of untreated or rotenone-treated platelets together with RBCs and leukocytes did not change baseline Kf. However, in IPLs perfused with untreated platelets, acid instillation increased Kf 2.5-fold above baseline (n=4, P<0.05), indicating that acid instillation caused major microvascular injury. Notably, in IPLs perfused with rotenone-treated platelets, acid instillation increased Kf 5-fold above baseline (n=4, P<0.05), indicating that mitochondrial inhibition augmented lung injury.

Conclusion. Our findings show for the first time that inhibiting platelet mitochondrial function increases lung injury in the acid-aspiration model of ALI. We interpret: first, since rotenone-treated platelets did not increase baseline Kf, inhibition of platelet mitochondria does not itself cause lung injury. Second, increased injury in the presence of both acid instillation and perfusion with rotenone-treated platelets resulted from loss of the protective effects of platelets on the lung microvascular barrier. We suggest, loss of function of platelet mitochondria decreased platelet-endothelial interactions, that are likely to be critical for the barrier protective effects of platelets.

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