Platelet microvesicles in vascular inflammation

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Background: Microvesicles are gathering increasing attention as mediators of cell communication and as integral effectors of disease. Platelets present a major source of microvesicles and release these microvesicles either spontaneously or upon activation. Platelet microvesicles (PMVs) retain many features as integral effectors of disease. Platelets present a major source of microvesicles and release these microvesicles either spontaneously or upon activation. Platelet receptors implicated in PMV-SMC interaction were identified by blocking antibodies. PMV binding to SMCs was specifically abrogated by the integrin αIIbβ3 inhibitor (integrilin) indicating an integrin-dependent mechanism of interaction. A proliferative effect on SMCs was measured after adhesion mainly determined by a flow adhesion assay. Relative quantification of gene expression was determined by real time and quantitative PCR.

Methods: PMVs were isolated from aging human platelet concentrates by serial centrifugation steps. PMVs were quantified and characterized by flow cytometry using annexin A5/phosphatidylserine and antibodies against CD41a/GPIIb. Size calibrated micro beads were used to quantify the absolute amount of PMVs/mL. Cell migration experiments were performed using a boyden chemotaxis chamber. Platelet receptors implicated in PMV-SMC interaction were identified by blocking antibodies. Proliferation of SMCs was measured by the BrDU-cell proliferation kit. Adhesion of monocytes to SMCs was determined by a flow adhesion assay. Relative quantification of gene expression was determined by real time and quantitative PCR.

Results: In the presence of PMVs, SMCs showed increased migration. Under resting conditions, the PMV binding to SMCs was specifically abrogated by the integrin αIIbβ3 inhibitor (integrilin) indicating an integrin-dependent mechanism of interaction. A proliferative effect on SMCs was measured after 48 hours after incubation with PMVs and this proliferation relied on interactions via integrin αIIbβ3, CD40 and P-selectin. The firm adhesion of monocyte cells to PMVs stimulated SMCs under flow conditions was significantly increased compared to untreated, resting SMCs. The adhesion mainly depended on the integrin αIIbβ3 and P-selectin but also CD40 and fractalkine. PMVs decreased gene expression of contractile proteins, i.e. αSMA and calponin.

Conclusion: PMVs have shown to exert an immunomodulatory activity on various cell types. The present data indicate a role of PMVs in inducing a phenotypic switch towards a synthetic inflammatory SMC phenotype, thus contributing to vascular atherogenesis, in particular vascular remodeling.

Platelets: Old Players Revisited

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285 Pharmacological depletion of serotonin promotes atherosclerotic plaque formation in apoE−/− mice

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Cardiovascular disease, like myocardial infarction and stroke, is the major cause of death in western countries, which mainly arise from atherosclerosis. This chronic disorder is characterized by inflammation of the vessel wall driving lesion formation. These so called plaques contain macrophages, T cells and other immune cells as well as an accumulation of lipids. In the early phase an activation of the endothelium induces adhesion molecule expression and secretion of pro-inflammatory cytokines and chemokines leading to the recruitment of leukocytes. Platelets also contribute to the leukocyte recruitment by interacting with the endothelium and secretion of granule content including serotonin. Platelet serotonin was recently shown to promote selectin-dependent leukocyte interaction and recruitment to post-capillary venules in a mouse model of acute inflammation. Clinically available serotonin receptor inhibitors (SERT) used as anti-depressive drugs might be a useful strategy to impair peripheral serotonin uptake. Pharmacological depletion of serotonin promotes atherosclerotic plaque formation in apoE−/− mice.

Methods: Pharmacological depletion of serotonin promotes atherosclerotic plaque formation in apoE−/− mice.

Results: Pharmacological inhibition in early plaque formation. Our findings might have important clinical implications in particular for cardiovascular risk patients treated with SERT inhibitors for depression.

Conclusions: Pharmacological depletion of serotonin promotes atherosclerotic plaque formation in apoE−/− mice.