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Platelet microparticles: small payloads with profound effects on tumor growth

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It has long been known that platelets facilitate metastasis formation (1). In cancer, platelets are known to contain tumor related microRNA and serve as a biomarker for cancer (2–4). Cancer related platelet profiles also associate with consensus molecular subtypes of colorectal cancer (5).

Platelets are 1–4 μm in size and are produced by a complex cytoplasmic and membrane process from megakaryocytes in the bone marrow, which are also the largest cell in the body ranging between 50–100 μm in diameter (6). This process involves proplatelet formation that includes thin cytoplasmic extensions that radiate from megakaryocytes that bleb off and mature into functional platelets (6). As a membrane vesicle product of platelets, microparticles have been known for some time (7). Platelet-derived microparticles (PMPs) are 0.02–0.10- μm fragments shed from plasma membranes of platelets that are activated, stressed, or apoptotic and may play a role in the normal hemostatic response to vascular injury (8–10). PMPs display multiple platelet surface glycoprotein (GP) receptors including GPIIb/IIIa (integrin $\alpha\text{IIb}\beta\text{3}$) and GPIb/IX (11,12). PMPs also can contain surface procoagulant activity (13–15) that could potentially influence the hypercoagulability associated with cancer related Trousseau's syndrome (16). Human platelet PMPs contain numerous diverse contents including miRNAs that can influence platelet mRNAs, protein synthesis, and reactivity. PMPs are the most abundant microparticles in the peripheral blood and contribute 70–90% of all extracellular vesicles (17,18). PMPs are taken up by endothelial cells and can regulate their ICAM-1 expression (19). Similarly, Laffont *et al.* showed that thrombin activated human platelets release their miR-223 content in PMPs (9). These PMPs were internalized by human umbilical vein endothelial cells (HUVECs), leading to the accumulation of platelet-derived miR-223 (9). PMPs also contained functional Argonaute 2 (Ago2)/miR-223 complexes that can regulate HUVECs introduced reporter gene expression (9). PMPs can also be taken up by leukocytes (20). Similarly, PMP engulfment and miRNA delivery to neutrophils depends on the presence of platelet 12-

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lipoygenase and secreted phospholipase A2-IIA (21). Solid tumor vasculature is malformed and very leaky, which can potentially allow for PMP availability to tumor cells (22).

Michael *et al.* recently present data supporting the notion of PMPs infiltration and transfer of platelet-derived RNA, including miRNAs, into solid tumors. In this study, their data from humans and mice to tumor cells *in vivo* and *in vitro* suggest that this uptake triggers tumor cell apoptosis. Their data show that at least one microRNA (miR)-24 was a major species in PMP transfer. To validate these findings *in vivo*, they transfused PMP. This experiment revealed growth inhibition of both lung and colon carcinoma ectopic tumors. By extension this experiment showed a blockade of miR-24 in tumor cells accelerated tumor growth *in vivo*, and prevented tumor growth inhibition by PMPs. These authors also studied the reduction of circulating microparticles, which became reduced in protease-activated receptor 4 (PAR-4), also known as coagulation factor II (thrombin) receptor-like 3 (*F2RL3*)-deleted mice, that inhibited tumor growth and was negated by PMP transfusion. When targeted, PMP also associated with *in vivo* tumor cell apoptosis. As additional findings, these authors investigated direct RNA targets of platelet-derived miR-24 in tumor cells. These targets included a non-coding small nucleolar RNA and mitochondrial *mt-Nd2* along with *Snora75*. Expression of these RNAs in PMP-treated tumor cells was reduced causing mitochondrial dysfunction and growth inhibition in a miR-24-dependent fashion.

Based on these data, the authors concluded that platelet-derived miRNAs can be transferred into solid tumors via infiltrating platelet microparticles and thereby regulate tumor cell gene expression to influence tumor progression. They suggest further that their findings provide insight into horizontal RNA transfer mechanisms and regulatory roles of miRNAs influenced by PMP activity in tumor progression. In the context of enhanced vascular permeability associated with solid tumors, they postulate that plasma microparticle-mediated transfer of regulatory RNAs, which modulate gene expression, may be a common feature in cancer.

These are very thought-provoking observations that deserve further study. The novelty of PMP uptake by tumors triggering miR-24 induced apoptosis is very intriguing. The implication of this finding is potentially clinically significant given that PMPs constitute an overwhelming proportion of heterogeneous microparticles in the circulation (17,18,23). However, these findings are also in contrast to a very significant body of data that demonstrate an enhancement of tumor progression by platelets and their subcomponents (1,5,24). The complex molecular effects of miR-24 bearing PMPs on the behavior of Lewis lung carcinoma and MC38 syngeneic tumor cells illustrates the complexities of platelet and PMP function yet to be resolved in solid tumor progression. Many questions remain to be answered. Will the PMP based miR-24 effect be observed in other solid tumors? How does the variance in the vascular permeability of different tumors and tissue beds influence the uptake of PMPs? What influence do other circulating free macromolecules have on this process (25)? What sort of clinical interventions will be able to safely impact PMP production and management? As with all interesting research findings, provocative research findings lead to even more provocative questions.

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References

1. Menter DG, Kopetz S, Hawk E, et al. Platelet “first responders” in wound response, cancer, and metastasis. *Cancer Metastasis Rev* 2017 [Epub ahead of print].
2. Sol N, Wurdinger T. Platelet RNA signatures for the detection of cancer. *Cancer Metastasis Rev* 2017 [Epub ahead of print].
3. Tjon-Kon-Fat LA, Sol N, Wurdinger T, et al. Platelet RNA in Cancer Diagnostics. *Semin Thromb Hemost* 2017 [Epub ahead of print].
4. Wurdinger T, Tannous BA, Saydam O, et al. miR-296 regulates growth factor receptor overexpression in angiogenic endothelial cells. *Cancer Cell* 2008;14:382–93. [PubMed: 18977327]
5. Lam M, Roszik J, Kanikarla-Marie P, et al. The potential role of platelets in the consensus molecular subtypes of colorectal cancer. *Cancer Metastasis Rev* 2017 [Epub ahead of print].
6. Thon JN, Italiano JE. Platelet formation. *Semin Hematol* 2010;47:220–6. [PubMed: 20620432]
7. Wolf P The nature and significance of platelet products in human plasma. *Br J Haematol* 1967;13:269–88. [PubMed: 6025241]
8. Semple JW. Platelets deliver small packages of genetic function. *Blood* 2013;122:155–6. [PubMed: 23847185]
9. Laffont B, Corduan A, Ple H, et al. Activated platelets can deliver mRNA regulatory Ago2*microRNA complexes to endothelial cells via microparticles. *Blood* 2013;122:253–61. [PubMed: 23652806]
10. Italiano JE Jr., Mairuhu AT, Flaumenhaft R. Clinical relevance of microparticles from platelets and megakaryocytes. *Curr Opin Hematol* 2010;17:578–84. [PubMed: 20739880]
11. Breton-Gorius J, Lewis JC, Guichard J, et al. Monoclonal antibodies specific for human platelet membrane glycoproteins bind to monocytes by focal absorption of platelet membrane fragments: an ultrastructural immunogold study. *Leukemia* 1987;1:131–41. [PubMed: 3669739]
12. George JN, Thoi LL, McManus LM, et al. Isolation of human platelet membrane microparticles from plasma and serum. *Blood* 1982;60:834–40. [PubMed: 7115953]
13. Michelson AD, Barnard MR, Krueger LA, et al. Evaluation of platelet function by flow cytometry. *Methods* 2000;21:259–70. [PubMed: 10873480]
14. Hugel B, Socie G, Vu T, et al. Elevated levels of circulating procoagulant microparticles in patients with paroxysmal nocturnal hemoglobinuria and aplastic anemia. *Blood* 1999;93:3451–6. [PubMed: 10233897]
15. Beguin S, Kumar R, Keularts I, et al. Fibrin-dependent platelet procoagulant activity requires GPIb receptors and von Willebrand factor. *Blood* 1999;93:564–70. [PubMed: 9885217]
16. Stone RL, Nick AM, McNeish IA, et al. Paraneoplastic thrombocytosis in ovarian cancer. *N Engl J Med* 2012;366:610–8. [PubMed: 22335738]
17. Horstman LL, Ahn YS. Platelet microparticles: a wide-angle perspective. *Crit Rev Oncol Hematol* 1999;30:111–42. [PubMed: 10439058]
18. Nieuwland R, Berckmans RJ, Rotteveel-Eijkman RC, et al. Cell-derived microparticles generated in patients during cardiopulmonary bypass are highly procoagulant. *Circulation* 1997;96:3534–41. [PubMed: 9396452]
19. Faille D, El-Assaad F, Mitchell AJ, et al. Endocytosis and intracellular processing of platelet microparticles by brain endothelial cells. *J Cell Mol Med* 2012;16:1731–8. [PubMed: 21883894]
20. Ogura H, Kawasaki T, Tanaka H, et al. Activated platelets enhance microparticle formation and platelet-leukocyte interaction in severe trauma and sepsis. *J Trauma* 2001;50:801–9. [PubMed: 11371835]

21. Duchez AC, Boudreau LH, Naika GS, et al. Platelet microparticles are internalized in neutrophils via the concerted activity of 12-lipoxygenase and secreted phospholipase A2-IIA. *Proc Natl Acad Sci U S A* 2015;112:E3564–73. [PubMed: 26106157]
22. Amin C, Mackman N, Key NS. Microparticles and cancer. *Pathophysiol Haemost Thromb* 2008;36:177–83. [PubMed: 19176990]
23. van Doormaal F, Kleinjan A, Berckmans RJ, et al. Coagulation activation and microparticle-associated coagulant activity in cancer patients. An exploratory prospective study. *Thromb Haemost* 2012;108:160–5. [PubMed: 22535219]
24. Haemmerle M, Stone RL, Menter DG, et al. The platelet lifeline to cancer: challenges and opportunities. *Cancer Cell* 2017 [In press].
25. Kanikarla-Marie P, Lam M, Menter DG, et al. Platelets, circulating tumor cells, and the circulome. *Cancer Metastasis Rev* 2017 [Epub ahead of print].