This Month in APR

By Joo Young Lee, Associate Editor

Paclitaxel, a double-edged sword for tumor and platelets

Hemostasis and thrombosis are dynamically regulated by the interaction between vascular endothelial cells and platelets (Davì and Patrono, 2007; Vanhoutte and Houston, 1985; Packham, 1994). Endothelial cells continually produce vasomodulators such as nitric oxide, prostaglandin E_2 (PGE_2), and PGI_2 to control activation of platelets (Radomski et al., 1987). Damage or stress to blood vessel shifts the balance towards enhanced activation of platelets, leading to the secretion of platelet aggregation agonists such as ADP, thrombin, and serotonin from dense granules. These agonists further recruit platelets and other vascular cells to the site of injury and aggravate secondary platelet aggregation and thrombus formation (Houston et al., 1985; Kroll and Schafer, 1989; Willerson et al., 1989). Platelet activation is linked to the metabolism of phospholipids to produce arachidonic acid by phospholipase A_2 (PLA_2), which is subsequently metabolized to PGH_2 by cyclooxygenase (COX). PGE_2 and thromboxane A_2 (TXA_2) are generated from PGH_2 by PGE_2 synthase and TXA_2 synthase, respectively (Reilly and Fitzgerald, 1993). Platelet activation by agonists increases intracellular Ca^{2+}, which is released from the sarcoplasmic reticulum by inositol 1,4,5-triphosphate (IP_3) produced by activated phospholipase C (PLC) (Worner and Brossmer, 1975; Bergmeier and Stefanini, 2009). Elevated Ca^{2+} activates intracellular signaling pathways in platelets, including activation of MAP kinases and cytosolic PLA_2, formation of TXA_2, and granule release. Increased Ca^{2+} induces activation of myosin light chain kinase leading to subsequent cytoskeletal changes. Excessive platelet aggregation is a risk factor for cardiovascular complications, including thrombosis,

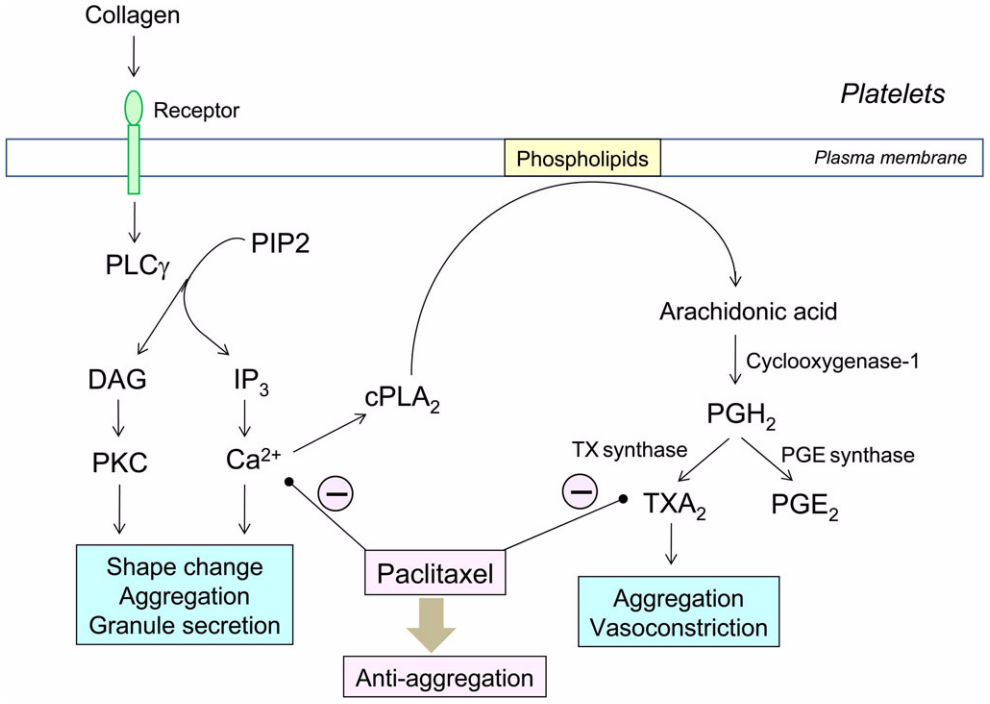

Fig. 1. Signaling pathways of platelet activation by collagen and anti-aggregation activity of paclitaxel. Collagen activates glycoprotein (GP) receptors such as GP Ia/IIa, GP IIb/IIIa, and GP VI, leading to the activation of PLCγ and the formation of IP_3 and DAG. IP_3 and DAG induce the release of Ca^{2+} from dense granules and the activation of PKC, respectively, resulting in shape changes and platelet aggregation. The increase in intracellular Ca^{2+} evokes the activation of PLA_2 and the metabolism of phospholipids and arachidonic acids. Prostaglandins (PGs) and TXA_2 are generated from arachidonic acids by cyclooxygenase-1, PG synthase, and TX synthase. TXA_2 further initiates the secondary aggregation of platelets and induces vasoconstriction. Paclitaxel attenuates collagen-induced increases in intracellular Ca^{2+} and suppressed TXA_2 formation stimulated by arachidonic acid to prevent platelet aggregation. DAG, diacylglycerol; IP_3, inositol-1,4,5-trisphosphate; PG, prostaglandin; PIP2, phosphatidylinositol-4,5-bisphosphate; PKC, protein kinase C; PLA_2, phospholipase A2; PLC, phospholipase C; TX, thromboxane.

ischemic stroke, atherosclerosis, and myocardial infarction (Jennings, 2009). Therefore, blocking platelet aggregation could help prevent cardiovascular diseases.

Paclitaxel, or Taxol, was first isolated from the bark of the Pacific Yew tree, *Taxus brevifolia* and is being used in cancer chemotherapy to treat patients with lung, ovarian, breast, head, and neck cancer (Wani et al., 1971). Paclitaxel is a microtubule stabilizer that inhibits cell division and proliferation (Horwitz, 1992). Paclitaxel is also clinically used in drug-eluting stents for the prevention of restenosis by prohibiting the unwanted proliferation of blood vessel walls (Herdeg et al., 1998). The development of restenosis is dependent on the balance between hemostasis and thrombosis, and paclitaxel may regulate platelet activation to prevent thrombosis and restenosis. When incubated with whole blood from human volunteers, paclitaxel concentration in platelets was 240-fold higher than that in plasma (Wild et al., 1995), suggesting that platelets are a critical target tissue for paclitaxel. Paclitaxel blocks platelet aggregation by stabilizing microtubules (Shiba et al., 1988; Horwitz, 1992; Canizares et al., 1997). Agonist activation, such as thrombin, induces morphological change from a smooth disk to an irregular spheroid, a process that requires the disappearance of tubulin microtubules from the cytosol (Steiner and Ikeda, 1979; Kenney and Chao, 1980). Th us, microtubule stabilization by paclitaxel may block the cytoskeletal changes and inhibit platelet aggregation. Paclitaxel is a platelet-sparing agent, as it improves thrombocytopenia in heavily pretreated ovarian cancer patients (Pertusini et al., 2001; Ishikawa et al., 2002). In this issue, Lee et al.(2010) present intriguing results that paclitaxel can modulate platelet signaling pathways to decrease aggregation. Paclitaxel inhibited collagen-induced platelet aggregation and decreased intracellular Ca^{2+} concentration, serotonin secretion, and arachidonic acid liberation. Paclitaxel was most potent against collagen, but showed weaker activity against thrombin or a TXA_2 mimic. Despite reducing increment in intracellular Ca^{2+} induced by collagen, paclitaxel did not inhibit phosphorylation of PLCγ, indicating that paclitaxel inhibits a component downstream of PLCγ. Paclitaxel inhibited arachidonic acid metabolism and reduced TXA_2 production, but did not affect PGD_2 formation. Thus, paclitaxel targets TXA_2 synthase rather than COX-1. TXA_2 is a potent platelet agonist and vasoconstrictor that regulates platelet aggregation and vasomotor activity (Nakahata, 2008). TXA_2 inhibition could prevent cardiovascular diseases, including thrombosis and atherosclerosis. TXA_2 synthase is also involved in cancer development (Moussa et al., 2005; Sakai et al., 2006). Inhibitors of thromboxane synthase significantly reduce tumor cell growth, invasion, metastasis, and angiogenesis (Moussa et al., 2008; Leung et al., 2009), suggesting that inhibition of thromboxane synthase may contribute to the anticancer effects of paclitaxel. Collectively, the results from Lee et al. suggest that paclitaxel may block restenosis by anti-aggregation effects on platelets and the subsequent blockade of thrombus formation. Further studies may show that paclitaxel exerts multiple actions in cancer patients, such as antiplatelet aggregation and inhibition of TXA_2 synthase, in addition to antiproliferation activity.

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