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EDITORIAL COMMENT

Theranostic Strategy Against Plaque Angiogenesis*

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Plaque destabilization and rupture are the major pathologic substrates of coronary thrombosis and acute coronary syndromes (1). Contributing to these, intraplaque hemorrhage is one of the most important accompaniments of plaque rupture (2). Hemorrhagic events in coronary plaques are confirmed by the presence of morphologically recognizable red cells, hemosiderin, or by glycophorin A immunoreactive material. Glycophorin A is exclusively associated with red blood cell membranes (3). In atherosclerosis

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caused by chronic thromboembolic pulmonary hypertension, thrombotic material seems to be the sole contributor to plaque formation, and glycophorin A immunoreactive material is the major constituent of the pultaceous-lipid cores of the pulmonary atherosclerotic plaques (4). Subsequent experimental and human studies have confirmed the role of red cell membranes in the composition of plaque cores. They also have documented that microhemorrhages and angioneogenesis typically occur in plaques with large cores (5) and play a critical role in plaque progression and rupture (Fig. 1) (6,7). Microvessel-related intraplaque hemorrhage is a potent stimulus for macrophage activation and plaque inflammation, which is also associated intimately with high risk of plaque rupture (8,9). Therefore, angioneogenesis is a potential therapeutic target for plaque stabilization. Current medical therapies of ischemic heart disease include statins that primarily reduce circulating lipids and cholesterol but also influence plaque stabilization through anti-inflammatory and anti-angiogenetic effects (10).

Furthermore, novel agents specifically acting on moieties expressed by neoangiogenic growth could offer plaque stabilization; integrins are one such target (11). Integrins are glycoproteins that comprise noncovalently bound alpha and beta subunits. Numerous combinations of the alpha and beta chains form an array of integrin heterodimers, which can specifically interact with extracellular matrix proteins and soluble ligands (12). Their affinity depends on the extent of activation, and the integrin-mediated signaling has been reported to influence tumor cell proliferation, survival, and apoptosis. The $\alpha_v\beta_3$ integrin is a well-characterized heterodimeric adhesion molecule that is widely expressed by vascular endothelial and smooth muscle cells and plays a critical role in cell migration and cellular adhesion in addition to the formation of new blood vessels (12,13). The $\alpha_v\beta_3$ integrin typically is expressed by neoangiogenic sprouting and, therefore, is considered a general marker of angiogenesis (14). A molecular imaging approach uses paramagnetic nanoparticles targeted to $\alpha_v\beta_3$ integrins to detect and characterize angiogenesis associated with growth factor expression (15), tumor growth (13), and atherosclerosis (11). From the initial diagnostic rationale (11), targeting nanoparticles have been used as carriers of therapeutic molecules (fumagillin) introducing the "theranostic" (i.e., therapeutic + diagnostic) strategy in the setting of atherosclerosis (Fig. 1) (16).

A number of inhibitors of various integrins are currently in clinical trials for the management of malignancies (17). TNP-470, a soluble form of fumagillin, is an antiangiogenetic drug that targets the metalloprotease methionine aminopeptidase-2, which is involved in the protein synthesis regulation (18). Fumagillin decreases both neovascular proliferation and plaque development in experimental atherosclerosis when administered in high doses (19). However, the doses necessary to obtain the

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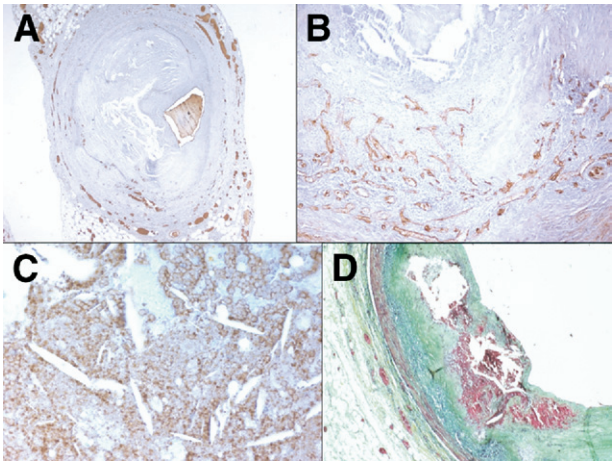

Figure 1. Role of Neoangiogenesis in Plaque Vulnerability

(A) Low-magnification view of a coronary atherosclerotic plaque with prominent vasa vasorum containing red cells that are immunostained with anti-glycophorin A antibodies. **(B)** A paraffin section of a large coronary atherosclerotic plaque immunostained with anti-CD34 antibodies is shown. The brown network of newly formed vessels is embedded in an intense inflammatory background that surrounds the core of the plaque. **(C)** Pultaceous core showing both intact and fragmented red cells immunostained with antiglycophorin A antibodies. **(D)** Hemorrhage of a small coronary plaque, suggesting that intraplaque bleeding is a common phenomenon.

antiatherosclerotic therapeutic effect also produce severe adverse effects in humans (20). In their earlier report, Winter et al. (21) combined the delivery of fumagillin with $\alpha_v\beta_3$ integrin-targeted paramagnetic nanoparticles, eliciting a marked antiangiogenetic response with a 50,000 times lower drug dose.

In this issue of *iJACC (JACC: Cardiovascular Imaging)*, Winter et al. (22) go a step forward and attempt quantification of the efficacy of theranostic drug administration. This strategy allows the simultaneous detection and monitoring of the therapeutic target and efficient treatment. The first aim of the study was to assess whether $\alpha_v\beta_3$-driven fumagillin could be effective when administered at very low doses. The second aim was to test whether the effects of acute administration of fumagillin was maintained over time when combined with daily statin treatment.

They observed that $\alpha_v\beta_3$-targeted fumagillin nanoparticles reduced aortic neovascular signal by 1 week and maintained the efficacy over the next 3 weeks. They also compared the antiangiogenetic effect of atorvastatin alone and in combination with $\alpha_v\beta_3$-targeted fumagillin nanoparticles. The combination lowered the neovascularization magnetic resonance signal and maintained it up to 8 weeks. They further demonstrated that the combined administration of fumagillin with statins was safe; liver enzymes levels showed mild increases but did not exceed upper normal values, which was similar to statin administration alone. There was no difference in other biochemical profile between the statin treatment and the combined-treatment groups; only platelet count exceeded the upper normal level in the combined treatment group. Further investigation is needed to assess the potential risk of thrombosis due to thrombocytosis associated with the fumagillin treatment.

This study provides new indications relevant for the future theranostic strategies in the field of plaque stabilization targeted against local angioneogenesis. The burden of atherosclerotic disease in the western society is a strong incentive for research and development of new therapeutic strategies that can either act in very early stages of the disease or prevent complications. Clinical trials based on nanomedical approaches are ongoing in malignancy to combat metastasis dissemination; most of them are aimed at investigating the efficacy of paclitaxel albumin-stabilized nanoparticle formulation in metastatic solid tumors or breast cancer (23). Winter et al. (22) propose a theranostic strategy in the field of atherosclerotic plaques with angioneogenesis to prevent or combat plaque hemorrhage and destabilization. Further research would test how the effects of the combined therapy endure beyond the first 8 weeks. Nonetheless, the novel strategy of selectively driving therapeutic molecules on specific targets opens new field of research for preventing plaque destabilization. The clinical need, the biologically plausible hypothesis, and the proven feasibility in the experimental setting make this new approach an attractive area of development of new treatments for plaque stabilization in vivo.

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