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EDITORIAL COMMENT

Perking Up Strategies to Control Restenosis*

Dario F. Riascos-Bernal, MD, PhD[a,b]

Restenosis has been observed since the beginning of percutaneous coronary intervention with the development of angioplasty in the late 1970s. Vascular smooth muscle cell (SMC) migration and proliferation leading to intimal growth are recognized as key contributors to this problem. Placement of vascular stents was developed to reduce restenosis after angioplasty, and stent technology has continuously evolved from bare-metal stents to drug-eluting stents (DES) in order to achieve this goal.

Although DES represent an improved strategy as they release antiproliferative drugs that limit intimal growth and restenosis, they are not free of deleterious effects. Thrombosis in the presence of DES (stent thrombosis) is a problem of major clinical importance that may have fatal consequences. Different aspects associated with DES implantation may favor thrombogenesis, such as deleterious effects of the eluted drug on endothelial cells (ECs), the polymer used as drug reservoir, stent strut thickness, the composition and architecture of the scaffold, incomplete stent apposition, and specific characteristics of the lesion, vessel, and patient to be treated (1). Newer DES feature biodegradable polymers and scaffolds and are under study (1).

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The lack of cell-type specificity of drugs released from current DES is notorious. DES supply compounds of 2 kinds: 1) inhibitors of mechanistic target of rapamycin kinase such as sirolimus, everolimus, and zotarolimus, which arrest the cell cycle near the G1-S transition; or 2) inhibitors of microtubule disassembly such as paclitaxel that induce mitotic arrest (1). These compounds exert their antiproliferative and cytotoxic effects not only on SMCs—which is desirable, as it opposes restenosis—but also on ECs, which leads to EC dysfunction, delays re-endothelialization, and provides the substrate for stent thrombosis. Identification of compounds with cell-type selectivity that do not alter but promote EC antithrombotic, anti-inflammatory, and barrier functions while inhibiting SMC accumulation would represent a major advance in our strategy to tackle restenosis.

In this issue of *JACC: Basic to Translational Science*, Wang et al. (2) show that GSK2606414, an inhibitor of protein kinase RNA-like endoplasmic reticulum kinase (PERK), decreases PERK phosphorylation and inhibits intimal growth in rat carotid arteries subjected to balloon angioplasty. This PERK inhibitor achieves this effect when supplied by either intravascular administration using biomimetic nanoclusters or by topical perivascular delivery. Interestingly, Wang et al. (2) also show that GSK2606414 given by oral gavage decreases thrombus formation in mouse carotid arteries subjected to ferric chloride-induced endothelial injury. Although these observations support the idea that this PERK inhibitor may oppose both restenosis after angioplasty and thrombosis in the context of endothelial injury, whether this compound simultaneously renders these outcomes in the setting of

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From the [a]Division of Cardiology, Department of Medicine, Wilf Family Cardiovascular Research Institute, Albert Einstein College of Medicine, Bronx, New York; and the [b]Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, New York. Dr. Riascos-Bernal was supported by a Career Development Award from the American Heart Association (19CDA34660217).

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angioplasty and stent placement is unknown. This is due to the fact that the PERK inhibitor was evaluated in distinct murine models as well as the lack of evaluation of re-endothelialization in the model of angioplasty. In addition, the potential effects of GSK2606414 on platelet function, coagulation, and thrombolysis, which could also contribute to the phenotype observed in the model of thrombosis, were not evaluated. Nevertheless, the in vivo data presented by Wang et al. offer a strong rationale to further assess the effect of PERK inhibitors on in-stent restenosis and thrombosis.

Wang et al. (2) also provide clues for potential cell-selective actions of the PERK inhibitor GSK2606414 on human SMCs and ECs in culture. PERK activation was induced in SMCs and ECs by platelet-derived growth factor (PDGF) and tumor necrosis factor (TNF)-α, respectively. As expected, these stimuli had rather opposite effects on the behavior of SMCs and ECs in culture, namely that PDGF increased SMC proliferation and dedifferentiation, whereas TNFα decreased EC proliferation and increased tissue factor expression, a thrombogenic protein. In these experimental settings, GSK2606414 inhibited SMC proliferation but stimulated EC proliferation and reduced EC tissue factor expression. Whether this and other PERK inhibitors exhibit this profile of cellular actions in arteries undergoing angioplasty was not explored. Addressing the latter is certainly an important research endeavor.

From a biological perspective, the work of Wang et al. (2) brings attention to the role of endoplasmic reticulum (ER) stress as a regulator of the SMC and EC phenotype during the response to vascular injury. In general, ER stress occurs when the supply of newly synthetized peptides or proteins that require folding and processing exceeds the actual folding and processing abilities of the ER machinery, leading to accumulation of unfolded or misfolded proteins and activation of the unfolded protein response (UPR) (3). This response serves to restore ER homeostasis by inhibiting protein translation, increasing ER folding capacity, and activating the ER-associated degradation system to discard misfolded proteins (3). Within this response, PERK, an ER transmembrane protein, is typically described as 1 of the sensors of ER stress (3). PERK is activated by the buildup of unfolded or misfolded proteins and triggers a series of downstream mechanisms that contribute to UPR (3). The following findings of Wang et al. suggest that PERK activity promotes intimal hyperplasia after angioplasty: 1) expression of phosphorylated active PERK and some downstream components was induced in the media and intima after vascular injury; 2) GSK2606414, a potent and selective PERK inhibitor, reduced carotid artery neointima formation in a rat model of balloon injury; and 3) overexpression of PERK increased vascular obstruction in the same model. The low dose of GSK2606414 used in these studies (2) reduces the probability of off-target effects; however, PERK-independent effects of this compound cannot be completely ruled out. The reported role of PERK activity as a factor that contributes to intimal hyperplasia after vascular injury (2) complements previous reports in the scientific literature that have explored the role of ER stress in this context. For instance, knocking down activating transcription factor 4, a downstream effector of PERK, reduces intimal hyperplasia in rat carotid arteries subjected to balloon injury (4); similarly, an SMC-selective genetic deletion of X-box binding protein 1, a downstream effector of the inositol requiring enzyme 1-mediated branch of the UPR, decreases neointima formation in mouse femoral arteries after wire injury (5).

The in vivo underlying molecular mechanisms that drive UPR in distinct cell types involved in restenosis, such as SMCs, ECs, and inflammatory cells, and that connect this response to cell death, proliferation, migration, or other cellular outcomes in injured arteries are largely unknown. The complexity of the UPR mechanism and the interaction of its downstream effectors with other signaling pathways offers the possibility that distinct cellular outcomes may result in different cell types upon ER stress. Thus, a better mechanistic understanding of the response to ER stress in the setting of vascular injury leading to restenosis may reveal pathways susceptible to therapeutic interventions that render cell type-specific effects, for instance inhibition of SMC proliferation and migration, and enhancement of EC function.

ADDRESS FOR CORRESPONDENCE: Dr. Dario F. Riascos-Bernal, Albert Einstein College of Medicine, Department of Medicine-Cardiology Division, 1300 Morris Park Avenue, Forchheimer Building, Room G46, Bronx, New York 10461. E-mail: dario.riascosbernal@einsteinmed.org.

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