Blockade of Cytidine Triphosphate Synthase Regulates Smooth Muscle Cell and Endothelial Cell Proliferation Differentially

Kimie Tanaka, Masataka Sata

Percutaneous coronary intervention with stents is currently the most commonly performed coronary revascularization procedure.1,2 Two types of coronary stents, bare metal stent and drug-eluting stent (DES), are used.2 The main complications of stent implantation are in-stent restenosis and stent thrombosis. DES reduced the incidence of restenosis compared with bare metal stent. However, the occurrence of very late stent thrombosis is significantly higher with DES.3 Clinical and basic studies suggested that DES implantation is associated with retarded re-endothelialization because the drugs eluted from the DESs have inhibitory effects not only on smooth muscle cells (SMCs) but also on endothelial cells (ECs).3,4 Thus, it would be an ideal strategy to inhibit SMC proliferation without affecting EC survival, proliferation, and migration.5

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Cytidine triphosphate (CTP) is a nucleotide with a pyrimidine base. Among all nucleotides, the cellular content of CTP is the lowest, suggesting that the activity of CTP synthase is tightly regulated.6 CTP plays an important role in DNA/RNA synthesis, phospholipid synthesis, and protein sialylation, which are required for cell proliferation and cell size expansion.7 The level of CTP is elevated in various types of cancer cells and, to a lesser extent, in normal proliferating cells.6 CTP is synthesized from uridine triphosphate by CTP synthase. In mammalian cells, there are 2 isozymes of CTP synthase, that is, CTPS1 and CTPS2.6 Cyclopentenyl cytosine (CPEC) is an analog of cytidine. CPEC is activated by phosphorylation in mammalian cells, and metabolized to cyclopentenyl cytosine 5′-triphosphate (CPEC-TP). CPEC-TP is a noncompetitive inhibitor of CTP synthase and blocks CTP synthesis. CPEC has toxic effects on various kinds of tumor cells.7

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Tang et al8 demonstrate that CTP synthase would be an SMC-sensitive therapeutic target for effective vascular repair. Expression of CTPS1 was upregulated in cultured SMCs stimulated by platelet-derived growth factor-BB (PDGF-BB) and in neointima after balloon injury in the rat carotid artery. CTPS1 blockade by CPEC or small hairpin RNA (shRNA) inhibited SMC proliferation in a dose-dependent manner. Low-dose CPEC inhibited SMC proliferation without any effect on ECs. Moreover, CPEC infusion or adenoviral-mediated delivery of CTPS1 shRNA inhibited neointima formation with enhanced re-endothelialization after mechanical injury of the carotid artery in rats and mice. In contrast to CPEC, low-dose paclitaxel, one of the drugs used for DES, inhibited proliferation of both SMCs and ECs. Importantly, ECs were more sensitive to paclitaxel than SMCs. We also reported that sirolimus has potent inhibitory effects on ECs.3

The mechanism by which CTPS1 blockade regulates proliferation of SMCs and ECs differentially is presumably because of endothelial-specific salvage pathway of CTP synthesis. CTP could be synthesized from cytidine in the presence of several salvage pathway enzymes (Figure).9 These enzymes were significantly induced in ECs, but not in SMCs, when CTP synthase pathway was blocked by CPEC. Therefore, CTPS1 blockade inhibits proliferation of SMCs without affecting ECs that can synthesize CTP using extracellular cytidine.

In a clinical phase I study, CPEC caused refractory hypertension in patients with solid tumors. Although this adverse effect seemed to be dose dependent, its unpredictable occurrence and the uncertainty concerning the mechanism preclude a recommendation of a tolerable dose of systemic administration for future studies.10 However, if a small dose of CPEC could be delivered at the site of percutaneous coronary intervention continuously as a CPEC-eluting stent, inhibition of neointima formation and promotion of re-endothelialization might be feasible without serious adverse effects (Figure). The study by Tang et al would lead to the development of an optimal strategy to promote vascular repair and avoid restenosis and stent thrombosis after coronary intervention by differentially regulating proliferation of SMCs and ECs.

Sources of Funding

This study was supported in part by grants from the Ministry of Education, Culture, Sports, Science, and Technology (Knowledge Cluster and New Research Area) and from the Ministry of Health, Labor, and Welfare of Japan.

Disclosures

None.

References


Key Words: cyclopentenyl cytosine ▪ cytidine triphosphate ▪ drug-eluting stents ▪ endothelial cells ▪ muscle, smooth ▪ neointima
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Arterioscler Thromb Vasc Biol. 2013;33:2286-2287
doi: 10.1161/ATVBAHA.113.302315
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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