# Antiproliferative Drugs for Restenosis Prevention

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**KEYWORDS**

• Restenosis • Mammalian target of rapamycin (mTOR) inhibitors • Endothelialization • Paclitaxel

**KEY POINTS**

- Mammalian target of rapamycin (mTOR) inhibitors are the predominant anti-restenosis agent used in drug-eluting stents (DES).
- Both mTOR inhibitors and paclitaxel drugs currently approved for use in DES do not discriminate between proliferating vascular smooth muscle cells and endothelial cells and thus delay re-endothelialization and vessel healing.
- mTOR inhibitors and their analogues, while very effective in preventing neointimal hyperplasia and target lesion revascularization, can also accelerate neointimal atherosclerosis ("neoatherosclerosis"), a common cause leading to late events (ie, in-stent restenosis and thrombosis).
- Paclitaxel is an effective anti-restenosis agent comparable to mTOR inhibitors; however, the former is cytotoxic, whereas the latter is cytostatic. Both are used in DES and only paclitaxel thus far has been used on drug-coated balloons in both coronary and peripheral vasculature.
- Novel anti-restenosis agents beyond mTOR inhibitors are not being actively pursued but should be a focus of future research in order to improve vascular responses.

## INTRODUCTION

Current endovascular devices in both the coronary and the peripheral vascular beds use antiproliferative agents to prevent restenosis. These antiproliferative agents mainly consist of 2 classes of agents, mammalian target of rapamycin (mTOR) inhibitors and the taxol derivative, paclitaxel. Initially, first-generation drug-eluting stents (DES) used the mTOR inhibitor, sirolimus (SRL), in 2003 (Cypher; Johnson and Johnson, New Brunswick, NJ, USA), and soon after, paclitaxel was used in 2004 (Taxus; Boston Scientific, Marlborough, MA, USA). Since then, the number of mTOR inhibitors has expanded in subsequent second- and third-generation DES to become the predominant antiproliferative agent eluted from these devices. Its use has extended into newer endovascular devices, such as the bioresorbable vascular scaffold (BVS), bioresorbable polymer DES (BP-DES), and polymer-free DES (PF-DES). Paclitaxel-eluting DES have proved to be less efficacious and more prothrombotic than limus-based DES with diminishing use in DES[1–3] in general. However, because of its particular tissue-binding characteristics, which distinguish it from limus-based drugs, it has seen resurgence in drug-coated balloons (DCB)[4] in both the coronary and the peripheral vascular beds.

Although the initial concerns with DES surround impaired endothelialization and risk of stent thrombosis, newer-generation DES with thinner struts, less polymer and drug load, and newer-generation mTOR inhibitors with specific side-chain modifications to SRL, meant to improve tissue penetration and binding, have

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reduced this risk.[2] However, current -limus agents may still contribute to overall endothelial dysfunction and the accelerated formation of atheroma (ie, "neoatherosclerosis"), leading to restenosis, late stent failure, and the need for target lesion revascularization.[2] Although current research and development of endovascular devices surround device development, there has been little research into the use and development of antiproliferative agents for local elution in vascular beds beyond -limus-based derivatives. The current -limus-based agents are discussed in addition to paclitaxel with their use in endovascular devices for restenosis prevention in addition to discussing future directions for this field.

## MOLECULAR MECHANISM OF MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

SRL or rapamycin, originally discovered on Easter Island (Rapa Nui), was developed as an immunosuppressant for cancer therapeutics and as an antitransplant rejection agent in 1972.[5,6] SRL and its subsequent analogues are macrocyclic lactones, which inhibit mTOR and are part of the phosphatidylinositol kinase–related family of serine/threonine kinase. mTOR forms 2 distinct complexes named mTOR complex 1 (mTORC1) and 2 (mTORC2) by combining with different proteins with resulting complexes having distinct sensitivities to SRL (Fig. 1). Each mTOR complex integrates information from upstream signaling and controls distinct mechanisms needed for endothelial and smooth muscle cell proliferation.[7] mTORC1 is the better characterized of the mTOR complexes and integrates signaling from multiple sources, including growth factors released on arterial injury to affect process critical for endothelial coverage after injury, such as migration and proliferation.[8] SRL inhibits mTORC1 but not mTORC2 through specific binding of the FKBP12, a ubiquitous, cytosolic 12-KD FK506-binding protein and key stabilizing component of ryanodine (RyR2) intracellular calcium release channels in various cell types.[9] SRL has subnanomolar affinity to FKBP12 with 50% inhibitory concentration for the mTORC1 signaling pathway at the nanomolar range.[10] mTORC1 directly phosphorylates translational regulators, eukaryotic initial factor 4E-binding protein 1 (4EBP-1) and S6 kinase (S6K1). The regulation of proteins critical for cell proliferation and migration might in fact be the most important mechanism by which mTORC1 regulates endothelialization and neointimal hyperplasia. With vascular smooth muscle and endothelial cells, inhibition of S6K1 leads to the cytostatic effects arresting cell-cycle progression at $G_0$ phase, leading to inhibition of neointimal hyperplasia and endothelialization (Fig. 2). Additional inhibition of S6K1 in human endothelial cells was far more effective at inhibiting cell proliferation versus 4EBP-1.[11] Moreover, SRL effect on inhibiting endothelial proliferation could be rescued by overexpressing S6K. The relationship of SRL to TORC2 is more complex. Because short-term treatment with SRL does not inhibit mTORC2 signaling, this complex was originally thought to be SRL insensitive. However, the situation was made more complex by the observation that long-term treatment with SRL inhibits mTORC2 signaling in some cell types, including endothelial cells.[12] Less is understood about the mTORC2 complex, including its upstream effectors. It does respond to growth factors, including insulin, through poorly understood mechanisms. mTORC2 controls several kinases including Akt

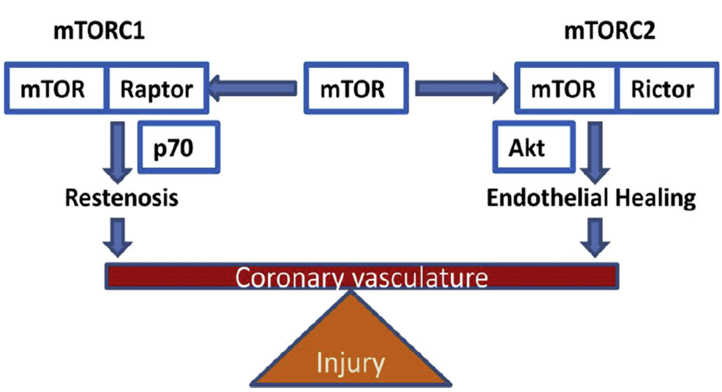


Fig. 1. The role of mTOR in vascular endothelial healing after arterial injury. mTORC1, consisting of mTOR and Raptor, phosphorylates p70, which is vital for cellular proliferation and migration of both endothelial and smooth muscle. Its inhibition leads to the prevention of restenosis after injury. However, mTORC2 positively regulates Akt activity, whose function includes endothelial survival processes such as VE-cadherins formation, which is important in endothelial barrier function and therefore healing. Current mTOR inhibitors affect both complexes in endothelial cells impairing healing after injury. Raptor, regulatory-associated protein of mTOR; Rictor, rapamycin-insensitive companion of mTOR-removed.