Coating Stents With Antirestenotic Drugs: The Blunderbuss or the Magic Bullet?

To the Editor:
We read with interest a recent article in *Circulation* that reported that the binding protein (FK506BP12) for the drug sirolimus (rapamycin) is up-regulated in in-stent restenotic tissue.1 This fact correlates with the observation that stents coated with sirolimus are associated with very low rates of neointima formation.2 These studies suggest a mechanism of action for this immunosuppressive, antineoplastic, and antifungal agent in the context of in-stent restenosis and provide proof-of-principle evidence that stent-based drug delivery can be achieved. Sirolimus therapy to date has been associated with a generally low incidence of side effects and toxicity.

The mechanisms of action of sirolimus are not entirely understood, but are thought to involve inhibition of mitogen-induced downregulation of p27Kip1 and p70s6K phosphorylation. Recently, however, Sun et al3 reported in *Circulation* that rapamycin inhibition of smooth muscle cell migration is both p27Kip1- and p70s6K-dependent and independent. At the present time this drug, like Tranilast and Paclitaxel (taxol), are also under investigation as antirestenotic agents, might be regarded as a “blunderbuss” because the mechanisms of action of these drugs do not appear to be gene-specific and are incompletely understood.

The opposite approach, the “magic bullet,” is to selectively target a specific gene or process that plays a pivotal role in the response to injury. One example is the immediate-early gene and zinc finger transcription factor, Egr-1. Using sequence-specific catalytic DNA molecules, or “DNAzymes,” that selectively target and cleave a specific site in Egr-1 mRNA, we have demonstrated reduced neointima formation after balloon angioplasty to rat carotid arteries4 and stenting in pig coronary arteries.5 Now, using human internal mammary arterial explants in an ex vivo model of intimal thickening, DzA (at 400 nmol/L final concentration), a DNAzyme targeting the 5’ region of human EGR-1 mRNA,5 could inhibit neointima formation in these segments compared with a non-cleaving DNAzyme (DzE) targeting the same gene. In this respect, neointima:media ratios (± SEM) were 0.06 (0.01) for DzA (P<0.05 using a Wilcoxon signed rank test for paired data compared with all other groups), 0.09 (0.03) for DzE, 0.08 (0.02) for the drug vehicle control, and 0.09 (0.02) for the control (no vehicle) (n=5 for each group).

So far, in the short-term and in small patient numbers, the promise of inhibiting restenosis using what might be a blunderbuss approach is clearly encouraging. However, it may be clinically more appealing to locally deliver gene-specific magic bullets (such as DNAzymes) in efforts to inhibit intimal regrowth with potentially greater specificity, decreased toxicity, and fewer side effects.

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Response
Drs Lowe and Khachigian suggest that the coating of stents with drugs including sirolimus is a “blunderbuss” approach, whereas the use of a DNAzyme such as one they are studying that cleaves Egr-1 mRNA is the “magic bullet,” with “potentially greater specificity, decreased toxicity and with fewer side effects.” Elsewhere Drs Lowe and colleagues1 refer to the target of their “magic bullet” as follows: “Early growth response factor-1 (Egr-1) controls the expression of a growing number of genes involved in the pathogenesis of atherosclerosis and postangioplasty restenosis. Egr-1 is activated by diverse proatherogenic stimuli.” It is not clear how targeting a transcription factor that controls “a growing number of genes” is and activated by “diverse” stimuli is more specific than rapamycin.

Over the past decade, many of the details regarding the molecular mechanisms underlying rapamycin’s actions have been elucidated, and these basic investigations are ongoing.2–3 At the same time, it is important to note that rapamycin has been approved by the FDA for long-term systemic administration as an immunosuppressant, indicating a degree of safety not yet demonstrated in humans for Egr-1 targeting by DNAzymes. Interestingly, Egr-1 deficient mice have been reported to be hyperresponsive to stress and infertile.4,5 Findings such as these suggest that a “magic bullet” targeted at Egr-1 could itself have unfortunate side effects and requires extensive in vivo testing before it is administered to patients.

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