Dual drug-eluting stent

A drug-eluting stent (DES) is a coronary stent that releases a drug for about a month to control proliferation of vascular smooth muscle cells (VSMC). Like a bare metal stent (BMS), DES of course provides mechanical support to a vessel after angioplasty. Because a DES provides controlled release of compounds that interfere with restenosis, it was regarded, since its introduction in 2003, as the solution to the problems associated with using a BMS. We only wish that was the case. Restenosis is an adverse re-narrowing of a stented artery characterized by neointimal hyperplasia that is driven by proliferation of VSMC. Stent-based delivery of anti-mitogenic drugs inhibiting VSMC proliferation has been effective, but they were shown to act non-selectively. Proliferation of endothelial cells is also inhibited, and this can lead to delayed vascular healing after stenting angioplasty, which contributes to an increased risk of late in-stent thrombosis [1]. In fact, a recent review suggests that delayed re-endothelialization around stent struts is the “single best predictor” of late stent-thrombosis [2]. Currently, there is a need for stent-based therapies that can both attenuate neointimal hyperplasia and promote endothelial healing.

Resveratrol (R) and quercetin (Q) are two polyphenols found abundantly in grapes and implicated in the vascular benefits associated with red wine consumption. (Cheers!) These two compounds have been shown to elicit many physiological effects in the vasculature, including attenuation of VSMC proliferation, oxidation, platelet activation, and inflammation [3,4]. Importantly, oral administration of R has been previously shown to promote re-endothelialization in a rat model of arterial angioplasty [5]. Additionally, Sanchez and colleagues have demonstrated that oral administration of Q protects against angiotensin II-induced endothelial dysfunction, suggesting that Q may attenuate dysfunction after arterial injury [6]. Due to poor oral bioavailability of these polyphenols, however, a more efficient way of delivery is necessary. A DES platform is favorable for treating restenosis because of the ability of localized drug delivery directly to the site of injury. Due to the reported anti-restenotic effect of R and Q, as well as literature reports demonstrating their positive influence on endothelial function, Professor Dugas and her colleagues hypothesized that the local delivery of these compounds from a stent platform could inhibit neointimal hyperplasia while promoting re-endothelialization, at least in a rat model of stenting angioplasty [7]. A stent that releases multiple cardioprotective polyphenols is attractive due to the potential for affecting different mechanisms associated with restenosis. The ability to affect multiple pathways may increase efficacy while decreasing the dose required, reducing side effects and providing a more selective therapy. Additionally, a combination approach takes advantage of their ability to synergistically inhibit VSMC proliferation and inflammatory cell activation [8].

These polyphenols were incorporated into an arborescent poly(styrene-b-isobutylene-b-styrene) tri-block polymer, which is similar to the polymer used in the Taxus™ DES. The polyphenols were loaded at a low-dose (RQ1) or high-dose (RQ2) combination, and the coatings were applied to miniature stainless steel stents using an electronanopary process. The stents were deployed into rat common carotid arteries and the arterial response to stenting was evaluated at 10 and 28 days.