



Cover story

Prevention of intimal hyperplasia by immobilized all-trans retinoic acid



Neointimal hyperplasia is the main factor that determines the long-term durability of vascular interventions, such as angioplasty and bypass grafting. As these interventions result in localized injury, several clinical therapeutics have been developed to deliver antiproliferative agents locally. Currently, several drug-eluting stents delivering antiproliferative drugs (e.g., sirolimus and paclitaxel) are clinically available for use after balloon angioplasty procedures [1]. However, to date, no durable alternatives are available to improve the patency of synthetic prosthetic grafts like expanded polytetrafluoroethylene (ePTFE) [2]. While similar pathophysiologic responses are involved following both interventions, injury that results following angioplasty is limited to the time of the procedure, while bypass grafting causes a continued stimulus for intimal hyperplasia due to changes in mechanical forces at the anastomosis and is influenced by the biocompatibility of the conduit utilized. These effects are greatest when prosthetic materials are utilized, and are responsible for the poor patency rates observed with these materials as compared with the performance of autologous saphenous vein. Cumulatively, the prior investigations suggest that successful inhibition of intimal hyperplasia requires sustained delivery of a selective therapeutic agent from new bypass grafts.

A large body of work has focused on the use of retinoids, specifically all-trans retinoic acid (atRA), which demonstrated efficacy in inhibiting intimal hyperplasia when delivered systemically in animal angioplasty models. Additional works have suggested that atRA has pleiotropic effects on vascular cells following injury, having both anti- and pro-proliferative effects based on the cell type and location [3]. The collaborative efforts of the Kibbe and Ameer labs in this issue have proposed a new modification of traditional ePTFE to inhibit intimal hyperplasia, associated with prosthetic bypass grafts [4]. In their current study, two atRA-containing ePTFE grafts were evaluated: atRA was immobilized either directly onto the ePTFE graft (atRA-ePTFE) or by surface-coating of ePTFE with poly(1,8 octamethylene citrate) (POC) (atRA-POC-ePTFE). atRA was immobilized onto the graft surface and throughout the wall via physisorption.

The study by Gregory et al. from the Kibbe and Ameer labs demonstrated the efficacy of atRA to inhibit intimal hyperplasia in a bypass graft setting. Importantly, the modifications of the ePTFE grafts included in this study did not result in any alteration in graft compliance or graft thrombogenicity. The addition of the POC polymer resulted in a 17-fold increase in drug loading and a 4-fold increase in atRA release after 30 days. atRA-POC-ePTFE was more effective than atRA-ePTFE in inhibiting intimal hyperplasia, resulting in a 50% reduction at the proximal and 56% reduction at the distal anastomoses. Moreover, only atRA-POC-ePTFE was associated with decreased infiltration of inflammatory cells including macrophages and leukocytes at both the

proximal and distal anastomosis. Most interestingly, endothelialization of the graft material was improved in animals treated with atRA-POC-ePTFE, with a 2.7-fold increase at the proximal and a 2.2-fold increase at the distal anastomosis.

Treatment of intimal hyperplasia that results from angioplasty or bypass grafting is quite complex. The pathophysiology of this response has not been completely elucidated and it involves the interaction of multiple cell types and systems. However, the localized nature of this injury lends itself to localized therapy that can achieve results at lower concentrations, decreasing the risk of systemic side effects. These current findings further support the use of atRA to inhibit intimal formation. However, although significant advances have been made in elucidating the mechanism by which atRA inhibits intimal formation, further study is necessary. While it is important to consider these results in the context of the limitations of the small animal models, the collaborative work by Gregory et al. has made a positive step towards developing a biocompatible vascular graft alternative. The beauty of their study is its simplicity of immobilizing atRA to vascular grafts by coating/physorption. Such a method can be applied for all types of vascular biomaterials, and the results can be easily reproduced, accelerating successful clinical translation.

References

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Kinam Park
Purdue University
Biomedical Engineering and Pharmaceuticals
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu