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Gene-eluting stents for the prevention of restenosis

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Abstract

Delivery of gene vectors from a stent surface for gene therapy of restenosis poses major challenges due to issues related to stent functionality, biocompatibility of coatings, vector retention, and maintenance of vector viability. Our group has introduced a family of polyallylamine bisphosphonate (PAB) compounds that can effectively activate stents for covalently attaching vector-binding molecules using affinity tethering, or directly immobilizing vectors through hydrolysable cross-linkers. A water-soluble PABs (with or without latent thiol groups) were synthesized combining vinylidene-bisphosphonic acid and polyallylamine ± succinimidyl 3-propyldithiopropionate. Following formation of a PAB monolayer on the surface of model stainless steel meshes or stents, the surface was activated by attaching a recombinant domain (D1) containing the adenovirus binding region of the Coxsackie-Adenovirus receptor and subsequent affinity binding of Ad vector. Alternatively, after deprotection of thiol groups, Ad or AAV vectors were directly bound to the steel surface of the stent using bifunctional thiol-, amine-reactive hydrolysable cross-linkers.

Both methods of vector immobilization allowed for sustained release of immobilized vectors, and site-specific localized expression both in vitro and in vivo, as demonstrated with Ad-GFP (fluorescence microscopy and immunohistochemistry) and Ad-Luc (bioluminescence imaging). Attachment of Ad vectors encoding inducible nitric oxide synthase (Ad-iNOS) to the surface of stents resulted in mitigation of post-angioplasty restenosis in the rat carotid model. The therapeutic effects of Ad-iNOS gene therapy delivered from the stent platform can be further modulated by pharmacological intervention with arginine and tetrahydrobiopterin to optimize the ratio between nitric oxide and reactive oxygen species produced by the stented arteries.

Biography

Ilia Fishbein received an MD degree from the University of Saratov (Russia) in 1987. He completed his PhD studies on polymeric delivery systems for the prevention of restenosis at the Hebrew University of Jerusalem (Israel) in 2000. His post-doctoral research at the Children's Hospital of Philadelphia (USA) has been concerned with vascular gene therapy and substrate-mediated delivery systems of viral vectors to diseased vasculature. Dr. Fishbein is an Assistant Professor at the University of Pennsylvania. His current work is related to gene-eluting stents and pharmacological modulation of vascular gene therapy for the prevention of restenosis.