Anand Ramamurthi, J Tissue Sci Eng 2012, 3:3
http://dx.doi.org/10.4172/2157-7552.S1.004

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Tissue Science & Engineering

October 1-3, 2012 DoubleTree by Hilton Chicago-North Shore, USA

Towards localized elastic matrix regenerative strategies to stabilize growing abdominal aortic aneurysms (AAAs)

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Abdominal aortic aneurysms (AAAs) involve gradual degradation of elastic matrix in the aortal wall, by inflammatory cell-generated MMPs. AAA stabilization by regenerative elastic matrix repair is difficult due to poor elastogenicity of adult vascular smooth muscle cells (SMCs). We have previously shown that with co-delivery of doxycycline (DOX, a global MMP inhibitor) along with elastogenic factors (HA-o and TGF-β1) to aRASMCs, net elastic matrix accumulation was enhanced due to the elastogenic factors, while DOX degraded MMP-2 into enzymatically inactive fragments, and reduced its activity. Towards localized delivery of the EFs and DOX to induced AAAs in rats, we formulated active-agent loaded PLGA nanoparticles (NPs) via double-emulsion/solvent evaporation and imparted to them a positive surface charge (ξ potential = +30-50 mV) using a choice of different cationic amphiphiles to enhance their uptake into the aortic wall, and in parallel target and bind elastic matrix (via hydrophobic residues), and repel elastases and enhance activity of the elastin crosslinking enzyme lysyl oxidase (LOX), both via charge effects.

In vivo studies in induced rat AAAs showed that FITC-tagged NPs with sizes of 500 nm effectively penetrated and remained in the media at 7 days post-infusion, while those of 200 nm were localized in the media and adventitia. The factor/DOX-loaded NPs (2-10 % w/w DOX to PLGA; 100-1000 ng TGF-β) we formulated were within this size range (average size = 350 ± 50 nm). We showed that steady-state release of TGF-β & DOX from these NPs was possible for > 40 days and that these agents maintained their biofunctionality following release. Both DOX and TGF-β released from the NPs were found to enhance elastic matrix deposition, while DOX caused a significant inhibition of MMP-2 production and activity. NPs functionalized with the different cationic amphiphiles also exhibited enhanced binding to elastin substrates, compared to those functionalized with anionic surfactant (poly-vinyl alcohol). Ongoing studies seek to optimize in vivo NP-based drug delivery towards demonstrating the co-benefits of improved elastic matrix deposition and fiber formation due to the HA-o/TGF-β factors and of MMP activity suppression by DOX towards improvement in net elastic matrix regenerative outcomes.

Biography

Anand Ramamurthi, PhD is Associate Professor of Biomedical engineering at the Cleveland Clinic with adjunct appointments at Case Western Reserve University, and Clemson University, where he was earlier a tenured faculty. He received a doctorate from Oklahoma State University and was an AHA postdoctoral fellow at the Cleveland Clinic. He directs a well-funded research program focused on biomimetic regenerative repair of ECM/elastic matrix, in vitro, and at sites of proteolytic disease. Anand is a member of several vascular disease-related professional societies and their committees, and an editorial-board member of repute in the JTSE. He is a peer-reviewer for several funding agencies and 20+ journals, and has 38 peer-reviewed publications.

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