OMICS Group Conferences
Accelerating Scientific Discovery
2nd International Conference on
Tissue Science & Regenerative Medicine
August 26-28, 2013 Raleigh-NC, USA

Multifunctional nanoparticles for controlled thrombolysis and stimulated elastogenesis in abdominal aortic aneurysms (AAAs)

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Abstract

Abdominal aortic aneurysms (AAAs), conditions which involve slow disruption of the aortic wall matrix by matrix metalloproteinases (MMPs), leading to wall thinning, weakening and rupture, are a leading cause of mortality among the elderly. They are frequently associated with the presence of an intraluminal thrombus (ILT) through which blood continues to flow. It propagates AAA growth, as a reservoir of inflammatory cells and proteases (including elastolytic MMPs-2 and -9). Additionally, it is undesirable from the standpoint that it serves as a barrier for endoluminal delivery of therapeutic agents to the AAA wall. Thus, there is a need to develop thrombolytic therapies for AAAs. However, this needs to be highly controlled so as to avoid systemic thromboembolisms. Additionally, plasmin which mediates clot fibrinolysis upon cleavage of plasminogen in the ILT by tissue plasminogen activator (tPA) degrades the matrix of the aortic wall directly, as well as indirectly via activation of MMPs, which coupled with the bulk release of MMPs from the ILT upon lysis, lead to further AAA progression.

Towards enabling controlled lysis of fibrin clots within AAAs, we have developed poly-lactic-co-glycolic acid nanoparticles (PLGA NPs) encapsulating tPA. NPs were either surface-functionalized with didodecyldimethylammonium bromide (DMAB) to impart a positive surface charge or polyvinyl alcohol (PVA) to impart a negative charge. DMAB-NPs exhibited more gradual tPA release and controlled clot lysis profile compared to NPs formulated with PVA. We attributed this to binding of cationic DMAB NPs to fibrin (anionic at physiological pH), which can enable localized and more efficient clot lysis. Together with our previous findings that showed even blank DMAB-functionalized PLGA NPs to have elastogenic benefit in aneurysmal smooth muscle cell (SMC) cultures, we believe that these NPs represent novel carriers for delivery of controlled thrombolytic therapies in AAAs. Ongoing studies seek to determine the tPA loading and NP delivery doses that would be conducive to controlled fibrinolysis, and which would yet minimally activate MMPs, while providing concurrent elastogenic benefit *in vitro* in aneurysmal SMC cultures and *in vivo*.

Biography

Anand Ramamurthi, Ph.D. 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.