Combination nanotherapy penetrates atherosclerosis

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This editorial refers to ‘Nanotherapeutics for inhibition of atherogenesis and modulation of inflammation in atherosclerotic plaques’ by D.R. Lewis et al., pp. 283–293.

Nanoparticle therapeutics are increasingly considered for applications beyond oncology. Whereas nanomedicine’s indication for the treatment of cancers is clear-cut, its use for atherosclerotic and atherothrombotic complications is not trivial. First and foremost, atherosclerosis is a very slowly progressing inflammatory disease. Therefore, injectable nanomedicines need to exhibit significantly elevated therapeutic benefits over existing lipid-lowering therapies, which are taken orally. Moreover, the subset of cardiovascular patients that would benefit from nanotherapy needs to be clearly defined. At what stage of the disease would an ‘aggressive’ intervention produce long-term health benefits? How do we screen and select subjects amendable for anti-atherosclerotic nanotherapy?

A number of preclinical studies in a variety of animal models signify the potential of nanoparticle therapy, especially in treating atherosclerotic plaque inflammation. Lanza, Wickline and colleagues demonstrated the use of fumagillin-loaded nanoparticles,²,³ while Fredman et al.⁴ recently showed therapeutic benefits of peptide-loaded polymeric nanoparticles in atherosclerotic mice. For the past 10 years, our laboratory has focused on the development of high-density lipo-protein mimicking nanoparticles for targeted imaging⁵ and treatment of inflammatory atherosclerosis.⁶,⁷

In preclinical cancer studies, nanomedicine research efforts are currently focused on combination treatments, for example by exploiting the intrinsic pharmacological activity of ligand-modified carrier materials with the cytostatic activity of an incorporated chemotherapeutic agent, as has been shown by Lammers and colleagues.⁸

This combination strategy has now also been trialed in the context of atherosclerosis. Lewis and colleagues have developed a nanoparticle platform based on mucic acid, which intrinsically interact with scavenger receptors and has been shown to inhibit atherogenesis previously.⁹ In their current study, the authors show the potential benefits of a combinatory approach by the inclusion of an additional antioxidant, i.e. $\alpha$-tocopherol.¹⁰ The resulting nanoparticles, which contain a coating of polyethylene glycol, measure a little over 200 nm in diameter. In vitro uptake was shown in smooth muscle cells, endothelial cells, and macrophages. More importantly, the treatment of these different cell types resulted in inhibited oxLDL uptake. Finally, in human carotid plaque specimens, reduced amounts of lipid deposits and decreased expression of inflammatory markers were observed.

Pro-inflammatory effects on cultured macrophages and the lack of in vivo data necessitate further investigations in atherosclerosis mouse models to tease out if the benefits of macrophage polarization outweigh the potential negative effects of enhanced monocyte recruitment. These studies will also shed light on the novel formulation’s pharmacokinetics, toxicity, and ability to penetrate atherosclerotic lesions in vivo. The latter may be facilitated by decreasing the nanoparticle’s size to the 100 nm range, which is straightforwardly realizable by modulating the fabrication conditions and changing the core/shell ratio or shell composition. The contribution of macrophage inflammation in a range of pathophysiological processes also warrants studies in other diseases, including cancer, RA, and ischaemic heart disease.

References


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