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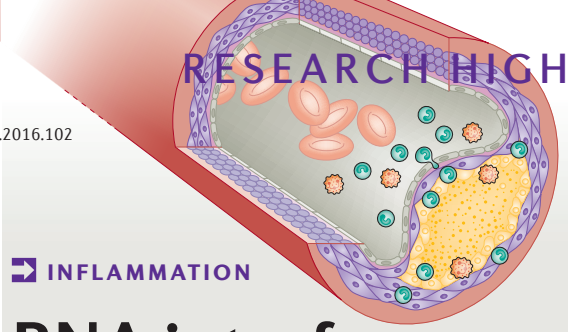

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INFLAMMATION

RNA interference after myocardial infarction

Targeted silencing of five major adhesion molecules using nanoparticle-based RNA interference (RNAi) effectively reduces immune-cell recruitment and improves recovery after myocardial infarction (MI) in mice. "RNAi-based multigene silencing may be a safe and viable treatment paradigm for endothelial dysfunction," conclude the investigators.

Current therapeutic approaches to atherosclerosis and MI focus on risk-factor reduction and revascularization, but both conditions are associated with chronic inflammatory processes. After MI, the increase in inflammation can cause other plaques to become unstable and trigger subsequent MIs. "Understanding these mechanisms," comments corresponding investigator Matthias Nahrendorf, "may help us to design improved secondary prevention strategies."

Recruitment of neutrophils and monocytes into the arterial wall is dependent on endothelial cell adhesion molecules and interaction between chemokines and their receptors. Steps involved in cell recruitment include rolling (mediated by E-selectin and P-selectin), firm arrest and adhesion (mediated by vascular cell adhesion molecule 1 [VCAM1] and intercellular cell adhesion molecule 1 [ICAM1]), and endothelial transmigration (mediated by ICAM2).

The investigators induced MI in *Apoe*$^{-/-}$ mice by ligating the coronary artery, and demonstrated that increased vascular sympathetic nervous signalling led to enhanced neutrophil and monocyte recruitment to atherosclerotic plaques. In these mice, levels of E-selectin, ICAM2, and VCAM1 were increased in aortic endothelial cells after MI.

The researchers developed nontoxic nanoparticles that delivered small interfering RNA (siRNA) targeting either luciferase (control) or the genes of the five adhesion molecules of interest (*Sele*, *Selp*, *Vcam1*, *Icam1*, and *Icam2*). *Apoe*$^{-/-}$ mice injected with the therapeutic siRNAs had significantly decreased target gene mRNA and protein levels in aortic endothelial cells, compared with those that received the control siRNA. Accordingly, atherosclerotic plaques in *Apoe*$^{-/-}$ mice injected with the therapeutic siRNAs had a reduced number of monocytes, neutrophils, and macrophages, as well as lower expression levels of myeloperoxidase (*Mpo*), matrix metalloproteinases (*Mmp2*, *Mmp3*, and *Mmp9*), and proinflammatory cytokines (*Il1b*, *Il6*, *Il12*, and *Tnf*). Consequently, these plaques had a smaller necrotic core and thicker fibrous cap.

In *Apoe*$^{-/-}$ mice after MI, therapeutic siRNA (weekly injections for 3 weeks) blocked inflammatory cell recruitment, reduced necrotic core expansion, and attenuated fibrous cap thinning. Magnetic resonance imaging revealed higher left ventricular ejection fraction at 3 weeks after MI in mice that received therapeutic siRNA (33 ± 4%) compared with those that received control siRNA (23 ± 4%). "RNAi efficiently attenuated myeloid recruitment to the ischaemic heart and consequently improved recovery after MI," conclude the investigators. "RNAi has become clinically feasible," comments Matthias Nahrendorf. "The delivery of nanoparticles with high avidity to endothelial cells, however, needs to be tested for safety [in animals larger than mice]".

Gregory B. Lim

ORIGINAL ARTICLE Sager, H. B. *et al.* RNAi targeting multiple cell adhesion molecules reduces immune cell recruitment and vascular inflammation after myocardial infarction. *Sci. Transl. Med.* **8**, 342ra80 (2016)
FURTHER READING Bäck, M. & Hansson, G. K. Anti-inflammatory therapies for atherosclerosis. *Nat. Rev. Cardiol.* **12**, 199–211 (2015) | Frangogiannis, N. G. *et al.* The inflammatory response in myocardial injury, repair, and remodelling. *Nat. Rev. Cardiol.* **11**, 255–265 (2014)