Medical care, Nucleic acid therapeutics

Effective transcatheter intracoronary delivery of mRNA-lipid nanoparticles targeting the heart

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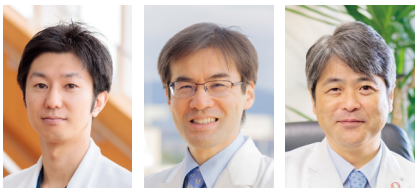


Abstract

Messenger RNA (mRNA) therapy has emerged as a promising therapeutic strategy for heart failure, yet efficient delivery of mRNA-lipid nanoparticles (mRNA-LNPs) to the heart remains a major challenge. This study investigated the efficacy of transcatheter intracoronary (IC) administration compared with intravenous (IV) and intramyocardial (IM) delivery in normal and ischemia-reperfusion (I/R) rabbit hearts. Firefly luciferase (FLuc) mRNA-LNPs were used to assess biodistribution, and VEGF mRNA-LNPs were used to evaluate therapeutic outcomes. IC administration induced significantly higher and more widespread myocardial expression than IV, while achieving expression intensity comparable to IM but distributed throughout the heart. In the I/R model, IC administration produced strong expression not only in infarcted but also in remote areas. VEGF mRNA-LNP delivered via IC suppressed fibrosis, promoted angiogenesis, prevented left ventricular dilation, and improved cardiac function more effectively than IV or IM administration. These findings identify IC administration as a rational and minimally invasive approach for cardiac mRNA therapy.

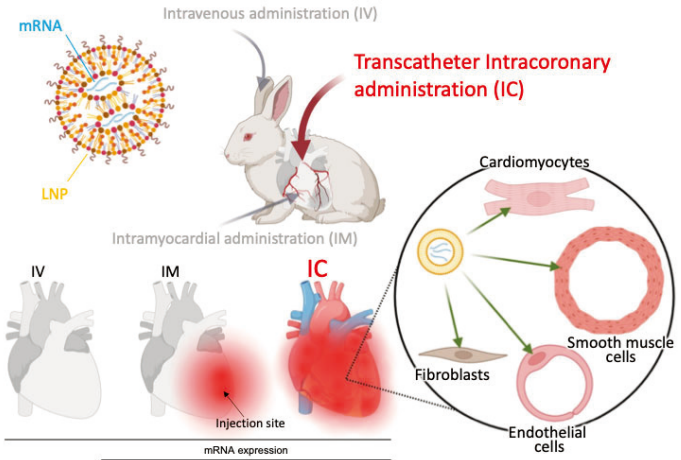
Background & Results

Heart failure remains a leading cause of mortality worldwide and in Japan, with limited access to transplantation or ventricular assist devices. mRNA therapy represents an innovative modality, and LNPs are well-established as drug delivery vehicles. However, IV administration results in minimal cardiac uptake, while IM administration is invasive and restricted to injection sites. To address these limitations, we directly compared IC with IV and IM delivery.

In normal rabbit hearts, IV administration showed little myocardial expression, IM administration produced strong but localized expression, whereas IC achieved strong and diffuse expression throughout the heart. In the I/R model, all routes yielded expression in infarct areas, but IC uniquely achieved robust expression in non-infarcted myocardium, surpassing IV and comparable to IM. Histological analysis confirmed expression in cardiomyocytes, endothelial cells, smooth muscle cells, and fibroblasts. Moreover, VEGF mRNA-LNP delivered via IC demonstrated the most significant therapeutic effects at two weeks, with marked fibrosis suppression in both border and remote regions, enhanced microvascular density, and improved cardiac function. Collectively, these results establish IC administration as an efficient method for delivering mRNA broadly to infarcted and non-infarcted myocardium.

Significance of the research and Future perspective

This study provides the first comprehensive evidence that IC administration enables widespread cardiac delivery of mRNA-LNPs. While IV administration is insufficient and IM administration remains highly invasive and locally confined, IC offers a minimally invasive alternative that can be performed alongside percutaneous coronary intervention during acute myocardial infarction. The ability to deliver mRNA to remote myocardium is particularly important, as it contributes to pathological remodeling after infarction and the progression of heart failure. By suppressing fibrosis and enhancing angiogenesis across the heart, IC administration establishes a foundation for versatile mRNA therapies, including antifibrotic and pro-angiogenic strategies. Future studies should optimize dosage, evaluate repeated dosing and safety, and combine IC delivery with cardio-tropic LNP formulations or cell-type-specific targeting technologies. Such advances will maximize efficacy, minimize off-target effects, and accelerate the clinical translation of innovative mRNA therapies for heart failure.



	mRNA expression		
	IV	IM	IC
Normal heart	–	+ (injection site)	+ (whole heart)
Infarct area	+	+	+
Remote area	–	–	+

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Patent
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