# Deciphering M6A Methylation in Monocyte-mediated Cardiac Fibrosis and Monocyte-hitchhiked Erythrocyte Microvesicle Biohybrid Therapy

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## Abstract

*Background:* Cardiac fibrosis and remodeling following ventricular septal defect (VSD) occluder implantation can precipitate severe complications such as conduction block (CB). The epigenetic regulation of monocyte activity via m6A RNA methylation represents a novel therapeutic target for mitigating these adverse outcomes. *Objective:* This study aimed to elucidate the role of m6A methylation in monocyte-driven cardiac fibrosis and evaluate the efficacy of a novel erythrocyte microvesicle-based delivery system for the targeted administration of a METTL3 inhibitor, STM2457, to combat post-implantation cardiac remodeling. *Methods:* Peripheral blood monocytes were isolated from pediatric patients with VSD occluder implantation–related conduction block and analyzed for m6A methylation levels and the expression of methylation enzymes METTL3 and METTL14 using ELISA, qRT-PCR, and western blotting. An innovative bioengineering approach was employed to develop erythrocyte microvesicles for precise delivery of STM2457. This system was assessed in an Ang II-induced mouse model of cardiac fibrosis, with evaluations including echocardiographic assessment of cardiac function and histological analysis of fibrosis. *Results:* Patients with persistent conduction block exhibited significant upregulation of METTL3 and METTL14, and increased m6A methylation levels correlated with elevated monocyte migration and fibrogenic and inflammatory markers. In the mouse model, STM2457-loaded microvesicles effectively targeted monocytes, leading to a marked reduction in myocardial inflammation and fibrosis, and improvement in cardiac function. *Conclusion:* Targeting m6A RNA methylation in monocytes through erythrocyte microvesicle-mediated delivery of METTL3 inhibitors offers a promising approach for treating cardiac fibrosis and remodeling associated with VSD occluder implantation. This strategy underscores the potential of leveraging epigenetic mechanisms and advanced bio-nanotechnology to develop effective therapies for cardiovascular diseases.

## Keywords

m6A Modification, Monocytes, Cardiac Fibrosis, Erythrocyte Microvesicles, Meta-phenolic Network