Applications of Induced Pluripotent Stem Cells in Cardiovascular Disease Modeling and Drug Discovery

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The discovery of induced pluripotent stem cells (iPSCs) from somatic cell reprogramming has revolutionized stem cell biology and regenerative medicine. Human iPSC-derived endothelial cells (hiPSC-ECs) serve as an excellent platform for disease modeling and drug discovery, particularly in cardiovascular disease, coronary artery disease, and vascular disorders. Marijuana is the most widely used illicit drug worldwide. Epidemiological studies indicate its increase in the risk of coronary artery disease. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects have also been reported. In addition, three synthetic cannabis drugs have been approved by FDA for treating chemotherapy-induced nausea and vomiting. Synthetic cannabis drugs also show cardiovascular side effects. These results suggest that cardiovascular side effects exist in both recreational and medical use of marijuana. However, the underlying mechanisms remain poorly understood. We found that Δ^9-tetrahydrocannabinol (Δ^9-THC), the main mind-altering ingredient in marijuana, induced endothelial dysfunction in human endothelial cells and mice models via activation of cannabinoid CB1 receptor. Using high-throughput drug screening, we discovered genistein, a soybean isoflavone, was a new CB1 antagonist that attenuated marijuana-induced endothelial dysfunction and atherosclerosis, while preserving clinically useful effects such as sedation and analgesia. Cannabinoid CB1 receptor signaling is implicated in various diseases, including obesity, diabetes, cardiovascular disease, coronary artery disease, atherosclerosis, liver cirrhosis, and cancers. Although selective CB1 antagonists like rimonabant (Acomplia®) demonstrated therapeutic potential, their severe psychiatric side effects led to market withdrawal. Our recent work focuses on developing peripherally restricted CB1 antagonists to circumvent these side effects. In this presentation, I will report our latest findings on the role of CB1 receptor in cardiovascular disease. In addition, I will introduce our advancements in developing next-generation CB1 antagonists.