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Discovery of miRNA therapeutic targets in the treatment of cardiac ischemia/reperfusion injury

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Timely reperfusion in acute myocardial infarction has improved clinical outcomes but gains are partially offset by ischemia-reperfusion injury (I/R). miRNA regulate multiple gene/protein effectors within injury and survival cell signaling pathways, therefore are potential therapeutic targets in the treatment of I/R injury. The purpose of our study was to establish a highly efficient approach to select miRNA targets and demonstrate their underlying mechanisms. Combined with isolated heart preparation and miRNA array technique, we pre-selected a panel of 20 miRNA targets from cardioprotection-induced changes rather than by revering disease-induced changes in I/R. Functional screening with gain and loss of function studies through transfections of miRNA mimic and inhibitor was performed. In a hypoxia re-oxygenation (H/R) model of myoblast H9c2 and neonatal rat ventricular myocytes (NRVM), the protective effects of miR-221, -150, -206, -184, and -140 were confirmed by increased cell metabolic activity (WST-1) and decreased LDH release. Among them, multiple predicted gene targets of miRNA-221 were validated by RT-qPCR, Western Blot and Luciferase reporter assay. Autophagosome formation was assessed by GFP-LC3 labeling and apoptosis by annexin V staining. Immuno-precipitation and specific gene cloning and function were used to identify the pathways underpinning miR-221 protective mechanisms. miR-221 significantly reduced H/R injury due to inhibition of H/R-induced autophagy and apoptosis in through (1) down-regulation of Ddit4 (disinhibiting the mTORC1/p-4EBP1 pathway) (2) down-regulation of Tp53inp1 (with reduced Tp53inp1/p62 complex formation) and (3) decrease of pro-apoptotic effectors of Bmf and Bim. Through inducing favorable changes in autophagy and apoptosis, miRNA-221 is a promising therapeutic target in the treatment of cardiac I/R injury.

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Multicomponent hybridization probes for nucleic acid analysis

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Hybridization of nucleic acid probes to DNA or RNA targets remains one of the most common strategy in nucleic acid analysis. Formats that use hybridization probes include rtPCR, microarrays, fluorescent *in situ* hybridization (FISH) to name a few. Instead of the traditional single stranded probes, we develop multicomponent hybridization probes (MHP). In MHP approach, several oligonucleotide strands cooperatively associate with a target DNA or RNA sequence and produce detectable signal. The MHP developed by us recently include split broccoli and split spinach aptamers, antenna tile-associated deoxyribozyme sensor, molecular beacon sensors among others. The sophisticated design of MHP enables improving selectivity, limit of detection and cost efficiency. Moreover, it allows detection of folded RNA at low temperatures and simplifies probe design in some cases.

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