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β-arrestin1-biased β1-adrenergic receptor signaling-mediated microRNA regulatory network: A new player in cardiac protection

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MicroRNAs (miRs) are small, non-coding RNAs that function to post-transcriptionally regulate gene expression. First transcribed as long primary miR transcripts (pri-miRs), they are enzymatically processed in the nucleus by Drosha into hairpin intermediate miRs (pre-miRs) and further processed in the cytoplasm by Dicer into mature miRs where they regulate cellular processes following activation by a variety of signals such as those stimulated by β-adrenergic receptors (βARs). Initially discovered to desensitize βAR signaling, β-arrestins are now appreciated to transduce multiple effector pathways independent of G protein-mediated second messenger accumulation, a concept known as biased signaling. We previously showed that the β-arrestin-biased β-blocker carvedilol activates cellular pathways in the heart. Our recent data demonstrated in human cells and mouse hearts that carvedilolup regulates a subset of mature and pre-miRs but not their pri-miRs in β1AR-, G protein-coupled receptor kinase 5/6- and β-arrestin1-dependent manner. Mechanistically, β-arrestin1 regulates miR processing by forming a nuclear complex with hnRNPA1 and Drosha on pri-miRs. Loss- and gain-of-function approaches in cardiomyocytes (CMs) and *in vivo* mouse hearts also uncovered that β-arrestin1-regulated miRs increased CM survival by repressing apoptotic genes. Our findings indicate a novel function for β1AR-mediated β-arrestin1 signaling activated by carvedilol in miR biogenesis, which may be linked, in part, to its mechanism for cell survival. These results also suggest that miR-target pairs regulated by β-arrestin1 may exert cardio protective effects.

Biography

Il-man Kim is an Assistant Professor at Georgia Regents University. He completed his Ph.D. at the University of Illinois and postdoctoral training at Duke University. He is working on multi-disciplinary research projects related to cardiac disease. Particularly he is studying G protein-coupled receptor-mediated signaling pathways. He was selected as a finalist for the American Heart Association (AHA) Katz Basic Research Prize. He has been awarded three AHA grants. He has served on the grant review committee of AHA and NIH as well as Medical Research Council in UK. He has served on the editorial board member of several cardiovascular journals.

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