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Aerobic exercise-based rehabilitation affects the activities of progenitor endothelial cells through EETs pathway

Li-min Deng³, Xiang-ping Li³, Dan-yan Xu^{3,*}, Christophe Morisseau¹, Chiamvimonvat Nipavan², and Bruce D Hammock¹

¹Department of Entomology and Cancer Center, University of California, Davis, CA, 95616, USA

²Division of Cardiovascular Medicine, Department of Internal Medicine, University of California, Davis, CA, 95616, USA

³Department of Cardiology, the Second Xiangya Hospital of Central South University, Changsha, Hunan, PR China. 410011

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Bone marrow (BM)-derived endothelial progenitor cells (EPCs) have shown regenerative potential in myocardial ischemic animal models with respect to cardiomyocyte formation and neoangiogenesis[1]. Paul et al [2, 3] reported that aerobic exercise-based cardiac rehabilitation in patients with coronary heart disease increased EPC counts, EPC survival, and endothelial differentiation potential, these findings suggest that aerobic exercise can modulate the circulating EPC numbers and function, but the mechanism is poorly understood.

Kutryk et al. [4] found that EPCs produced the microRNAs (miRNAs), miR-126, miR-130a, miR-221, miR-222 and miR-92a, which have been identified as the most important angiogenic miRNAs and which might play an important role in modulating EPC function, so their dysregulation might contribute to EPC dysfunction in patients with coronary artery disease. Using microarray detection, miRBase, and TargetScan 6.2 (mouse) to analyze the target genes of these miRNAs, we found that the miR-126-3p and miR-92a target genes might include key genes related to angiogenesis. The predicted miR-126-3p target genes were phosphoinositol-3 kinase regulatory subunit 2 (*PIK3R2*) and sprouty-related, EVH1 domain containing 1 (*Spred1*); whereas the predicted miR-92a target gene was integrin subunit $\alpha 5$ (*Itga5*). The target genes have been confirmed[11–13]. Consequently, we

*Corresponding author: Dan-yan Xu, MD., Department of Cardiology, the Second Xiangya Hospital of Central South University, Changsha, PR China, Tel: +86 731 88836045, Fax: +86 731 85295407, xudanyan02@sina.com.

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Conflict of Interest

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speculated that aerobic exercise promoted EPC function, contributing to angiogenesis following myocardial infarction (MI) mainly by regulating miR-126-3p and miR-92a. Aerobic exercise might therefore target EPC-related miRNAs.

Currently, studies related to the specific signaling pathways participating in miRNAs regulation are rare. Epoxyeicosatrienoic acids (EET) are epoxide derivatives of arachidonic acid formed by cytochrome P450 (CYP) epoxygenases that function as lipid mediators [5]. CYP epoxygenases, mainly the CYP2C and CYP2J families, catalyze the formation of the following four EET regioisomers: 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET; each regioisomer consists of a mixture of enantiomers [8]. The vascular actions of EETs mainly include dilation and angiogenesis. EETs were initially identified as endothelium-derived hyperpolarizing factors [6]. However, in addition to regulating vascular tone, EETs modulate several signaling cascades and affect cell proliferation, cell migration and most importantly, angiogenesis. The EET-modulated signaling molecules include tyrosine kinases and phosphatases, the pro-survival enzyme phosphoinositide 3 kinase (PI3K), protein kinase A (PKA), mitogen-activated protein kinase (MAPK) and several transcription factors. Therefore, EETs are important intracellular signaling molecules, and the pathway mediated is termed the EET pathway [6].

We have previously confirmed that EETs increased angiogenesis-related function in EPCs from patients and mice with acute MI (AMI) [7]. The mean circulating level of EETs was notably lower in patients with AMI than in normal control subjects. In mice with AMI, there was an obvious increase in EET concentrations following aerobic exercise. Hence, we speculated that aerobic exercise facilitates circulating EPC function by polarizing EETs.

The functional effects of EETs occur through a number of signal transduction pathways that could denominate EET pathways [8], which mainly refers to three signal pathways: the cyclic adenosine monophosphate (cAMP)/PKA pathway, PI3K/Akt pathway and the MAPK pathway. 11,12-EET acts through a cAMP-dependent process that activates the vascular smooth muscle calcium-activated potassium channels. EET stimulation increases steroidogenic acute regulatory protein and steroid hormone production through a cAMP/PKA mechanism; 8,9-EET, 11,12-EET and 14,15-EET inhibit endothelial apoptosis, which takes place through PI3K/Akt pathway activation, which inhibits extracellular signal-related kinase (ERK)1/2 dephosphorylation. 11,12-EET stimulates angiogenesis by activating an ephrin B4-coupled PI3K/Akt pathway, whereas others have found that it functions by activating sphingosine kinase-1 [9]. EETs also activate myocardial adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels by decreasing their ATP sensitivity and triggering a burst of reactive oxygen species, activating a PI3K/Akt pro-survival pathway [9]. Additionally, EETs attenuate apoptosis partly by inhibiting MAPK phosphorylation upstream of the intrinsic mitochondrial apoptosis pathway [10]. However, we do not know whether EETs modulate miRNAs through the above mentioned three signaling pathways.

We found that the miR-126-3p target genes included *PI3K*, and that, following aerobic exercise, Akt phosphorylation (Ser-473 P-Akt) in the mean circulating level of EPCs was noticeably higher in patients with AMI than in normal control subjects, but that the total Akt

level was unchanged, suggesting PI3K/Akt pathway activation. Hence, we speculated that an EET pathway might modulate circulating EPC function by activating the PI3K/Akt pathway on miR-126-3p. However, whether EETs modulate miR-126-3p through other signaling pathways and the relationship between EET pathways and miR-92a remain to be studied.

EET pathway modulation has emerged as a new promising pharmacological target that may improve the clinical management of patients with high cardiovascular risk. Given the impact of EETs on cardiovascular physiology, there is emerging evidence that developing EET-based therapeutics will be beneficial for treating cardiovascular diseases.

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