Bioactive Small Molecules in the Pathogenesis and Pharmacology of Cardiovascular Diseases: From Bench to Bedside

Lihui Jin and Yu Yu*

Department of Pediatric Cardiovascular, Xin Hua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200092, P.R. China

Cardiovascular Diseases (CVDs) are a leading cause of death worldwide and impose an enormous clinical and economic burden on humanity [1]. In 2015, a Global Burden of Cardiovascular Disease study showed that CVDs accounted for one-third of all deaths per year, and the estimated patient population of 422.7 million [2]. The prevalence is becoming higher in 2018 owing to the progressive aging of the global population as well as insufficient exploration of CVDs pathogenesis. Since formally recognized as a major concern for global health by the United Nations in 2011 [3], CVDs have continued to be a research hotspot in which all countries attempt to dramatically reduce their impact. Therefore, it is very necessary to carry out new research to prevent and treat CVDs globally.

Substantial progresses in understanding the pathogenesis of CVDs have been made by scientists in the past several decades. For example, heart failure, caused by various types of CVDs like coronary artery disease and hypertension, is associated with energetic deficiency [4], oxidative stress [5] and altered expression of long non-coding RNAs [6], and these abnormalities all contribute to exacerbate the disease. However, current therapeutic agents are limited to Angiotension-Converting-Enzyme (ACE) inhibitors, aldosterone antagonists, angiotensin-receptor blockers and β-blockers. Although considered as a hallmark of therapy in heart failure, many patients suffer from severe adverse effects caused by these agents, such as sleep disturbances, hypotension and dyspnea. The same situation can be found in other types of CVDs like myocardial infarction and atherosclerosis. Therefore, it is necessary to discover new drugs to treat CVDs with fewer adverse effects. And the translation of our knowledge about newly understood pathogenesis into novel therapeutic agents will help. Recently, bioactive small molecules have aroused considerable interests among scientists, such as protease inhibitors, non-coding RNA, the physiological gaseous transmitter hydrogen sulfide and so on. And these molecules play significant roles in the metabolism associated with cardiovascular system as well as the pathological process of CVDs, highlighting novel targets for cardiovascular therapeutic interventions.

LIPID MOLECULE

The approval of Alirocumab and Evolocumab—two new lipid-lowering monoclonal antibodies that inhibit Proprotein Convertase Subtilisin-Kexin type 9 (PCSK9)-by the US FDA and EMA in 2015, is a remarkable breakthrough in the cardiovascular translational medicine field. PCSK9 is a hepatic protease that accelerates LDLR degradation by attaching to and internalizing LDLR into lysosomes [7], thus hindering ingestion of LDL-particles from extracellular fluid into cells. Consequently, circulating LDL concentrations elevate and hyperlipidemia occurs. PCSK9 inhibition strategies serve as ideal treatments for hyperlipidemia patients with statin intolerance. Among them, monoclonal antibodies are the most effective by far [8, 9], and at least six monoclonal antibodies including Alirocumab and Evolocumab are being developed and tested in clinical trials. Besides bioactive small molecules associated with lipid metabolism pathways, there are also many other molecules involved in the occurrence and development of CVDs. The following analysis focuses mainly on microRNA, hydrogen sulfide and reactive oxygen species, and discusses their roles in the pathogenesis of CVDs and potential targeted therapeutic agents, respectively.

MicroRNA

MicroRNAs (miRNAs), a class of small single-stranded and highly conserved non-coding RNAs, are emerging as key roles in the regulation of gene expression at post-transcriptional level. Recently, a large number of researches have emphasized the importance of miRNAs in modulating pathogenesis of CVDs. For example, the expression levels of miR-15 family members [10], miR-34 family members [11], miR-16 [12], miR-92a [13], and miR-195 [14] are significantly upregulated in heart tissue after myocardial infarction, partly promoting cardiac cell death through modulating apoptosis, necrosis, and autophagy. The miR-15 family [15] and miR-133a [16] also exacerbate myocardial infarction by inhibiting cardiomyocytes proliferation. Accumulating research reveals that miRNAs degrade mRNAs encoding Ca²⁺-handling proteins and proteins involved in Ca²⁺-responsive signaling pathways, resulting in the development of pathological hypertrophy and heart failure [17]. All these findings support the possibility of utilizing novel miRNA-based therapeutic approach in CVDs.
HYDROGEN SULFIDE

The biological function of the Hydrogen Sulfide (H2S)-producing enzyme, CSE (cystathionine-γ lyase), was first discovered in 1996 [18], followed by the blossom in the field of H2S biology during the past decade. H2S either produced endogenously or administered exogenously, plays a critical role in the pathogenesis of CVDs, including hypertension, atherosclerosis, angiogenesis, and myocardial infarcts. Laboratory and clinical investigations have revealed that various CVDs, especially myocardial ischemia reperfusion injury and heart failure, weaken the production of endogenous H2S, consequently contributing to the progression of diseases [19]. In addition, recent work has found that exogenous H2S improves cardiac function and attenuates cardiac hypertrophy and myocardial fibrosis in diabetic mice via FoxO1 phosphorylation [20]. H2S may also upregulate cardiovascular protective signaling pathways through sulfhydration of relevant substrates [21]. Based on these findings, enthusiasm for developing novel H2S-releasing agents is growing. Several H2S donors (like SG1002, NSHDs and ATTM) have been designed and successfully tested in various animal models of CVDs [22], and the future of H2S-targeted therapeutic drugs is promising.

REACTIVE OXYGEN SPECIES

Reactive Oxygen Species (ROS) includes free oxygen radicals, oxygen ions and peroxides. Oxidative stress occurs when there are excessive endogenous ROS, that induces dysfunction of vascular endothelial cells and consequently impaired vascular homeostasis by disrupting the Nitric Oxide Synthase (NOS)-NO pathway [23]. Endothelial dysfunction has been recognized as a common denominator of diverse cardiovascular risk factors, and individuals under persisting vascular oxidative stress have a higher risk developing various types of CVDs, like atherosclerosis and hypertension [24]. In addition, increased emission of ROS can be observed in heart failure patients with mitochondrial function derangements [25]. All these results provide new insights for utilizing a novel class of agents-ROS targeted medications-in treating CVDs. At present, Coenzyme Q (a physiological component of the electron transport chain) [26] and SS-31 (a tetrapeptide that accumulates in mitochondria and binds to cardiolipin) [27] are being tested in clinical trials on patients with heart failure, and more ROS-targeted agents are on the way.

In summary, the pathogenesis of CVDs resembles a complicated and tightly regulated network in which a diversity of bioactive small molecules plays their roles. In addition to microRNA, H2S and ROS discussed above, there are other bioactive small molecules that are crucial in the pathophysiology of heart and vascular diseases. Although substantial progress has been made in understanding the pathogenesis of CVDs, future efforts are indispensable to translate this knowledge into viable therapeutic approaches. The use of bioactive small molecules as novel drugs treating CVDs is very exciting, and we will organize a special issue about these contents and welcome you to submit your reviews.

REFERENCES


---

Yu Yu

Executive Guest Editor

Department of Pediatric Cardiovascular

Xin Hua Hospital, School of Medicine

Shanghai Jiao Tong University, Shanghai

China