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REVIEW ARTICLE

The Role of PKR as a Potential Target for Treating Cardiovascular Diseases

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Abstract: Cardiovascular diseases are the leading cause of death globally with limited treatment options. Despite improved pharmacological therapy, scientific understandings on the root mechanisms of cardiovascular diseases are still not fully understood. It is well known that inflammation plays a key role in the pathogenesis of cardiovascular diseases and controlling this inflammatory pathway may inhibit the progression of this chronic disease. Protein Kinase R (PKR), a serine threonine kinase is activated during various pathological conditions. Activation of PKR can induce apoptosis, inflammation and oxidative stress. Since PKR has multidimensional roles, thus PKR is an attractive target for treating cardiovascular and metabolic disorders. The goal of this review is to discuss potential role of PKR in cardiovascular diseases, pathways activated by it and association between pathways activated.

Keywords: PKR, cardiovascular disease, inflammation.

INTRODUCTION

Cardiovascular diseases (CVDs) such as myocardial infarction, angina, hypertension, stroke and other circulatory disorders are the most common cause of death globally and will become more prevalent as the population ages. The explosive increase in CVDs in the past 2-3 decades has been attributed to change in diet combined with a sedentary lifestyle [1-5]. An important approach to deal with this problem is to gain more in-depth knowledge about molecular and cellular mechanisms so that new targets can be identified that can ultimately lead to new treatments. Inflammation plays a vital role in the pathogenesis of CVDs and controlling this inflammatory pathway may be one of the treatment options to deal with this chronic disease [3, 5]. Obesity as well as diabetes further increases the burden of CVDs [6].

Under cardiovascular and metabolic disease states, several stress and inflammatory pathways get activated which in turn lead to the activation of inflammatory signaling molecules like c-Jun- N-terminal kinase (JNK) and inhibitory kappa B kinase (IKK). These pathways play an important role in the development of cardiovascular and metabolic diseases by controlling the inflammatory responses in metabolic tissues, inhibition of insulin signaling, and alteration of lipid and glucose homeostasis [7]. One of the kinase activated during these pathological conditions is RNA activated/dependent protein kinase R (PKR). PKR is a ubiquitously expressed serine threonine kinase and is activated by a number of signals, such as interferons, viral infection, high cholesterol diet, cytokines, pathogens, irradiation, heme limitation [7-15] as well as endoplasmic reticulum (ER) stress [16]. PKR contributes to inflammation and immune regulation through activation of mitogen-activated protein kinases (MAPKs) [11, 12], inhibitor of κB (IκB) kinase (IKK) [13, 14], and IFN-β-promoter simulator 1 (IPS-1) signaling [14] and, thus affects various transcriptional factors, including interferon regulatory factor 3 (IRF3) [15], nuclear factor κB (NF-κB) [13, 14], c-Jun, and activating transcription factor 2 (ATF2) [16, 17], which are required for the expression of genes encoding proinflammatory cytokines and interferons [8, 17-21]. PKR blocks translation initiation under stress conditions by phosphorylating eIF2D at Ser 51 [22-24]. PKR is also activated or induced by numerous other conditions such as oxidative stress, metabolic stress and mechanical stress [8, 25-28].

PKR is required for the activation of inflammasome, a multiprotein oligomer, which in turn triggers the release of various proinflammatory cytokines such as interleukin-1β(IL-1β), IL-18, and high-mobility group box 1 (HMGB1) [29]. HMGB1 is a nuclear and cytosolic protein and is released into the extracellular space during inflammation and infection [29]. HMGB1 is recognized by several cell surface receptors such as receptor for advanced glycation end prod-

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ucts (RAGE),toll-like receptor 4 (TLR4),T cell immunoglobulin (Ig) and thus facilitates inflammation and immunity [30]. Moreover, in macrophages derived from wild-type ($PKR^{+/+}$) and PKR-knockout (PKR −/−) mice and stimulated with immuno stimulant poly(I:C), there was significantly lower HMGB1 secretion in PKR-knockout derived macrophages compared to macrophages of wild type mice [29]. Further, Caspase-1 activation and IL-1β cleavage were significantly inhibited in PKR knockout ($PKR^{-/-}$) macrophages stimulated by exposure to inflammatory immune stimulants (ATP, monosodium urate and adjuvant aluminum) compared to wild type macrophages ($PKR^{+/+}$) [29, 30]. In addition, pharmacological inhibition of PKR using 2-aminopurine, suppressed monosodium urate induced caspase-1 activation and IL-1β cleavage [29]. All these findings suggest that PKR is important for caspase-1 activation, IL-1β cleavage and HMGB1 release, and mediates inflammasome activity. PKR is also reported to induce apoptosis via interactions with Fas-associated death domain protein and up-regulation of the Bax [31-33]. Recently Wang *et al* and group reported that PKR deficiency protected the human heart from systolic overload-induced congestive heart failure [34]. Thus, PKR inhibition is recognized as an attractive therapeutic target for diseases such as hypertension, diabetes, cancer, and novel pharmacological PKR inhibitors are under development.

DISCUSSION

Congestive heart failure (CHF) is associated with inflammation, cardiomyocyte hypertrophy, and apoptosis [34]. Various factors have been reported to contribute to the development of CHF such as oxidative stress, chronic inflammation, and toll receptor activation [34-36]. Chronic inflammations also play role in defence against viral myocarditis [37]. Epidemiological and clinical studies have shown strong and consistent relationships between markers of inflammation and risk of future cardiovascular events. From reported literature, it is evident that PKR is not only an antiviral factor activated by interferons but also induced or activated under various pathological conditions [25-27, 38, 39]. PKR selectively regulates pro-inflammatory cytokines such as IL-10 at both the transcriptional and translational level *in vitro* as well as *in vivo* [40]. It has also been reported earlier that pharmacological inhibition of PKR prevented the NF-κB activation and production of tumor necrosis factor alpha (TNFα) and interleukin (IL)-1β, the markers of inflammation in transgenic mouse model of Alzheimer's disease [41]. Activated PKR may induce cellular stress in the heart leading to significant increase in inflammation and apoptosis and ultimately leading to chronic pathological conditions such as hypertension, atherosclerosis, CHF and stroke [42].

Wang *et al.* and group reported PKR expression in human patients suffering from CHF. There was a significant increase in myocardial expression and translocation of PKR in human patients and mice suffering from CHF [34]. They utilized left ventricular (LV) samples from a human CHF patient, and PKR knockout mice to investigate role of PKR in CHF. PKR exacerbates the development of CHF by inducing apoptosis and inflammation of cardiomyocytes. They further reported that knockout or blocking of PKR in mice protected the heart from systolic-overload-induced congestive heart failure [34]. It has been reported previously that natural RNA derived from bacteria binds to and activates PKR and induces human cardiac myocyte apoptosis in a PKR-dependent manner [43]. Activation of PKR results in its dimerization and autophosphorylation which in turn initiates the production of interferons and proinflammatory cytokines. Moreover, caspase-8 pathway mediates the proapoptotic activity of PKR, whereas the eIF2α pathway mediates the proautophagic activity of PKR and both important in the regulation of inflammation and immunity [44].

Although initial studies revealed antiviral effect of PKR, however as the studies progressed it was soon recognized that PKR exerts a wide range of cellular effects such as induction of apoptosis, inflammation and oxidative stress [8, 25-28]. These multiple biological effects are proposed to have major consequences in clinical settings. PKR is activated by inflammatory cytokines such as interferon gamma and tumor necrosis factor alpha via autophosphorylation [29]. In fact, overexpression of PKR substantially enhanced caspase-1 activation and IL-1β cleavage, the inflammatory gene markers, whereas knockdown of PKR inhibited caspase-1 activity and IL-1β cleavage in several different cell types, such as macrophages, dendritic cells and embryonic kidney cells [29]. Moreover, its ability to induce apoptosis of cardiomyocytes in response to a variety of stresses including hyperglycemia [45] makes this protein a therapeutic target that needs to be investigated at the clinical level as a potential biomarker and as a pharmacological target.

At present the main limitation we have is that the role of PKR in various aspects of the cardiovascular diseases is still in the early stages of exploration. Even then, these reports deal with the conditions of congestive heart failure, obesity and diabetes as single entities and describe incomplete findings on the effects of PKR change in cultured cells and animal models. Apparently, it will take some time before an integrated picture of the role of PKR in the pathogenesis of cardiovascular diseases start emerging.

CONCLUSION AND FUTURE PROSPECTS

As the global problem of cardiovascular diseases continues, it will be important to determine new therapeutic targets that can be used to prevent cardiovascular diseases from developing and to treat individuals after the pathologies occur. Several questions still remain unclear regarding the role of PKR in the regulation of inflammation since PKRs activity is regulated by direct interactions with activating and inhibitory molecules. Also PKR has been reported to activate MAP kinase and NFKB pathway, so it will be of great importance to determine whether these pathways are involved in regulation of PKR mediated inflammation. Further studies are required to study the molecular mechanism by which PKR regulates inflammation.

ABBREVIATIONS

PKR	=	double stranded RNA dependent protein kinase R
CVDs	=	Cardiovascular diseases
NFkB	=	nuclear factor kappa-light-chain-enhancer of activated B cells

IKK = inhibitory β kinase

JNK = c-Jun N-terminal kinases

eIf-2α = eukaryotic initiation factor α.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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