Renalase: a novel regulator of cardiometabolic and renal diseases

Anupama Vijayakumar1 · Nitish R. Mahapatra1

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Abstract
Renalase is a ~38 kDa flavin-adenine dinucleotide (FAD) domain-containing protein that can function as a cytokine and an anomerase. It is emerging as a novel regulator of cardiometabolic diseases. Expressed mainly in the kidneys, renalase has been reported to have a hypotensive effect and may control blood pressure through regulation of sympathetic tone. Furthermore, genetic variations in the renalase gene, such as a functional missense polymorphism (Glu37Asp), have implications in the cardiovascular and renal systems and can potentially increase the risk of cardiometabolic disorders. Research on the physiological functions and biochemical actions of renalase over the years has indicated a role for renalase as one of the key proteins involved in various disease states, such as diabetes, impaired lipid metabolism, and cancer. Recent studies have identified three transcription factors (viz., Sp1, STAT3, and ZBP89) as key positive regulators in modulating the expression of the human renalase gene. Moreover, renalase is under the post-transcriptional regulation of two microRNAs (viz., miR-29b, and miR-146a), which downregulate renalase expression. While renalase supplementation may be useful for treating hypertension, inhibition of renalase signaling may be beneficial to patients with cancerous tumors. However, more incisive investigations are required to unravel the potential therapeutic applications of renalase. Based on the literature pertaining to the function and physiology of renalase, this review attempts to consolidate and comprehend the role of renalase in regulating cardiometabolic and renal disorders.

Keywords Renalase · Cardiometabolic disorders · Anomerase · Cytokine · Genetic variation

Introduction
First reported by Desir laboratory at the Yale School of Medicine in 2005 [1], the renalase gene was identified from the archives of the Mammalian Gene collection project [2] while looking for renal secretory proteins that contain a signal peptide sequence, lack transmembrane domains and have less than 20% sequence homology to known proteins. Renalase, named after its context of discovery, is a novel enzyme/hormone. It is a 342 amino acid protein with a predicted mass of ~38 kDa whose primary structure partially resembles that of monoamine oxidases. Owing to the dependence on flavin-adenine dinucleotide (FAD) for its catalytic activity, renalase was considered as a novel FAD-containing amine oxidase [1].

Contrary to the initial understanding that it could be predominately of renal origin, renalase is detected in myocardium, adipose tissue, liver, peripheral and central nervous systems, small intestine, and skeletal muscles [1, 3–5]. This gene is located on chromosome number 10 at q23.31, and it has ten exons [6] spanning approximately 311,000 base pairs [1]. The human renalase gene exists in seven isoforms (viz. renalase 1–7) [7]. Of these, isoform 1 is the predominant form and accounts for almost all of the biological functions of renalase [6, 8]. Renalase isoform 1 contains a signal peptide (amino acids 1–17), a FAD-binding region (amino acids 3–42) and an amine oxidase domain (amino acids 75–335) (Fig. 1).

The discovery of renalase propelled a rapid proliferation of research owing to its scientific conjuncture [9–16]. Initial claims suggested that renalase catalytically degrades catecholamines in vitro, with dopamine being the preferred substrate, and effects cardiovascular dynamics in vivo by lowering blood pressure and heart rate [1]. Although a multitude of research articles on renalase suggested catecholamines as its substrate, subsequent studies disputed the catalytic link between renalase and catecholamine oxidation [11, 12]. Furthermore, studies using recombinant renalase failed to observe monoamine oxidation [13–16].

It is now established that renalase is more efficiently synthesized in the liver than in the kidneys [11]. Although renalase is a renal secretory protein, a fraction is synthesized in the liver and enterocytes and has been identified in the blood, liver, intestine, and adipose tissue [11]. A recent report also underscored the presence of renalase in human adipocytes, which may have implications in obesity and metabolic disorders [17].

In summary, renalase is a multifunctional protein with roles in cardiovascular and renal homeostasis. Its unique properties make it an attractive target for therapeutic intervention, and further research is needed to elucidate its precise mechanisms of action and therapeutic potential.

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oxidase activity on different biogenic amines [13], thus challenging the findings of Xu et al. [1]. A new dimension to the physiological role of renalase has emerged from the studies by Graham H Moran’s group demonstrating that renalase can act as an α-NAD(P)H oxidase/anomerase and oxidize α-NAD(P)H to β-NAD(P)⁺ and H₂O₂ [14]. In a subsequent article, the research team amended their findings and convincingly demonstrated that renalase oxidizes two specific substrates, namely, 2- and 6-dihydrO- NAD(P), which inhibit primary metabolism dehydrogenases, to produce β-NAD(P)⁺ and H₂O₂ [15]. These studies foretell a more pertinent intracellular/metallic function for renalase since it might be beneficial for
According to this pathway, renalase, which exists in between renalase, catecholamines, and sympathetic tone logical effects including cytoprotection [17]. The activated renalase binds to its receptor, PMCA4b, in an organ (viz. kidney), which by some unknown mechanism facilitates a decrease in sympathetic tone leading to a drop in cardiac contractility and heart rate, finally resulting in a decrease in blood pressure (indicated in the figure using red arrows). b Renalase, by virtue of its oxidase property, converts β-NAD(P)H isomers to H₂O₂ and β-NAD(P)+ which might exert vasodilatory effects and reduce blood pressure (indicated in the figure using blue arrows). Dotted lines indicate pathways that require experimental confirmation. This figure was created using Microsoft PowerPoint and Inkscape. (Abbreviations: PMCA4b, plasma membrane Ca²⁺ ATPase 4b; β-NAD(P)H, β-nicotinamide-adenine dinucleotide phosphate reduced; β-NAD(P)+, β-nicotinamide-adenine dinucleotide phosphate)
Regulation of renalase gene expression

Although a significant amount of research pertaining to the biochemistry and physiology of renalase has been carried out since its discovery, the breadth of inquiry into the molecular basis of renalase gene expression is far too small. In this regard, recent studies from our laboratory have identified the transcription factors Sp1, STAT3, and ZBP89 as the key molecular factors in the regulation of human renalase gene expression [20]. Renalase has been reported as a hypoxia-responsive gene in cardiomyocytes, and hypoxia-inducible factor-1α (HIF-1α)-mediated renalase gene expression confers protection against myocardial ischemia–reperfusion injury [21]. Similarly, in the kidneys, HIF-1α-induced renalase expression contributes to ischemia preconditioning-mediated renoprotection [22]. Furthermore, under conditions of fatty liver, a decrease in renalase expression coincides with a reduction in STAT3 levels [23]. This finding suggests that renalase might contribute to the probable role of STAT3 in the pathogenesis of fatty liver because it is a transcriptional target of STAT3 [23]. The α-adrenoceptor/NFκB pathway mediates epinephrine-induced renalase expression in proximal tubular epithelial cells [24]. The NFκB-dependent upregulation of intestinal renalase expression protects against fasting-induced oxidative stress [25]. Moreover, we also found that renalase is under the post-transcriptional regulation of two microRNAs, namely, miR-29b and miR-146a [26]. Studies by Dziedzic et al. [27] showed that subjects with low miRNA-146a expression and high levels of renalase may have a significantly longer survival time than other hemodialyzed patients. The transcriptional and post-transcriptional regulation of renalase gene expression is illustrated in Fig. 3. Additional mechanistic insights from in vitro and in vivo experiments are required for a comprehensive understanding of the regulation of the renalase gene under basal and pathophysiological conditions.

Association between renalase and hypertension: a riddle yet to be solved

The association between renalase and blood pressure came to light when Xu et al. [1] demonstrated that recombinant renalase caused a reduction in systolic, diastolic, and mean arterial pressure. Furthermore, they also showed using in vitro experiments that renalase metabolized catecholamines or vasoactive hormones, such as dopamine, epinephrine, and norepinephrine; this prompted the speculation that renalase-mediated hypotensive effects could occur via catecholamine metabolism. This became a topic of intense research interest, and a plethora of articles pertaining to catecholamine-dependent renalase-mediated blood pressure regulation were published. According to studies by the Desir group [28], renalase degrades catecholamines into their respective aminochromes in a superoxide-dependent manner in the presence of NADH as a cofactor. As described earlier in this article, a slight elevation in blood pressure or an increase in catecholamine levels in blood converts inactive renalase to its active form [6, 18]. Upon activation, renalase metabolizes circulating catecholamines or catecholamine-like compounds via a negative feedback mechanism [29] and exerts significant in vivo hemodynamic effects. The most notable effect is the reduction of blood pressure. Interestingly, the hemodynamic effects caused by renalase are similar to those of nonselective β-adrenoceptor blockade [1, 29]. Although the increase in stroke
volume in response to renalse infusion can be treated as a compensatory mechanism to reduction in heart rate, a decrease in cardiac contractility suggests that renalse-mediated catalolism of catecholamines can lead to an increase in cardiac lusitropy as well as the optimization of diastolic-systolic coupling [29].

**Renalse-mediated mechanisms of blood pressure regulation**

To obtain a better picture of the role of renalse in regulating blood pressure, researchers used a genetically modified renalse-deficient animal model. These global renalse knockout (KO) mice lack promoter region and a large part of the renalse gene coding region [30]. Renalse KO animals developed tachycardia and demonstrated increased blood pressure, especially diastolic pressure which is suggestive of severe vasoconstriction caused presumably by sympathetic activation due to the elevated levels of catecholamines in the system in the absence of renalse. Similarly, studies using salt-sensitive Dahl rats maintained on an 8% salt diet, which is an excellent model to study mechanisms that mediate hypertension [31], have convincingly demonstrated that these animals develop moderately severe hypertension even in the absence of any apparent renal dysfunction because of the early onset of renalse deficiency [31]. Some studies have suggested that renalse could regulate blood pressure and sympathetic tone by controlling the pressor response of the adrenergic system [18]. Studies in rats treated with renalse antisense RNA show that the attenuation of renalse was associated not only with increased systolic blood pressure but also augmented norepinephrine-mediated pressor effect, by almost doubling the blood pressure [18]. Interestingly, however, subcutaneous administration of recombinant renalse caused a significant decrease in blood pressure in 5/6 Nx rats without affecting the heart rate [19].

Since the sympathetic nervous system is known to interact with dopaminergic receptors to regulate blood pressure [32], studies on the effect of renalse on dopamine metabolism have also attracted considerable research interest. Given the importance of the renal dopamine system on sodium and phosphate homeostasis and the inhibitory effect of sodium overload on renalse expression in animals [3, 31], it was reasonable to assume that renalse might have a regulatory effect on blood pressure via the dopamine system. Studies using renalse knockout mice suggest that renalse deficiency augmented the urinary excretion of phosphate ions through a mechanism involving the increased synthesis of renal dopamine [33]. Although the reasons for the increase in the renal dopamine synthesis and the associated rise in urinary DA and phosphaturia remain largely elusive, it can be a homeostatic mechanism to counteract the increase in blood pressure and maintain sodium balance in the absence of renalse.

Furthermore, in another study published by Santos et al. [34], it was found that under conditions of renalse deficiency, the expression of a L-DOPA transporter called L-type amino acid transporter like (LAT) 1 is increased. This increased LAT1 expression, resulting in an increased uptake of L-DOPA as well as the activation of the renal dopaminergic system, is reversed upon external recombinant renalse administration. Furthermore, the D5 receptor, a member of the D1-like receptor subfamily of dopamine receptors, was found to regulate renalse expression in renal proximal tubule cells (RPT). The D1-like receptor agonist fenoldopam increased renalse mRNA and protein expression in the RPT of Wistar Kyoto rats in a PKC-dependent fashion. In contrast, fenoldopam not only decreased renalse mRNA and protein levels but also facilitated renalse protein degradation in spontaneously hypertensive rats [35]. These findings in combination with the previous report that the activation of D1-like receptors attenuates catecholamine production [36] indicate that the dopaminergic system may be involved in regulating catecholamine metabolism via renalse.

As sympathetic overactivity is one of the major triggers of hypertension, selectively destroying the sympathetic nerves can blunt its activity and create an impact on elevated blood pressure [37]. A nondrug method to lower blood pressure by suppressing the hyperactive sympathetic nervous system in the kidney by radiofrequency ablation of renal sympathetic nerves is called renal denervation. A study by Jiang et al. [38] provided proof-in-principle evidence that renal denervation in spontaneously hypertensive rats caused a significant reduction in mean arterial pressure and a dramatic increase in renalse expression. These findings indicate that renal denervation-mediated blood pressure lowering could occur via renalse expression.

Taken together, as mentioned in a recent review article by Li et al. [39], these findings indicate that renalse may regulate blood pressure by (a) catecholamine metabolism, (b) the inhibition of renal dopamine activation, and (c) the attenuation of the renal sympathetic nervous system. Pertinently, however, since some of these theories have raised well-reasoned skepticism, renalse researchers have now presented the new hypothesis that renalse might influence blood pressure and vascular tone by virtue of its α-NAD(P)H oxidase/anomerase activity [14]. Accordingly, the H2O2 and β-NAD(P)H released as a result of renalse-mediated oxidation of isomeric forms of β-NAD(P)H molecules may act as signals for vasodilation and exhibit antihypertensive properties [15, 40]. Although this idea seems to be an attractive prospect, additional evidence-based studies are required to validate this mechanism.

**Renalse gene polymorphisms and hypertension**

Another milestone in the research pertaining to renalse was the finding that the renalse gene harbored genetic
variants associated with essential hypertension. These reports not only underscore the earlier mechanistic observations but also act as proof of the concept that renalase can regulate blood pressure. The first report on the role of renalase as a “novel susceptibility gene for essential hypertension” was published by Zhao et al. [41]; this was a two-stage case-control study in Chinese cohorts. In a study conducted using 2586 subjects, two SNPs (namely, rs2576178 and rs2296545) were found to be significantly associated with essential hypertension. The rs2576178 SNP is located at the 5′ flanking region, and the rs2296545 SNP is located on exon 2 of the renalase gene. Interestingly, while rs2576178 may influence the initiation of transcription or differential splicing, rs2296545 causes an aspartic acid to glutamic acid substitution at codon 37 (Asp37Glu) in the flavin-adenine dinucleotide-binding domain of the human renalase gene. Thus, this SNP affects the function of its gene product. In yet another study conducted using 892 patients with type 2 diabetes and 400 controls in a Caucasian population of Polish origin, the rs2296545 polymorphism was also associated with hypertension in type II diabetes [42]. The study also identified another SNP, rs10887800, near the exon/intron boundary of the renalase gene, which increased the risk for stroke in patients with and without diabetes. The authors presume that the G allele of this polymorphism might be considered a risk factor for stroke in diabetes patients and other individuals. Genetic studies in the Chinese Han population also showed an association between renalase gene polymorphisms and ischemic stroke [43]. Surprisingly, however, contrary to the above findings, in 2015, Shi and Wang [44] reported that the Glu37Asp polymorphism (rs2296545) in the renalase gene was not associated with a risk of hypertension. In a meta-analysis involving four association studies [41–43, 45] pertaining to the rs2296545 renalase polymorphism and risk for hypertension, it was found that the renalase gene polymorphism was not linked to hypertension risk in four genotype models. Further studies in various world populations are required to conclusively determine the associations between renalase SNPs and hypertension.

Nevertheless, having described the role of renalase in regulating blood pressure and the apparent conundrums regarding the mechanism surrounding it, there were also studies that seem to have refuted the role of renalase in regulating blood pressure [46–49]. The relationship between renalase and blood pressure regulation has been intensively investigated since its discovery in 2005. Studies have shown that the hypotensive effect of recombinant renalase (1.3 mg/kg) administered subcutaneously could be as efficient in decreasing blood pressure as any established drug of choice for hypertension, such as enalapril (5 mg/kg), administered orally over 24 h [19]. It was claimed that renalase modulation could be beneficial for stringent blood pressure regulation, particularly when associated with kidney disease [28]. In a study conducted by Akbari et al. [50], it was demonstrated that atorvastatin and losartan therapy significantly increased renalase activity in hypertensive patients when compared to controls. This finding suggests that these therapies might be more efficient in combating hypertension via two mechanisms: directly via drug-specific mechanisms and indirectly via renalase, probably through the degradation of catecholamines. Similarly, while valsartan, an AT1 receptor blocker, stabilized atherosclerotic plaques by upregulating renalase expression [51], the ACE inhibitor lisinopril was observed to be renoprotective in rat models of adriamycin-induced nephropathy probably by increasing renalase protein expression in renal tissues [52]. These findings suggest that renalase could be a novel target of RAAS.

However, laudable progress in corroborating the clinical potential of renalase has not been made since the physiological role of renalase in the context of hypertension is still an enigma [53]. Of note, the hypotensive action of renalase is based on the assumption that an inactive form of renalase is secreted into the circulation from the kidneys and is activated by catecholamines. However, this concept has been contested by subsequent studies. Furthermore, the catecholamine-degrading activity/amine oxidase activity of renalase has also faced experimental refutation, thereby dispelling the promising claims about the hypotensive activity of renalase [9–14]. Nonetheless, additional studies need to be undertaken to fully understand the effect of renalase on blood pressure as well as its role as a therapeutic target for the management of the overstimulated sympathetic system. Generation of such knowledge is a desirable clinical goal, since a great potential is foreseen for renalase replacement therapy or the use of renalase as a druggable target to control hypertension that is not adequately controlled by conventional drugs.

**Effect of renalase on cardiac hypertrophy, ventricular remodeling, and cardiac function**

Left ventricular hypertrophy (LVH) is commonly seen in people with uncontrolled hypertension, and over a period of time, it can be an independent risk factor for heart failure and sudden death [54]. Although primarily a cardiovascular disorder, people with end-stage renal failure are at the disadvantage of being vulnerable to LVH [55]. A study by Ghosh et al. [56] revealed that neonatal rats subjected to renal injury exhibited a high heart weight to body weight ratio and increased plasma norepinephrine levels. Apart from highlighting the role of catecholamine metabolism in the development of cardiac hypertrophy, this study also showed decreased renalase expression in...
cardiac tissue. These findings indicate the plausible role of renalase in the development of LVH. Further insights into the effect of renalase on cardiac structure and physiology were convincingly demonstrated using rat models of 5/6 nephrectomy [Nx], where 85% of the kidney is surgically removed. Studies conducted by Baraka et al. [4] suggest that in addition to an increase in mean arterial blood pressure, nephrectomized animals showed decrease in DT (developed tension) of LV papillary muscle and an elevated ratio of LV/BW (ratio of left ventricle and body weight). These findings are suggestive of cardiac hypertrophy. Furthermore, these animals showed increased levels of hydroxyproline (HPO) in their left ventricular tissues. Since the hydroxyproline levels correlate with the levels of collagen, augmented HPO levels in these animals are suggestive of abnormalities involving collagen breakdown. Interestingly, however, these structural and functional changes in the heart of 5/6 Nx rats were reversed at least partly by administering renalase, suggesting that renalase deficiency can perturb myocardial homeostasis. The authors also foresee a promising future for renalase as a therapeutic modality to modulate cardiac physiology and function. This is because, unlike some of the conventional antihypertensive drugs that do not reverse myocardial cell hypertrophy, renalase-treated animals not only demonstrated a lesser degree of cardiac hypertrophy and dysfunction but also modified adrenergic activity when compared to untreated animals [4].

In this regard, a functional missense polymorphism of the renalase gene can increase the susceptibility for cardiac hypertrophy, ventricular dysfunction, and ischemia [29] in persons with stable coronary artery disease. In a Heart and Soul Study involving Caucasian subjects, rs2296545 (Glu37Asp) single-nucleotide polymorphism occurs at FAD-binding region which is critical for its FAD-dependent oxidoreductase activity. This can alter the renalase gene product, reduce maximal velocity, interfere with its enzymatic activity and lower its affinity toward its cofactor, NADH. Ultimately, this would lead to impaired catecholamine metabolism and the associated cardiovascular complications. However, this particular study could not find an association between the Glu37Asp polymorphism and either systolic or diastolic blood pressure. The probable reason for this is the stringent medical therapy for the management of blood pressure in patients with coronary artery disease [29]. As an extrapolation to this particular study, another research group found that the renalase polymorphism rs2296545 was associated with LVH in a female population, but not a male population, with aortic stenosis. Additionally, the study also surmised that apart from altering the binding affinity of the cofactor, the Glu37Asp polymorphism may also modulate renalase gene expression by modifying the binding affinity

of the transcription factors related to hypertrophy and hypoxia [57].

When there is myocardial ischemic injury, the renalase gene is activated and helps ameliorate the deterioration of cardiac function [21]. Wu et al. [30] demonstrated that the isolated perfused heart models of renalase knockout mice subjected to an episode of ischemia–reperfusion exhibited more myocardial damage and tissue necrosis than the wild-type animals. This finding suggests that renalase deficiency can augment cardiac injury under ischemic stress [30]. Likewise, animal models with renalase-silenced cardiac tissues, when subjected to myocardial ischemia–reperfusion injury, exhibited diminished levels of myocardial renalase and heightened cell necrosis and apoptosis [58]. Interestingly, recombinant renalase therapy protected the myocardium during and after myocardial ischemia–reperfusion, reduced the myocardial cell necrosis and decreased the infarct area, thereby highlighting its cardio-protective effects [58]. Additionally, renalase was found to be a novel target of HIF-1α, and HIF-1α-mediated renalase expression helped confer protection against IR injury [21]. Furthermore, the mechanisms by which renalase might help cardiac cells circumvent ischemic insult could also be related to its NADH oxidase activity [30]. In the absence of renalase, a drop in the cellular NAD/NADH ratio was observed in cardiac tissue, which can augment myocardial injury during ischemia and impair cardiac contractility during reperfusion. Additionally, plasma NADH oxidase activity was also markedly reduced in renalase KO animals [30]. All these findings suggest the potential usage of renalase supplementation as a new treatment modality in treating ischemic heart diseases.

Of note, ischemic heart diseases are an important predisposition to the development and progression of chronic heart failure. With respect to the expression of renalase in the animal models of infarction-induced heart failure, what begins as a compensatory mechanism in the earlier phases of heart failure turns out to be a decompensatory mechanism at the later stages [59]. The authors put forward the hypothesis that the increase in renal expression of renalase when cardiac dysfunction just sets in is to circumvent the increased catecholamine concentrations caused by sympathetic overactivity, a hallmark of heart failure. However, as cardiac function deteriorates further, the renal expression of renalase may decrease owing to reduced blood flow to the kidney. This could possibly lead to an increase in circulating norepinephrine, resulting in catecholamine accumulation in the system [59]. Although the multifaceted role of renalase in regulating various aspects of the cardiovascular system has been of intense research interest and many intriguing theses have come out of it, additional experimental evidence is required to establish the role of renalase in the physiology and pathology of heart diseases.
Role of renalase in lipid metabolism and atherosclerosis

Apart from its role in regulating sympathetic tone and blood pressure, renalase exerts important effects on the cardiovascular system by being a “gene potentially related to lipid metabolism” [51]. Experimental evidence suggests that disrupting the homeostasis of lipid metabolism can alter the expression of renalase. Knockout of the ApoE gene in mouse models caused the transcriptional upregulation of the renalase gene in adipose tissues, suggesting that the renalase gene could be under the regulatory control of ApoE. Furthermore, apoE knockout mice fed on high-fat diet exhibited augmented expression of renalase in the kidneys, testis, and brain [51]. Interestingly, a high-fat diet attenuated the hepatic expression of renalase. This finding suggests how renalase expression might be involved in the disturbance of lipid metabolism via its expression in the liver, which is the primary organ involved in cholesterol biosynthesis and lipid metabolism.

Furthermore, perturbation of lipid metabolism might also cause vascular injury and lead to the onset and progression of atherosclerosis when coupled with hyperlipidemia and reductant catecholamines [60–62]. An atherosclerotic plaque becomes more detrimental when it is unstable. This is because an unstable plaque is vulnerable to rupture and trigger thrombosis, resulting in severe cardiovascular morbidities [63]. Known as a key factor in the genesis of atherosclerosis, hypertension is caused by the inappropriate activation of the renin-angiotensin system (RAS) [64]. Moreover, angiotensin II has been reported to orchestrate the onset of atherosclerosis by modulating microvascular permeability, stimulating the uptake of Ox-LDL by macrophages, facilitating leukocyte infiltration, and plaque size and destabilization [51, 65, 66]. In this regard, it is pertinent to note that recent studies indicate RAS as an important regulator of renalase gene expression [52]. Studies report that valsartan, an angiotensin II receptor antagonist, increases renalase gene expression through the functional inhibition of the RAS [51]. Interestingly, Zhuo et al. [51] also showed that the expression of renalase is reduced in the fibrous cap of an atherosclerotic plaque as it transitions from a stable plaque to an unstable plaque, suggesting that renalase could be involved in plaque stabilization. Nonetheless, treatment with valsartan augmented renalase expression in serum as well as in the fibrous cap of atherosclerotic plaques, thus imparting plaque stability [51]. These findings considerably broaden our understanding of the physiological functions of renalase and its translational aspect.

Renoprotective mechanisms of renalase

Over the years, research has equivocally shown that renalase is far more than an “innocent bystander in hypertension and kidney disease” [67]. Although it is expressed in tubule epithelial cells, glomeruli, proximal/distant tubules, mesangial cells and podocytes, renalase is primarily secreted by tubule epithelial cells [68, 69]. Apart from being the major site of renalase production, the kidney also plays a pivotal role in orchestrating the secretion of renalase into the circulation. The amount of renalase that is secreted into the bloodstream is influenced by renal function, renal perfusion, and catecholamine levels [69]. Rats subjected to subtotal nephrectomy (5/6 Nx) or with chronic renal failure show diminished renalase expression, highlighting the importance of renal function in regulating renalase expression [4, 18]. Likewise, by using a rat model of unilateral renal artery stenosis, Gu et al. [59] demonstrated the importance of renal perfusion on renalase synthesis by showing a significant reduction in renalase protein expression in the ischemic side of the kidney compared to the nonischemic side. The role of catecholamines in regulating renalase synthesis and secretion was determined from studies [18] showing augmented renalase secretion in response to catecholamine infusions.

Renalase and kidney diseases

A persistent and progressive deterioration of renal function can be considered chronic kidney disease (CKD) [70]. As mentioned earlier, several lines of evidence indicate that subjects with chronic or end-stage kidney diseases and animals subjected to subtotal nephrectomy show severe renalase deficiency at the tissue level and/or in the circulation [18, 28, 31, 71]. Sympathetic overactivity, triggered primarily by the diseased kidney, as well as increased blood pressure in patients with CKD seem to corroborate this deficiency [6, 31, 72, 73]. Furthermore, it was also reported that significant crosstalk exists between the sympathetic nervous system and kidneys [73, 74]. While renal hemodynamics are maintained by α-adrenergic mechanisms [75], kidneys via chemoreceptors and baroreceptors generate activating afferent signals resulting in increased sympathetic tone and elevated catecholamine levels [76–79]. These signals are stronger and more long-lasting in people with kidney injuries or compromised kidney functions, and they ultimately lead to high blood pressure and cardiovascular complications in chronic kidney disease [73]. Over the course of time, renal interstitial fibrosis, marked by excessive extracellular matrix deposition in the renal interstitium [80], causes the progression of CKD to end-stage renal disease.
Renal interstitial fibrosis (RIF) caused by the epithelial–mesenchymal transition of tubular epithelial cells was found to be mediated by transforming growth factor-β1 (TGF-β1). Interestingly, renalase supplementation in unilateral ureteral obstruction animal models decreased the expression of fibrosis markers and ameliorated RIF. These findings were corroborated in cultured human kidney-2 cells by demonstrating that renalase abrogated TGF-β1-mediated tubular EMT and fibrosis by silencing the ERK1/2 MAPK activation pathway [81].

Contrary to the above statements regarding renalase deficiency in CKD, a retrospective analysis using the data obtained from the Kremezin Study Against Renal disease progression in Korea (K-STAR) [82] showed that circulating renalase levels were elevated in CKD stage 3 and 4 patients compared to healthy controls. Interestingly, the authors found that every 10 µg/ml increase in serum renalase levels amplified the risk for mortality and renal outcomes in these patients, indicating that renalase may be used as a prognostic marker to predict the complications and progression of CKD [82]. Since several other organs (apart from kidneys) also express renalase, an increase in circulating renalase level in subjects with compromised renal function could possibly suggest a compensatory production in extrarenal organs in response to catecholamine excess or activation of the sympathetic nerve system or changes in the cardiovascular system or rise in blood pressure or oxidative stress which is prevalent in CKD or ESRD [82, 83].

**Role of renalase in cardiorenal interaction**

CKD and cardiovascular disease work closely together and exhibit a cause-effect relationship in the manifestation of various pathologies by multisystem crosstalk between the kidney and heart. CKD is an important risk factor for the development of cardiovascular diseases, such as left ventricular hypertrophy, heart failure, and coronary heart disease, and can affect the morbidity and life expectancy of patients [70, 84]. In addition to classic risk factors, such as hypertension and hyperlipidemia, failure to perform important endocrine functions, inflammation, disrupted calcium and phosphate metabolism, arterial calcification, RAAS activation, increased sympathetic tone, and oxidative stress, which are secondary in CKD patients, also make patients vulnerable to the development of cardiovascular diseases [6, 31, 39, 67, 72, 79, 82, 85]. In this regard, renalase could be a definitive link between the kidney and heart and might act as a mediator for the therapeutic targeting of cardiorenal syndrome. For instance, animal models of subtotal nephrectomy (5/6 Nx), an excellent animal model of CKD, exhibit reduced levels of renal and cardiac renalase [18]. This reduction may presumably lead to increased plasma catecholamine levels and the development of cardiovascular pathologies, such as hypertension and left ventricular hypertrophy [4, 18]. Treatment with renalase rescued cardiac function and reversed LV hypertrophy associated with CKD to some extent [4]. Moreover, a synergistic effect of high serum renalase and CKD on increases in endothelin-1 levels in patients with coronary artery disease could aggravate cardiovascular disease risk [86].

**Role of renalase in combating kidney injury**

Apart from the deleterious effects on the cardiovascular system, there is mounting evidence that CKD can also act as a risk factor for or a potent predictor of acute kidney injury (AKI) [87]. What is more intriguing is that the relationship seems to be bidirectional, with AKI acting as a driver for the progression of CKD [88]. AKI can be caused by several conditions, such as sepsis, surgery, drugs, and ischemia–reperfusion injury (IR injury). Renalase or its recombinant peptide, RP-220, have been found to be renoprotective and help cells ameliorate tissue injury and inflammation irrespective of the insult [7, 89]. One of the most common causes of AKI is IR injury, which usually manifests as a postoperative syndrome [89]. Upon renal injury following a stint of ischemia–reperfusion, renalase levels are diminished in the kidney and plasma, and there is a concomitant increase in circulating norepinephrine levels. These findings suggest that renalase could be used as biomarker to detect ischemic AKI [89]. Remarkably, elevated levels of plasma creatinine and pro-inflammatory markers in the kidney and evidence of heightened renal tissue injury in renalase-deficient animals subjected to IR suggest that these animals are more susceptible to kidney injury than normal wild-type animals [89]. The administration of recombinant renalase to wild-type animals rescued the cells and provided protection from the hazards of renal IR injury. However, it is important to note that the cytoprotective effects of renalase are not in tandem with their catecholamine-degrading activity, as demonstrated by the protective effects of renalase peptides, such as RP-220, that lack amine oxidase activity [7]. It is interesting to note that apart from being inextricably involved in renoprotection following an injury caused by ischemia–reperfusion, renalase has been found to be an important player in mediating the beneficial effects of ischemia preconditioning (IPC) in kidneys [22]. In rodent models of IPC, renal IPC increases renalase expression in kidney cells, which in turn mediates the protective effects of IPC against IR injury. Further blocking renalase action partially abolished the protective effects of renal IPC and exacerbated kidney injury.
Interestingly, HIF-1α acts as a key player in the renalase-mediated renal protection of delayed IPC [22]. Of note, remote IPC can also confer the same protective effects as local IPC. In contrast-induced nephropathy (CIN), limb IPC [90] was found to be beneficial in maintaining renal structure and function via a renalase-dependent mechanism. Under conditions of limb IPC, TNF-α released from the injured muscle tissue enters the circulation and mediates NFkB-induced renalase synthesis in kidney cells [90]. Zhao et al. [91] demonstrated that the renoprotective effects of renalase in CIN are not just limited to dispelling the cytotoxicity of contrast media but also involve activating cellular antioxidant, antiapoptotic, and anti-inflammatory pathways to preserve renal physiology.

Administration of exogenous renalase protected HK-2 cells against cisplatin- and H2O2-induced toxic injury. By inhibiting the activation of pro-apoptotic caspases, namely, Caspase-3, and increasing the expression of the antiapoptotic protein Bcl-2, renalase treatment attenuates the cytotoxic effect of cisplatin [7]. As with ischemic insult, kidney injury caused by cisplatin was more deleterious in renalase knockout animals, indicating that renalase might modulate the severity of the injury. Furthermore, the renalase KO animals not only exhibited a disrupted RP-220-mediated MAPK signaling in kidney, which is considered to be a key player for imparting renalase-mediated cytoprotection, but were also resistant to the protective effects of exogenous renalase peptide against renal ischemia–reperfusion injury. The authors surmised that there could be an unknown receptor with which RP-220 would interact to protect against toxic/ischemic injury and that the renalase transcript isolated from these mouse strains [94, 95], and (c) shorter transcript length of renalase in these mouse strains [95]. Once these and other relevant conundrums are

Signaling pathways involved in renalase-mediated cytoprotection are shown in Fig. 4. Renalase might have renoprotective effects and attenuate the progression of diabetic nephropathy by inhibiting glomerular hypertrophy [92]. According to this study, renalase expression was diminished in renal tissue biopsies of human subjects with diabetic nephropathy and in the kidneys of genetically diabetic db/db mice. Furthermore, heterozygous knockout of renalase in db/db mice resulted in increased albuminuria and the kidney weight index, suggesting that renalase insufficiency can accelerate the progression of renal injury in these animals. However, renalase overexpression in db/db mice decreased albuminuria and the kidney weight index. More interestingly, heterozygous knockout of renalase in db/db mice worsened renal mesangial fibrosis and elevated the expression of fibroctic markers as well as CDK inhibitor p21. Nevertheless, overexpression of renalase improved mesangial fibrosis and reduced the expression of fibroctic markers and p21. These findings suggest that the protective effect of renalase against the progression of diabetic nephropathy could be linked to the inhibition of p21-mediated mesangial fibrosis [92]. Taken together, these results indicate that renalase could be a novel therapeutic target for the treatment of diabetic nephropathy, and its translational outcome would satisfy the unmet need for therapies that can counter the progression of this disease.

Thus, renalase demonstrates dual roles, as it can be used to both indicate the prognosis and aid in the treatment of renal diseases. First, it acts as a biomarker of CKD [93] and AKI, and second, it attenuates renal necrosis, apoptosis and inflammation [89]. However, despite substantial evidence of an association between renalase and kidney pathophysiology, the exact role of renalase in renal physiology and pathology remains unclear even 15 years after its discovery due to the existence of apparently contradicting reports surrounding renalase. The discussion among various groups of researchers regarding the renal origin of this “novel intriguing protein” began with the use of HEK-293 cells in the progenitor article published by Xu et al. [1]. Because of its neuronal connection, HEK-293 cells cannot be wholly considered kidney cells; therefore, the renal origin, synthesis and secretion of renalase need to be re-examined. Additionally, the appropriateness of the renalase knockout mouse model generated from C5BL/6 mice [30] has been challenged by researchers owing to the (a) insignificant difference in the left ventricular mass of knockout mice when compared to the wild-type mice [94], (b) shorter transcript length of renalase in these mouse strains than rat and human renalase [94, 95], and (c) absence of N-terminal FAD-binding domain in the renalase transcript isolated from these mouse strains [95]. Once these and other relevant conundrums are
Delineating the correlation between renalase and diabetes

The insulin-secreting β cells of the pancreas are known to express renalase [19]. Therefore, it is reasonable to assume that any alteration in renalase gene expression may directly or indirectly be related to the onset and progression of disorders associated with impaired glucose metabolism. Studies on renalase gene polymorphisms represent a credible thesis for underscoring its link to glucose metabolism. While trying to find an association between type I diabetes and SNPs published in a previously reported Genome-Wide Association Study (GWAS) [96], Reddy et al. [97] found a putative association between type I diabetes and SNPs10509540. This SNP corresponds to a renalase gene polymorphism at chromosome 10q23.31. These data suggest that renalase could be considered a causal gene or T1D susceptibility gene that could be employed as a biomarker for the prediction and prognosis of diabetes. Interestingly, in a recent article published by Cai et al. [98], it was demonstrated that deleting the renalase gene by CRISPR technology conferred protection to pancreatic beta cells from autoimmune killing. This finding could be beneficial to patients who are undergoing cell replacement therapy for T1D because the destruction of transplanted cells by autoimmunity is one of the greatest challenges they face. Renalase gene deletion may help modify beta cell vulnerability in T1D and may eventually emerge as a novel therapeutic target to prevent beta cell loss in T1D.

Even though the mechanisms by which renalase gene polymorphisms are associated with diabetes are unknown, it
would be interesting to assess whether these SNPs could alter the expression of one or more steps involved in glucose metabolism starting from insulin receptors, glucose transporters, or protein kinases. Furthermore, although the relationship between diabetes and hypertension has not been fully decoded, it is tempting to assume that they could be controlled by some common regulatory systems, such as the renin-angiotensin-aldosterone system (RAAS). Given the importance of RAAS activation in hypertension and the probable involvement of glucose in the genesis of hypertension via the upregulation of AT1 receptor, it is tempting to speculate that RAAS might have a regulatory influence on hypertension and diabetes. Notably, renalase might act as a definitive link between hypertension and diabetes via the RAAS. Linking RAAS, hypertension, hyperglycemia, and renalase within a molecular circuitry would possibly identify renalase as a factor with significant diagnostic and therapeutic utility by providing valuable insights into the hitherto unclear mechanism of how renalase regulates blood pressure in subjects with and without diabetes.

**Renalase as a solution for the “oncogenic paradox”**

A paradigm shift in the understanding of the origin and progression of cancer is the fact that cancer could be a metabolic disease in which cancerous tumors rewire their metabolic programs to meet the increasing energy requirements [102, 103]. Recently, renalase has been acknowledged to facilitate tumor growth and act as a survival factor for cancer cells [104, 105]. This occurs by activating, through the PMCA4b receptor [17], metabolic pathways, such as PI3K and MAPK, which are in turn known to alter tumor cell metabolism [106, 107]. Studies have shown that renalase expression can alter the pathology and progression of various types of cancer, such as pancreatic cancer, bladder cancer, melanoma, and breast cancer [104, 105, 108].

In pancreatic ductal adenocarcinoma (PDAC), where renalase is found to be expressed in all four grades of tumor, renalase expression may act as an index to determine the survival advantage of patients [105]. Apparently, higher renalase expression in tumors is considered a marker of lower overall survival of patients. More recently, it has been reported that renalase levels are high in premalignant pancreatic tissues compared with the normal pancreas, indicating that renalase may have a potential role in the early development of PDAC [109]. Moreover, inhibitors of renalase signaling compromised the viability of cultured PDAC cells. The inhibition of renalase also decreased the tumor volume in xenograft mouse models, ultimately leading to tumor cell apoptosis and cell cycle arrest. Interestingly, a positive feedback loop was found to exist between renalase and STAT3 in which the continuous and long-lasting STAT3 expression [105] in turn can act as a driver of tumor cell proliferation. It can also help to create a niche where the inflammation is sustained by the expression of a large number of genes. Additionally, the cytoprotective mechanism of renalase was abrogated by inhibiting ERK activation, suggesting that renalase facilitates the survival of pancreatic cancer cells in an ERK-mediated and STAT3-dependent manner. In normal breast tissue, renalase is expressed at basal levels in epithelial and stromal cells and aids in normal mammary cell growth. However, under conditions of invasive breast cancer, renalase expression was augmented, with different molecular subtypes of breast cancer exhibiting different concentrations of renalase [108]. Furthermore, ER-positive IBC tissues also exhibited a strong positive correlation between renalase and estrogen receptor expression [108]. Renalase might be used as an indicator of the ER-positive/HER2-negative subtype of breast cancer.

In the study conducted by Hollander et al. [104], renalase expression was found to be progressively elevated during the transformation of tissues from normal skin to benign nevi to primary malignant melanoma and finally metastatic melanoma. Interestingly, renalase expression was inversely correlated with the disease-specific survival of patients. Attenuation of renalase signaling decreased the survival of melanoma cells in vitro, and anti-RNLS therapy abrogated tumor growth in murine xenograft models. While the apoptosis of tumor cells was caused by p38 MAPK-mediated Bax activation, inhibition of cell growth was achieved by augmenting the expression of the CDK inhibitor p21. Furthermore, renalase expression in melanoma was primarily due to the infiltration of immune cells, specifically CD163+ macrophages, and not because of resident melanocytes.

Since the expression of renalase is seemingly high in various types of cancers, determining renalase levels can serve as a molecular biomarker to facilitate the primary detection or diagnosis of tumors and shed light on the pathological mechanisms. Furthermore, renalase can be used as a prognostic marker and can also be employed as a tool to determine the subset of patients with aggressive phenotypes. As a secreted protein, renalase may be used as a surrogate marker to elucidate treatment response or recurrence. Furthermore, the inhibition of renalase signaling could be a novel therapeutic option in treating patients with cancerous tumors. Although there can be various regulatory factors that inhibit renalase expression and signaling, post-transcriptional regulation by miRNAs is emerging as a novel regulatory molecule for
Table 1 List of putative microRNAs that might interact with the human Renalase gene and regulate its expression

| miRNA         | No of tools predicted | RNA hybrid(ΔG), kCal/mol |
|---------------|-----------------------|-------------------------|
| hsa-miR-1301-3p | 6                     | −28.4                   |
| hsa-miR-5047   | 6                     | −27.0                   |
| hsa-miR-1271-5p | 6                     | −24.3                   |
| hsa-miR-182-5p  | 6                     | −24.2                   |
| hsa-miR-4799-5p | 6                     | −23.4                   |
| hsa-miR-4643   | 6                     | −22.7                   |
| hsa-miR-3675-5p | 6                     | −22.8                   |
| hsa-mir-4290   | 6                     | −22.5                   |
| hsa-miR-892c-5p | 6                     | −22.4                   |
| hsa-miR-96-5p   | 6                     | −22.3                   |
| hsa-miR-4482-3p | 6                     | −21.3                   |
| hsa-miR-506-5p  | 6                     | −21.1                   |
| hsa-miR-4698   | 6                     | −21.0                   |
| hsa-miR-545-5p  | 6                     | −20.7                   |
| hsa-miR-548p   | 6                     | −20.6                   |
| hsa-miR-548as-3p | 6                   | −20.1                   |
| hsa-miR-1273d  | 5                     | −36.0                   |
| hsa-miR-4515   | 5                     | −29.0                   |
| hsa-miR-4691-5p | 5                     | −29.0                   |
| hsa-miR-4474-3p | 5                     | −28.5                   |
| hsa-miR-4496   | 5                     | −25.9                   |
| hsa-miR-3169   | 5                     | −24.8                   |
| hsa-miR-548as-5p | 5                   | −24.5                   |
| hsa-miR-323b-3p | 5                     | −22.9                   |
| hsa-miR-147a   | 5                     | −22.6                   |
| hsa-miR-548w   | 5                     | −21.9                   |
| hsa-miR-4768-5p | 5                     | −21.6                   |
| hsa-miR-548b-5p | 5                     | −21.5                   |
| hsa-miR-548aq-5p | 5                   | −21.3                   |
| hsa-miR-548c-5p | 5                     | −20.2                   |
| hsa-miR-548am-5p | 5                   | −20.2                   |
| hsa-miR-5480-5p | 5                     | −20.2                   |
| hsa-miR-548y   | 5                     | −20.2                   |

“Six prediction tools (viz., miRanda, miRDB, miRWalk version 2.0, RNA hybrid, miRmap, and TargetScan) were used to predict the putative miRNAs that may bind to the human renalase gene. miRNAs that were predicted by at least five programs and had ΔG values of less than −20 kcal/mole (as per the RNA hybrid program) are included in this table.”

therapeutic targeting [110]. This is due to their aberrant expression in many pathophysiological conditions as well as the ease in measuring their concentrations in any biological fluid [27, 110]. A list of some putative microRNAs that might possibly interact with the human renalase gene and regulate its expression is shown in Table 1. Among the predicted miRNAs, there are many members of the miR-548 family, suggesting that miR-548 could be an important post-transcriptional regulator of renalase gene expression.

Conclusions and future perspectives

Owing to its multifaceted role in cardiovascular/renal pathophisiology, renalase has been vigorously studied by multiple research groups for its potential therapeutic applications. However, a major impediment to this goal is the clear divergence in the literature regarding the basic biochemical functions of renalase, in both its catecholamine-metabolizing activity and its function as an enzyme or cytokine. In view of the conflicting evidence and controversies, understanding the mechanism of action of renalase is an area of active research. Recent studies suggest that renalase acts as an anomerase and that it might have some other physiological function that could be completely unrelated to blood pressure control. Moreover, a daunting proposition about renalase is the ambiguity, “whether it is a causative factor or just an innocent bystander”, in many cardiometabolic conditions. Nonetheless, the lack of comprehensive understanding of the regulation of the renalase gene is another gap in translational research. Further studies in large human populations with different ethnicities are required to confirm the associations between renalase genetic variants and cardiometabolic/renal disease states. Table 2 summarizes the remarkable odyssey of renalase from its serendipitous discovery as a kidney-secreted hormone to an important determinant of cardiometabolic and renal disorders.

The current gold-standard antihypertensive therapies have partial success in conferring the best blood pressure control and risk reduction in hypertension. Several novel approaches are on the horizon to better combat hypertension, and renalase supplementation is an attractive candidate. Similarly, antirenalase therapy may be a promising alternative treatment modality to prolong the lives of cancer patients. More recently, in light of the novel corona virus COVID-19 pandemic, it is of immense translational significance that renalase levels were found to be diminished in patients infected with this virus. Although study is in the pipeline, Wang et al. [111] speculate that renalase could be a good additional biomarker for COVID-19 screening that could assess the severity of the disease owing to its anti-inflammatory property. Due to the limited availability of clinical and experimental data, it is possible that there are unidentified substrates for renalase, which may turn out to be more relevant to its physiological role and cardiorenal protective properties. Even though renalase is relatively “a new kid on the block”, much importance should be given to its significance. Proof of concept studies should be carried out to explore and substantiate the physiological and
biochemical properties of renalase to harness its various therapeutic potentials.

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| Year | Milestones/Key findings | References |
|------|-------------------------|------------|
| 2005 | First report of identification of renalase from kidney Defined as a catecholamine-metabolizing hormone | Xu et al. [1] |
| 2007 | Reported to regulate blood pressure and modulate cardiac function First report on association of renalase gene polymorphism (Glu37Asp) with essential hypertension | Desir [21] |
| 2008 | Renalase deficiency was observed in CKD | Desir [31] |
| 2010 | Renalase gene polymorphism Glu37Asp was associated with cardiac hypertrophy, dysfunction and ischemia | Farzaneh-Far et al. [29] |
| 2011 | Association of Renalase gene polymorphism with hypertension in T2DM and stroke Renalase deficiency was suggested to aggravate ischemic myocardial injury Genetic association of renalase SNP with type 1 diabetes | Buraczynska et al. [42] |
| 2013 | Protective effect against ischemic acute kidney injury Identified as an α-NAD(P)H oxidase/anomerase | Lee et al. [89] |
| 2014 | Role as a cytokine Likely correlation with hypertension and insulin resistance in T2DM | Guo et al. [16] |
| 2015 | Identified as a potential-regulator of lipid metabolism Facilitates atherosclerotic plaque stabilization Confers protection to IR injury in heart by being a hypoxia-responsive gene Suggested to mediate beneficial effects of Ischemic Preconditioning Identification of receptor for extracellular renalase | Zhou et al. [51] |
| 2016 | Renalase inhibition has anti-tumor effects in pancreatic cancer Identified to have increased expression in melanoma | Guo et al. [105] |
| 2018 | Overexpression in ER-positive breast cancer | Yu et al. [108] |
| 2019 | Mitigates liver steatosis and protects against liver IR injury | Zhang et al. [23] |
| 2020 | Reported to have a protective role in diabetic nephropathy A plausible additional biomarker for identifying COVID-19 disease severity Renalase gene deletion modifies the Beta cell vulnerability in Type 1 Diabetes | Yin et al. [92] |

*CKD chronic kidney disease, CVD cardiovascular disease, COVID-19 coronavirus 2019 disease, ER estrogen receptor, IR ischemia–reperfusion, SNP single-nucleotide polymorphism, T2DM type 2 diabetes mellitus*
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