[Frontiers in Bioscience 12, 4179-4190, May 1, 2007]

The serine protease corin in cardiovascular biology and disease

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1. ABSTRACT

Corin is a type II transmembrane serine protease expressed primarily in the heart. Functional studies have shown that corin converts pro-atrial natriuretic peptide (pro-ANP) to mature ANP, a cardiac hormone important in regulating salt-water balance and maintaining normal blood pressure. In corin-deficient mice, pro-ANP processing is abolished, demonstrating that corin is the physiological pro-ANP convertase. Corin-deficient mice develop hypertension that is exacerbated by a high-salt diet and during pregnancy, indicating the importance of this enzyme in controlling blood pressure. More recently, single nucleotide polymorphisms (SNPs) are found in the human corin gene, which are associated with an increased risk for hypertension and cardiac hypertrophy. This review describes the biology of corin and its potential role in cardiovascular disease.

2. INTRODUCTION

Proteases participate in a variety of biological processes (1, 2). These enzymes play a key role in many pathological conditions such as thrombosis, bleeding disorders, inflammation, cancer, viral infection, and neural degenerative diseases. There have been tremendous interests in both academia and pharmaceutical industry in studying proteolytic enzymes. The efforts have helped to discover new biological mechanisms and develop more effective therapeutics.

The heart is a central organ of the circulatory system. It not only acts as a pump driving blood flow but also regulates blood volume and pressure through its endocrine system (3). Many trypsin-like serine proteases including tissue kallikrein, chymase, tryptase, and urokinase are present in the heart, and may contribute to

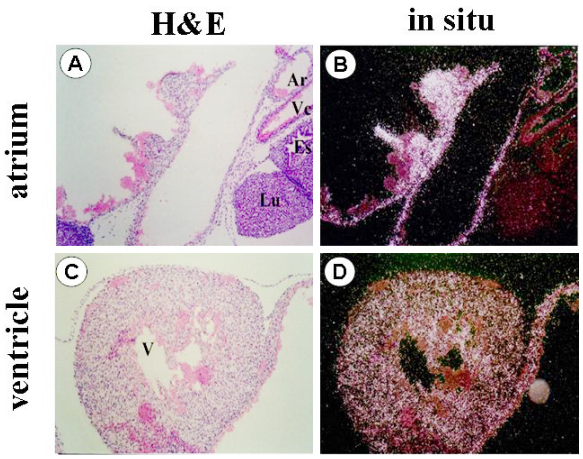

Figure 1. Corin mRNA expression in the heart. Arial (panels A, B) and ventricular (panels C, D) sections from a mouse embryonic heart at day E15.5, were prepared and stained with hematoxylin/eosin (H&E) (panels A, C). Corin mRNA was detected by *in situ* hybridization (panels B, D). In panel A, aorta (Ar), vena cava (Vc), esophagus (Es), and lung (Lu) are indicated. The original data was published by Yan *et al.* (7).

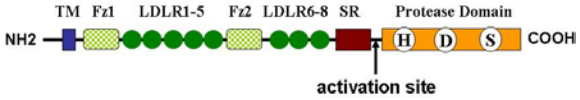

Figure 2. Corin protein domain structure. The transmembrane domain (TM), frizzled-like cysteine-rich domains (Fz), LDL receptor repeats (LDLR), scavenger receptor cysteine-rich repeat (SR) and protease catalytic domain (Protease Domain) with active site residues histidine (H), aspartate (D) and serine (S) are indicated. An arrow indicates the activation cleavage site.

cardiovascular diseases such as hypertension, cardiac hypertrophy, and heart failure (4). Most recently, another membrane serine protease, corin, has been found in the heart (5, 6). Biochemical and genetic studies have identified the biological function of this newly discovered enzyme and provide new insights into the molecular basis of cardiac function.

3. MOLECULAR BIOLOGY

Human corin cDNA was cloned in the late 1990s in the midst of the 'gene rush'. Yan *et al.* found a partial human cDNA in an expressed sequence tag database, which appeared to encode a novel trypsin-like protease (7). Northern analysis of human tissues showed that the gene was expressed primarily in the heart. The length of the mRNA was ~5 kb, suggesting that the protein it encoded was large and might have a structure more complex than that of trypsin. Subsequently, the full-length cDNA was isolated by screening of human heart libraries and named corin (7).

Independently, Hooper *et al.* isolated human corin cDNA from a HeLa-derived cell line that was resistant to tumor necrosis factor-α induced apoptosis (8). Using degenerate oligonucleotides based on the conserved serine protease sequences, they cloned a cDNA, designated ATC2, which encoded a novel serine protease. When the full-length ATC2 cDNA was completed, it turned out to be identical to human corin cDNA (8). Separately, Tomita *et al.* cloned mouse corin cDNA while searching for novel low-density lipoprotein (LDL) binding proteins, and named it LDL receptor-related protein 4 (LRP4) (9). When expressed in COS cells, recombinant mouse LRP4 did not show any detectable LDL binding activities, suggesting that the molecule is not an LDL-binding protein (9).

The human and mouse corin genes are mapped to chromosomes 4p12-13 and 5D, respectively (7). Pan *et al.* isolated DNA fragments spanning the entire human and mouse corin loci (10). Both corin genes have 22 exons and span ~200 kb. Thus, the corin gene is one of the longest genes in the trypsin family identified to date. On human chromosome 4 p12-13, a genetic locus is linked to a congenital heart disease called total anomalous pulmonary venous return (TAPVR) (11). In TAPVR patients, the pulmonary vein connects abnormally to the right atrium or one of the venous tributaries instead of the left atrium. The molecular defects of the disease remain unknown. Hooper *et al.* showed that corin protein expression in heart samples from a TAPVR patient was similar to that of normal heart controls (8). We also examined DNA samples from two TAPVR patients by Southern analysis and did not detect any DNA rearrangements in the corin gene (unpublished data). Based on currently available data, the disease is unlikely caused by corin gene mutations.

Corin mRNA and protein are detected by *in situ* hybridization and immunohistochemistry in atrial and ventricular cardiomyocytes (7, 8). Corin mRNA expression in the atrium appeared to be higher than that in the ventricle (Figure 1). Recently, corin mRNA is also found in scar myofibroblasts from rat post-myocardial infarcted heats (12). In addition, corin mRNA is detected in other tissues such as mouse developing bones and kidneys, and in some human cancer cells (7). In human small cell lung cancer, corin expression may contribute to the pathogenesis of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (13).

4. BIOCHEMISTRY

The full-length human corin cDNA encodes a polypeptide of 1042 amino acids (7, 8). The protein has an integral transmembrane domain near its N-terminus and a short cytoplasmic tail. In its extracellular region, there are two frizzled-like cysteine-rich domains, eight LDL receptor repeats, a scavenger receptor repeat, and a trypsin-like protease domain at the C-terminus (Figure 2). The overall corin structure is similar to that of type II transmembrane serine proteases of the trypsin family (14-16).

The calculated mass for human corin protein is ~116 kDa. In SDS-PAGE and Western analysis,

recombinant human corin from HEK 293 cells appeared as a band of ~150 kDa under reducing conditions (17). Native human corin appeared to have a similar molecular mass (8). The difference between the calculated and actually observed values in corin molecular mass may be due to post-translational modifications. In the extracellular region of human corin, there are 19 predicted *N*-linked glycosylation sites (7). Recombinant corin from cells treated with tunicamycin, which inhibits glycosylation, appeared to have a reduced molecular mass (~120 kDa) on Western analysis (unpublished data). To date, the effects of the carbohydrate moieties on corin protein stability and biological activity have not been determined.

Several experiments supported corin as a membrane protein and confirmed its orientation on the cell surface. Yan *et al.* showed by Western analysis that recombinant human corin from 293 cells was in cell lysate and membrane fractions but not in the conditioned medium (17). The results indicate that corin is associated with the cell membrane and that there was minimal shedding of the protein under the culture condition. In another experiment, Knappe *et al.* labeled cell surface proteins with biotin and showed by Western analysis that the extracellular region of human corin was indeed exposed on the cell surface (18).

Like most trypsin-like proteases, corin is made as a single-chain molecule, as indicated by a single band on Western analysis under reducing conditions (8, 17). The human corin protein has a conserved activation cleavage sequence Arg-Ile-Leu-Gly-Gly at residues 801-805 (7, 8). Proteolytic cleavage at Arg-801 is required to activate corin. Knappe *et al.* constructed a mutant corin, R801A, by replacing residue Arg-801 with an Ala (19). The mutation is predicted to abolish the activation cleavage site. In functional assays, mutant corin R801A did not have any detectable activity, suggesting that the single-chain corin is not active (19). In this regard, corin is similar to other type II transmembrane serine proteases that require activation cleavage for their activities. At this time, it is not known how corin is activated *in vivo*.

To study corin catalytic activities, Knappe *et al.* inserted an enteropeptidase (EK) recognition sequence at the corin activation site, which allowed corin to be activated in a controlled manner (19). In chromogenic substrate assays, EK-activated corin exhibited hydrolytic activities that favored Arg/Lys residues at the P1 position, Pro/Phe/Gly at the P2 position, and small neutral amino acids at the P3 position. The activity was inhibited by nonspecific trypsin-like protease inhibitors including benzamidine, phenylmethylsulfonyl fluoride, antipain, leupeptin, aprotinin, tosyl-Lys-chloromethylketone, and soybean trypsin inhibitor (19). On the other hand, the activity was not inhibited by chymotrypsin-like protease inhibitors such as chymostatin and Tosyl-Phe-chloromethylketon, or metallo- and cysteine-protease inhibitors such as phosphoramidon, EDTA, peptstatin, and bestatin (19). To date, no endogenous corin inhibitors have been identified. Knappe *et al.* showed that the corin activity was not inhibited in the presence of human plasma (19).

5. BIOLOGICAL FUNCTION

Studies have been performed to define the biological function of corin. Because corin is a transmembrane protein and is expressed in cardiomyocytes, it was reasonable to predict that corin functions in the heart. As a trypsin-like protease, corin was expected to cleave target molecules at a basic residue. It was also reasonable to predict that the corin target molecules should be present and possibly made in the heart. The rationale led Yan *et al.* to hypothesize that corin may play a role in processing a cardiac peptide, atrial natriuretic peptide (ANP) (17).

ANP, also called atrial natriuretic factor, is a cardiac hormone discovered in the early 1980s by Adolfo de Bold who found that the rat atrium contained a substance promoting renal sodium and water excretion (20). Subsequent isolation and characterization of ANP and its related peptides by many laboratories have revealed an elegant mechanism by which the heart acts as a sensor to regulate blood pressure and salt-water balance (3, 21-25). When blood pressure elevates, cardiomyocytes in the atrial wall are stretched, which triggers ANP release from the cells into the circulation. In target organs such as kidneys and peripheral blood vessels, ANP activates its receptor, natriuretic peptide receptor-A (NPR-A), and increases intracellular cGMP production, which stimulates renal sodium and water excretion and relaxes resistance vessels, thereby lowering blood volume and pressure. Such a mechanism is essential for maintaining normal blood pressure. In mice, deficiency in either ANP or NPR-A causes hypertension (26-28).

In cardiomyocytes, ANP is made as a 151-amino-acid precursor, prepro-ANP. After the signal peptide is removed, the 126-amino-acid pro-ANP is stored in dense granules. Upon secretion, pro-ANP is converted to an active hormone by proteolytic cleavage at residue Arg-98. Many laboratories had tried to identify the responsible enzyme. Seidah and colleagues reported a trypsin-like enzyme, IRCM-serine protease 1, from porcine pituitary and rat atria and ventricles, which cleaved pro-ANP *in vitro* (29, 30). The cleavage, however, appeared to be non-specific as the enzyme cleaved pro-ANP at residues Arg-102, Arg-101, and Arg-98 in that order of preference (30). Inagami and colleagues reported another trypsin-like protease, atrioactivase, from bovine atria, which was in membrane fractions and specifically cleaved pro-ANP at Arg-98 (31, 32). However, the enzyme was only partially purified and its identity remained unknown. Several other groups reported that thrombin and kallikreins also cleaved pro-ANP *in vitro* but the biological significance was unclear (33-35). Thus, for more than twenty years after the discovery of ANP, the physiological pro-ANP convertase remained elusive.

To determine if corin is the pro-ANP convertase, Yan *et al.* did a cell-based experiment where plasmids

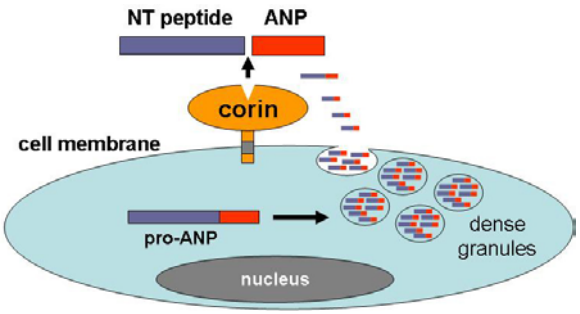

Figure 3. A model of corin-mediated pro-ANP processing. Pro-ANP is stored in the dense granule of cardiomyocytes. Upon secretion, pro-ANP is cleaved by corin on the cell surface, generating the N-terminal (NT) inactive peptide and the C-terminal mature ANP.

expressing corin and pro-ANP were co-transfected in 293 cells (17). Analysis of pro-ANP and its derivatives in the conditioned medium showed that pro-ANP was converted to ANP in the presence of corin but not other proteases.

The result was encouraging but further experiments were needed to show the corin-mediated pro-ANP processing in a physiologically-relevant cell. Wu *et al.* then used HL-5 cells, a murine atrial cell line, and showed that overexpression of an active site mutant corin, S985A, inhibited pro-ANP processing, suggesting a dominant negative effect of the mutant corin on the endogenous enzyme (36). Moreover, transfection of small interfering RNA against the corin gene blocked pro-ANP processing in the cardiomyocytes in a dose-dependent manner (36).

To exclude the possibility that other proteases might contribute to the observed pro-ANP processing in the cell-based experiments, it was important to show directly that purified corin possessed pro-ANP processing activity. Knappe *et al.* made a recombinant soluble corin and purified it to homogeneity (18). The purified corin cleaved pro-ANP specifically at residue Arg-98, generating active ANP as measured by a cGMP-stimulating assay (18). The data demonstrate that corin indeed has the pro-ANP processing activity.

Because other proteases such as thrombin and kallikreins had been reported to process pro-ANP *in vitro* (33-35), it was critical to show that corin acts as the pro-ANP convertase *in vivo*. If corin is the only physiological pro-ANP convertase, one would expect that lack of corin would prevent pro-ANP processing in an animal. Chan *et al.* made a corin-deficient mouse using the homologous recombination technique (37). Corin-deficient mice were viable and fertile, indicating that the enzyme is not essential for embryonic development and postnatal survival. HPLC analysis of pro-ANP and its derivatives in atrial tissues showed elevated levels of pro-ANP but no detectable mature ANP in the knockout mice. The results indicate that in the absence of corin, pro-ANP processing is abolished in the animal. Infusion of a soluble corin transiently restored pro-ANP conversion, producing circulating active ANP in the knockout mice. These results show that corin is the long-sought physiological pro-ANP convertase.

The human natriuretic peptide family has two additional members: brain or B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) (3, 21-25, 38). These peptides share sequence similarities but are encoded by separate genes. Like ANP, BNP is made mainly in cardiomyocytes and has a role in natriuresis, diuresis, and vasodilation. On the other hand, CNP is made in many tissues and cell types including the brain, kidney, vascular cells and chondrocytes. CNP is believed to have a role in vascular smooth muscle cell growth and bone differentiation. The biological activities of these peptides are mediated by their receptors: NPR-A for both ANP and BNP, and natriuretic peptide receptor-B (NPR-B) for CNP. There is another receptor, natriuretic peptide receptor-C, which acts as a clearance receptor removing the peptides from the circulation.

Like ANP, BNP and CNP are synthesized as pro-forms, which are activated by proteolytic cleavage. Corin has been tested for processing pro-BNP and pro-CNP. Human corin cleaved pro-BNP in transfected cells (17). The cleavage, however, appeared less efficient than that for pro-ANP. On the other hand, corin did not cleave pro-CNP in similar experiments (39). The results are consistent with the fact that pro-ANP and pro-BNP cleavage site sequences are similar but differ from pro-CNP. Pro-CNP is most likely processed by furin. Wu *et al.* showed that pro-CNP was processed intracellularly and that the processing was abolished in the furin-deficient LoVo cell (39). Incubation of purified furin with pro-CNP converted the pro-hormone into active CNP. Further studies are needed to determine the role of corin in processing pro-BNP *in vivo*.

The studies of corin suggest a cellular mechanism by which pro-ANP is activated (Figure 3). Normally, corin is anchored on the cell surface whereas pro-ANP is stored in dense granules. When cardiomyocytes are stretched, pro-ANP is secreted from the cell and converted into ANP by corin in the extracellular space. This model is based on several experimental findings. Thibault *et al.* showed that the dense granules isolated from rat atria contained only pro-ANP but no ANP, indicating that the pro-hormone is stored inside the cell (40). Studies from our laboratory showed that corin-generated ANP was not detected in cell lysate, suggesting that the cleavage occurs extracellularly (17, 39). Sei *et al.* also showed that in cultured cardiomyocytes pro-ANP processing took place on the cell surface but not in the medium (41).

Many peptide hormones are processed by the subtilisin-like proprotein convertases that act intracellularly (42-45). The corin-medicated pro-ANP processing occurs extracellularly. The apparent difference may be of biological significance. By allowing large amounts of hormone precursor accumulated inside cells and converting them rapidly into active hormones upon their release, this "extracellular cleavage" mechanism provides the cell with an efficient way to supply hormones on demand. This is

especially important for the hormones that are unstable inside the cell after processing. Corin possibly is not the only type II transmembrane serine protease involved in producing peptide hormones. It will be interesting to find out if other members from this protease family also have such a function.

6. STRUCTURE AND FUNCTION RELATIONSHIP

Corin has an integral transmembrane domain near its N-terminus. For many soluble serine proteases such as blood clotting enzymes, cell membrane association enhances their catalytic activities (1). To assess the functional importance of the corin transmembrane domain, Knappe *et al.* expressed a soluble corin containing only the extracellular region (19). In cell-based assays, the soluble and full-length corin processed pro-ANP with similar efficiency, indicating that the transmembrane domain is not necessary for the activity.

Studies of other type II transmembrane serine proteases including enteropeptidase (46), matriptase/MT-SP1 (47, 48), hepsin (49, 50), spinesin (51), human airway trypsin-like protease (52), and polyserase (53) have also shown that the transmembrane domain is dispensable for their catalytic activities. This raises the question regarding the biological function of this domain in these proteases. It is possible that the transmembrane domain is to localize the enzymes to specific tissues or cells where their activities are needed. Some type II transmembrane proteases such as matriptase/MT-SP1 (54) and hepsin (49) are found to be shed from the cell surface. Kim *et al.* have shown that the cytoplasmic tail of mouse matriptase binds to filamin, which connects to the actin cytoskeleton, and that this interaction is importance for matriptase shedding (55). The physiological importance of the shedding event still remains to be defined.

Between the N-terminal transmembrane domain and the C-terminal protease domain of corin, there are two frizzled-like cysteine-rich domains, eight LDL receptor repeats, and a scavenge receptor-like repeat. This domain combination is unique among the trypsin-like proteases. In fact, corin is the only member that contains the frizzled-like cysteine-rich domains. Propeptide domains in trypsin-like proteases are known to be functionally important. For example, the kringle domains in prothrombin are important for its activation by factor Xa (56). Similarly, the kringle domains in plasmin(ogen) are critical for fibrin-binding (57, 58). In enteropeptidase, the propeptide motifs are involved in cell surface expression and interactions with the substrates and inhibitors (46).

The corin propeptide domains have been analyzed biochemically. Knappe *et al.* studied two soluble corin proteins, EKshortCorin containing only the protease domain and EKsolCorin containing the entire extracellular region (18). Both proteins had similar K_m and k_{cat} values for the chromogenic substrates S-2366 and S-2406, indicating that the propeptide is not necessary for the catalytic activity toward small peptide substrates. Unlike the long soluble EKsolCorin, however, EKshortCorin failed to process pro-ANP, suggesting the importance of the propeptide for pro-ANP processing. Knappe *et al.* subsequently showed that frizzled 1 domain and LDL receptor repeats 1-4 were important for corin to interact with pro-ANP (18).

The frizzled-like cysteine-rich domains are found mostly in proteins that interact with Wnt molecules (59-63). The domain structures bind directly to Wnt proteins. In mouse Frizzled 8, mutations in the cysteine-rich domain impair the binding to Wnt8 protein (64). The results from the corin studies indicate that the frizzled-like domains also participate in protease and substrate interactions (18). It is noted that carboxypeptidase Z, a widely expressed metallocarboxypeptidase, also contains a frizzled-like cysteine-rich domain near its N-terminus (65, 66). To date, however, its functional significance has not been determined.

7. GENE REGULATION

Many type II transmembrane serine proteases are regulated under pathophysiological conditions. For example, hepsin is highly up-regulated in advanced prostate cancer (67-73). The plasma levels of pro-ANP/ANP and related natriuretic peptides are also increased in cardiovascular diseases such as hypertension, myocardial infarction, cardiac hypertrophy, and congestive heart failure (74-77). The increase of these cardiac hormones is an important regulatory mechanism to maintain normal intravascular volume and blood pressure.

Tran *et al.* have studied corin gene regulation in hypertrophic cardiomyocytes stimulated by phenylephrine (PE), an α1-adrenergic receptor agonist (78). RT-PCR showed that corin mRNA expression in the PE-treated cells was 3.5-fold higher than that in control cells. The corin gene up-regulation was dose- and time-dependent, and correlated with the increase of cell size and ANP mRNA levels. The PE-treated cardiomyocytes also had an increased activity (~3 fold) in converting pro-ANP to active ANP, as measured by Western analysis and a cGMP stimulating assay. The results indicate that the corin gene is up-regulated in cardiomyocytes in response to hypertrophic stimuli.

Several groups also have studied corin mRNA expression in animal models of heart failure. Tran *et al.* performed a rat model of heart failure induced by left coronary artery ligation (78). The animals developed heart failure eight weeks after the surgery. Northern and RT-PCR analyses showed that corin mRNA expression in the non-infarcted left ventricular (LV) myocardium increased by ~3 fold. The data was consistent with the results from hypertrophic cardiomyocytes in culture. Similar corin mRNA up-regulation was also reported in a rat model of myocardial necrosis and in human end-stage failing hearts (79, 80). On the other hand, corin mRNA up-regulation was not detected in the atrium in another rat model of heart failure within 4 weeks after an aortacaval shunt (81). The data suggest that the induction of corin expression is a

compensatory mechanism when the enzyme becomes a rate-limiting factor in the setting of heart failure.

To understand the mechanism by which the corin gene is regulated, Pan *et al.* isolated the 5'-flanking region of the human and mouse corin genes and identified conserved binding sites for TBX5, GATA, NKX2.5, and Kruppel-like transcription factors (10). Pan *et al.* further showed that the sequence from -646 to -77 bp in mouse and from -405 to -15 bp in human DNA segments contained the corin promoter activity (10). Within these sequences, a conserved GATA binding site is located proximal to the TATA box. Previous studies have shown that GATA transcription factors is important for controlling cardiac gene expression (82-84). Alterations of the GATA sites in the corin promoter eliminated the binding to GATA proteins and reduced the promoter activity in cardiomyocytes (10). Pan *et al.* also showed that the GATA element bound to GATA-4 but not other GATA proteins in the cell, indicating that GATA-4 protein is a major transcription activator for cardiac corin expression (10).

GATA-4 protein is a known regulator for ANP and BNP gene expression (85-87). In response to fluid volume overload or a hypertrophic signal, the heart produces more ANP and BNP to reduce blood volume and lower blood pressure. An important signaling pathway in this mechanism involves the GATA elements and/or NF-AT-binding sites in the ANP and BNP promoters (87-89). It is believed that stretching myocyte increases intracellular Ca^{2+} concentration, leading to calcineurin activation and translocation of the transcription factor NF-ATc3 to the nucleus. NF-ATc3 then interacts with GATA-4 protein, which stimulates ANP and BNP gene expression. In the corin gene promoter, there are also several NF-AT binding sites (10), although their functional importance has not been verified. It is possible that the ANP, BNP, and corin genes are regulated similarly under hypertrophic conditions. Further studies of corin gene regulation will help to understand the role of corin in human heart disease.

8. ROLE IN CARDIOVASCULAR DISEASES

8.1. Hypertension

Hypertension is the most prevalent cardiovascular disease, afflicting nearly one in every three American adults (90). The disease is a major risk factor for stroke, myocardial infarction, congestive heart failure, and kidney failure. Numerous studies have demonstrated the physiological importance of the ANP-mediated pathway in controlling blood pressure.

If corin is essential for pro-ANP activation, corin deficient mice are expected to have a hypertensive phenotype similar to that in ANP-deficient mice. Using radiotelemetry, Chan *et al.* showed that corin-deficient mice indeed developed spontaneous hypertension (37). Both male and female corin-deficient mice had elevated systolic, diastolic, and mean arterial blood pressure compared to that of control mice. Blood pressure increased further when the animals were fed with a high-salt diet, a similar phenotype reported in ANP-deficient mice (26). The results show that corin is critical in maintaining normal blood pressure in mice.

To date, no mutations in the human ANP or BNP genes have been reported that cause hypertension. Nakayama *et al.* have found a deletion in the human NPR-A gene promoter that is associated with hypertension and cardiac hypertrophy, suggesting that genetic defects in the ANP pathway may contribute to human disease (91). Recently, Dries *et al.* have found two SNPs in a corin gene allele that is more common in blacks than whites and is associated with an increased risk for hypertension (92). It is well known that the prevalence of hypertension is high in blacks (93, 94), but the underlying causes are not clear. Genetic alleles encouraging salt and water retention are believed to contribute to the disease (95-98). To date, genetic variants in epithelial sodium channel (99, 100) and proteins involved in epinephrine synthesis (101) and the rennin-agiotension-aldosterone system (102-108) are found to be associated with hypertension in blacks. The corin SNPs result in amino acid changes (T555I and Q568P) in the second frizzled-like domain in the propeptide. It will be important to determine if the SNPs alter corin function and contribute to hypertension in patients.

8.2. Pregnancy-induced hypertension

When hypertension develops in pregnant women, it poses a significant risk for both the mother and fetus. The disease occurs in ~8-10% of pregnancies but its cause remains poorly understood. One important pathological feature in preeclampsia is suboptimal placentation that may result from abnormal trophoblast invasion and inadequate maternal spiral artery remodeling (109-111). As a result, placental perfusion is reduced, leading to placental hypoxia in preeclampsic pregnancies. Studies have shown that endothelial dysfunction, oxidative stress, and inflammatory cytokines are important contributing factors in this disease (112-115). Recently, several placenta-derived soluble angiogenic factors such as VEGF, sFlt1 and endoglin are found to play an important role in preeclampsia (116-122).

Corin is expressed primarily in the heart but not the non-pregnant uterus. Unexpectedly, Yan *et al.* detected abundant corin mRNA in mouse uterine decidual cells (7), suggesting a potential role of corin during pregnancy. Because the corin-mediated pro-ANP processing is critical in controlling blood pressure, it is possible that corin expression in the uterus is a physiological mechanism designed to control body fluid balance and prevent high blood pressure during pregnancy when blood volume is increased significantly.

If this hypothesis is correct, further blood pressure increase is expected when corin-deficient mice become pregnant. Chan *et al.* showed that systolic blood pressure in corin-deficient mice rose within days of pregnancy, reached the highest level at mid-gestation, and eventually returned to pre-pregnancy levels after delivery (37). Urine protein concentrations doubled in corin-deficient mice at late gestation stages (37). The phenotype

is reminiscent to preeclampsia in humans. The results support a role of corin in regulating blood pressure during pregnancy. To date, it is not known if hypertension in ANP- and NPR-A-deficient mice is exacerbated during pregnancy. The information will be important to understand if the role of corin during pregnancy is mediated by the ANP signaling pathway.

8.3. Cardiac hypertrophy

Cardiac hypertrophy is a compensatory mechanism to maintain cardiac output, but often represents an early sign for more severe conditions such as heart failure. The ANP signaling pathway has been shown to have a local anti-hypertrophic function in the heart (123). Several groups have shown that ANP inhibits DNA and protein synthesis in agonist-stimulated cardiac myocytes and fibroblasts in culture (124-126). Conversely, inhibition of NPR-A increased the protein synthesis and cell size in rat neonatal cardiomyocytes (127). The anti-hypertrophic effect of ANP appears to depend on the guanylyl cyclase activity of NPR-A (126, 127).

Studies in animal models demonstrate that the ANP-mediated anti-hypertrophic effect is independent of its systemic function on blood pressure. For example, expression of an NPR-A transgene in the heart of NPR-A knockout mice did not alter blood pressure but reduced cardiac myocyte size (128). Similarly, cardiac expression of an ANP transgene reduced hypoxia-induced right ventricular hypertrophy in mice (129). On the other hand, dietary or pharmacological interventions in either ANP or NPR-A knockout mice lowered blood pressure, but did not alter the hypertrophic phenotype (128, 130). In another knockout mouse model, Holtwick *et al.* selectively disrupted the NPR-A gene in cardiomyocytes (131). The mice did not have hypertension but exhibited cardiac hypertrophy that was exacerbated upon aortic constriction. Together, these studies provide strong evidence for a role of the ANP signaling pathway in preventing cardiac hypertrophy.

Chan *et al.* also assessed cardiac hypertrophy in corin-deficient mice (37). Measured by 2D transthoracic echocardiography at 12 and 35 weeks of age, corin-deficient mice had an increased LV mass compared to that in control mice. Consistently, the cardiac function of corin-deficient mice declined at 35 weeks of age. When the knockout mice were older (>1 year), their left and right ventricular weights increased significantly, confirming the cardiac hypertrophic phenotype. It remains to be determined, however, whether this phenotype was caused primarily by blood pressure increase or the lack of a local corin/ANP action in the heart.

Most recently, Rame *et al.* reported that the human corin I555/P568 gene allele is associated with an enhanced cardiac hypertrophic response to hypertension in blacks who are not treated with antihypertensive drugs (132). In two large study populations, patients with the corin I555/P568 allele had a greater LV mass compared to that in control patients with the wild-type allele but similar systolic blood pressure. The results indicate that the corin I555/P568 allele is an independent predictor of LV mass in hypertensive patients. Further studies are needed to understand the biochemical basis of the apparent anti-hypertrophic function of corin. The results may help to design new strategies to treat patients with heart disease.

9. ACKNOWLEDGMENTS

The author is grateful to the formal and present members in the laboratory who contributed to the corin studies, especially Joyce Chan, Sabine Knappe, Mary Rose Madlansacay, Junliang Pan, Katherine Tran, Chengliang Wu, Faye Wu, and Wei Yan. This work is supported in part by a start-up fund from The Cleveland Clinic Foundation.

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Key Words: Corin, ANP, BNP, Hypertension, Cardiac Hypertrophy, Preeclampsia, Review

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