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CORIN AS A BIOMARKER IN HEART FAILURE: AN INSIGHT

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Abstract

Corin is a transmembrane serine protease expressed in cardiomyocytes, cleaves pro-ANP and pro-BNP into biologically active peptide hormones. Like many membrane proteins, corin is shed from the cell surface. By promoting salt and water excretion, the corin and the atrial natriuretic peptide (ANP) system should help to maintain fluid balance in heart failure. Yet, the development of fluid retention despite high levels of ANP-related peptides suggests that this compensatory system is limited. Low corin levels and impaired pro-ANP cleavage may contribute to pathogenesis of heart failure and that plasma corin may be used as a biomarker in the diagnosis of heart failure.

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1. INTRODUCTION

The cardiac serine protease corin is the pro-atrial natriuretic peptide convertase. Corin is primarily secreted in atrial and ventricular cardiomyocytes [1]. Corin is secreted as a zymogen, which is activated by proteolytic cleavage. In cardiomyocytes, corin converts pro-atrial natriuretic peptide (pro-ANP) to active ANP, a hormone that regulates blood pressure by promoting natriuresis, diuresis, and vasodilatation. ANP also suppresses rennin and endothelin release. Which represents an additional mechanism regulating vascular tone [2,3,4].

Chemistry:

Structurally, corin belongs to the type II transmembrane serine protease family, predominantly expressed by cardiomyocytes; therefore, corin appears to be the long sought after "NP convertase". Corin has a short N-terminal cytoplasmic tail and an integral transmembrane domain. In its extracellular region, there are two frizzled-like cysteine-rich domains, eight low density lipoprotein receptor repeats, a scavenger receptor-like cystein-rich domain, and a trypsin-like protease domain at the C terminus [5]. Topologically, corin belongs to a newly defined type II transmembrane serine protease family, which includes enterokinase (EK), hepsin, matriptases, TMPRSS2-5, human airway trypsin-like protease, and polyserase-I. The combination of the domain structures in corin is unusual among this family of serine proteases [6]. Human corin is a trypsin-like serine protease first cloned from the heart, suggesting that corin might have a role in the cardiovascular system [7]. Corin mRNA and protein are abundantly expressed in cardiomyocytes of the atrium and ventricle. Human corin is a polypeptide of 1042 amino acids that contains a short cytoplasmic tail at the N terminus followed by an integral transmembrane domain [6]. Studies indicate that the transmembrane domain is not required for corin catalytic activity but may serve as a mechanism to localize corin on the surface of cardiomyocytes, allowing efficient processing of natriuretic peptides upon their release from the cells [8].

Like most trypsin-like proteases, corin is made as a single chain zymogen. Human corin contains a conserved activation cleavage sequence Arg↓ Ile-Leu-Gly-Gly at residues 801-805 [1]. In human corin, the predicted cleavage is located at Arg ^{801} – Ile ^{802}. Mutant corin R801A, in which Arg-801 was replaced by an Ala, had no detectable activity in functional assays, indicating that proteolytic cleavage at Arg-801 is required to

convert corin zymogen to an active enzyme [1].

Importance of domain structures:

Corin is a mosaic protease that contains a transmembrane domain near the N terminus and several distinct domain structures in its C-terminal extracellular region. In its extracellular region, there are two frizzled-like cysteine-rich domains, eight low density lipoprotein receptor repeats (LDLR), a scavenger receptor-like cysteine-rich domain, and a trypsin-like protease domain at the C terminus [1]. Frizzled 1 domain and LDLR repeats 1-4 in the propeptide of corin are required for the processing of pro-ANP [6,8].

The frizzled-like cysteine-rich domain, which is ~120 amino acids in length and contains 10 conserved cysteine residues, was first discovered in members of the frizzled family of seven transmembrane receptors for Wnt signaling proteins [9,10]. Subsequently, the frizzled-like cysteine-rich domain also has been found in soluble frizzled-related proteins that act as antagonists of Wnt signaling [11]. Studies have shown that the frizzled-like cysteine-rich domain interacts directly with Wnt proteins. In addition to Wnt receptors and inhibitors, other proteins such as human carboxypeptidase Z, mouse collagen (XVIII) α 1 chain, and several receptor tyrosine kinases including muscle-specific kinase and smoothened also contain frizzled-like cysteine-rich domains. Deletion of frizzled 1 domain reduced the activity of corin in pro-ANP processing by 60%, indicating that the frizzled 1 domain is involved in the interaction of corin with pro-ANP. Thus, frizzled-like cysteine-rich domains have a much broader role in protein-protein interactions [6].

In the extracellular region of corin, there are eight LDLR class A repeats in two separate clusters. This type of repeat, which is ~40 amino acids in length and contains six conserved cysteine residues, was first identified in the LDLR as lipoprotein binding sites. Naturally occurring mutations in the LDLR repeats alter the function of the receptor and cause familial hypercholesterolemia in patients. Site-directed mutagenesis studies have shown that an individual repeat in the LDLR binds differentially to lipoproteins and has an additive effect on ligand binding. In corin, however, the LDLR repeats are unlikely to interact with lipoproteins. LDLR repeats 1-4 are important for corin to recognize pro-ANP. Corin mutants lacking single LDLR repeats 1-4 (ΔR1, ΔR2, ΔR3, and ΔR4) exhibited ~49%, ~12%, ~53% and ~77% of

pro-ANP processing activities, respectively, compare with that of the full length corin. Corin mutants with a single mutation at a conserved Ca2+ - binding Asp residue in LDLR repeats 1,2,3,or 4. The mutation is expected to affect only the function of the individual LDLR repeat in which it resides but not the overall protein structure. Corin mutants ΔR1, ΔR2, ΔR3, and ΔR4, showing that LDLR repeats 1-4 all contribute to the binding of pro-ANP and that among these LDLR repeats repeat 2 appears to be most critical, whereas repeat 4 is less important. Based on this, pro-ANP binds to corin by interacting with frizzled 1 domain and LDLR repeats 1-4. The binding of pro-ANP to this region of corin may allow the protease domain to cleave the substrate more efficiently. It is equally possible that the binding induces conformational changes in pro-ANP, making its activation cleavage site accessible to the protease domain of corin [6,7,11].

Human Corin Isoforms:

Corin belongs to the type II transmembrane serine protease family, defined by the presence of a transmembrane domain near the N terminus and an extracellular protease domain at the C terminus. All type II transmembrane serine proteases contain a cytoplasmic tail of various lengths, but its functional significance was poorly understood [8].

Like trypsin, corin is made as a one-chain zymogen that is converted proteolytically to a two-chain active enzyme. The enzyme(s) responsible for corin activation is unknown. Mouse and rat corin proteins are homologous to human corin, and their sequences around the zymogen activation cleavage site are identical to that of human corin, suggesting that other elements in the corin protein may influence its activation. The apparent difference in cytoplasmic tail length and sequence between mouse/rat and human corin suggested that corin isoforms with different N termini may exist.

Human corin has two isoforms-E1 and E1a, which contain 45 and 15 amino acids, respectively, in their cytoplasmic tails. In both HEK 293 and HL-1 cells, human corin isoform E1 was more readily activated than isoform E1a. Cell surface labeling, glycosidase digestion, and flow cytometry showed that the difference was due mainly to their efficiencies in cell surface targeting. Corin activation depends on cell surface expression. By testing a series of mutants, found that it is specific amino acids (but not the length) in the cytoplasmic tail that are critical for corin cell surface targeting. Short

motifs in cytoplasmic tails are known to act as signals to sort proteins to the cell surface or different subcellular compartments [8,12,13].

Both corin isoforms E1 and E1a exist in human hearts. The expression of isoform E1 appears to be higher than that of isoform E1a. If human corin isoform E1 is more active than isoform E1a, it will be interesting to determine whether mechanisms exist to regulate corin isoform expression. It is possible that the expression of these corin isoforms is altered selectively under physiological or pathological conditions, resulting in enhanced or reduced corin activities. In patients with heart failure, corin mRNA and protein expression appears to be increased, but corin activity did not increase potentially. Soluble corin was detected in human blood, and its levels were found to be lower in patients with heart failure. Soluble corin levels in plasma were measured by ELISA method. It remains to be determined whether alternative expression of corin isoforms contributes to different levels of corin protein and/or activity in these patients, which may be part of the pathological mechanisms underlying their heart disease [8,14].

Corin shedding and Autocleavage:

The transmembrane domain anchor the proteases on the cell surface, localizing the biological activities at specific sites. Under physiological and/or pathological conditions, type II transmembrane serine proteases can be shed from cell surface. Soluble corin was detected in human blood, indicating that corin is shed from the heart. Interestingly, plasma corin levels were lower in patients with severe heart failure compared with those of normal controls or patients with mild heart failure, suggesting that corin shedding from the cells may be important in regulating corin function and that altered corin shedding and/or cleavage may play a role in heart failure [15].

Ectodomain shedding is an important post translational process in a variety of cell membrane proteins, including adhesion molecules, enzymes, cytokines, growth factors, and receptors [16]. Corin is a membrane protease that processes natriuretic peptides in cardiomyocytes. To date, the mechanisms that regulate corin activity remain unclear. Soluble corin was detected in human blood, suggesting that corin may be shed from the cells [15].

In the cultured medium from transfected HEK 293 cells, detected three distinct human corin fragments of ~180, ~160 and ~100 kDa, respectively. Similar results were found when human corin was expressed in mouse atrial HL-1 cells, which

retained all structural and functional characteristics of cardiomyocytes. Expressed recombinant mouse and rat corin in HEK 293 cells and HL-1 cells and detected shed fragments of ~180 kDa. Mouse and rat corin also had several soluble fragments that differed in molecular mass from those of autocleaved human fragments, which may reflect different corin sequences in these species, supporting that corin shedding was physiologically relevant [15].

In experiments with protease inhibitors, ionomycin and PMA (phorbol 12-myristate 13-acetate) stimulation, and gene knockdown by siRNA, showed that the ADAM10 (a disintegrin and metalloprotease), a major membrane protein sheddase, was most likely responsible for shedding the ~180 kDa corin fragment. Studies have shown that ADAMs usually cleave their substrates between the membrane domain and the first globular extracellular domain. The recognition mechanisms by these proteases largely depend on a substrate structure close to the cell membrane but not specific amino acid sequences.

Unlike the ~180 kDa fragment, the ~160 and ~100 kDa fragments were generated by corin autocleavage, which was inhibited by benzamidine. Mutations at the corin active site, Ser-985, or the zymogen activation cleavage site, Arg-801, which abolish corin protease activity, prevented the production of these two fragments.

In functional assays, the ~180 kDa fragment, which represented the near-entire extracellular region of corin, exhibited the biological activity in processing pro-ANP. In contrast, the ~160 and ~100 kDa fragments had little activity. Thus, ADAM-mediated shedding generated a long soluble corin that was biologically active. In contrast, corin cleaved itself, producing two shorter fragments that were inactive.

The ~180 kDa fragment is biologically active suggests that corin may function not only in the heart but also in blood and other distant organs. Corin shedding and autocleavage were closely related to its activation. It is possible that low plasma levels of corin may reflect inadequate corin activation in failing hearts. The reduction of the overall corin activity in the heart and blood is expected to impair the ANP pathway, which may exacerbate body fluid retention and poor cardiac function in patients with severe heart failure [15].

Mechanism of action:

Processing of pro-ANP to ANP by corin in Cardiomyocytes

Corin is a type II transmembrane serine protease abundantly expressed in the

heart. Corin converts pro-atrial natriuretic peptide (pro-ANP) to atrial natriuretic peptide (ANP), suggesting that corin is likely the pro-ANP convertase [16].

Atrial natriuretic peptide (ANP) is a cardiac hormone stored in the dense granules of cardiac myocytes. In response to increases in cardiac volume or pressure, cardiomyocytes and fibroblasts synthesize and secrete atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). ANP and BNP are peptide hormones that circulate and activate the type A natriuretic peptide receptor (NPR-A) leading to the generation of cGMP pool by activation of the particulate gunaylate cyclase domain of the NPR-A receptor [16, 17]. Through this mechanism, ANP triggers sodium excretion, (natriuresis), causes vasodilation, interferes with the renin-angiotensin system, inhibits mitogenesis, and mediates other effects [18].

The biological effects of ANP are to promote salt excretion, reduce blood volume, and relax vessel tension, thereby reducing blood pressure. High plasma concentrations of ANP and brain-type natriuretic peptide (BNP) are found in patients with congestive heart failure. The levels of these natriuretic peptides are often correlated with the extent of ventricular dysfunction and development of arrhythmias. ANP and BNP have been used as therapeutic agents in patients with decompensated congestive heart failure and acute myocardial infarction to improve cardiac function and clinical status [16,18].

In cardiomyocytes, ANP is synthesized as a 126 amino acid prepropeptide. After the signal peptide is removed, pro-ANP is stored in the dense granules of the cell. Upon secretion from the dense granules, pro-ANP is activated on the surface of the cardiac myocytes by proteolytic cleavage at residue arginine 98, generating an N-terminal propeptide and a mature 26 amino acid C-terminal peptide that is biologically active. Studies showed that a high molecular weight trypsin-like enzyme associated with the membrane of cardiac myocytes was responsible for the activation cleavage of pro-ANP [16].

Proteolytic cleavage of propeptides is a fundamental process in the activation of polypeptide hormones. For most of the peptide hormones, the activation cleavage is mediated by a family of subtilisin-like serine proteases, known as precursor convertases (PCs). These convertases are located in the secretory pathway inside of the cell and cleave proproteins at specific sequences commonly composed of single or paired basic amino acids. Processing of pro-ANP, however, appears to be mediated by a

different mechanism. Following removal of its single peptide, pro-ANP is stored in the dense granules of cardiac myocytes. The activation cleavage occurs on the cell surface when the pro-hormone is secreted from the cells. Earlier biochemical studies have indicated that a high-molecular weight trypsin-like protease present on the cell surface is responsible for the processing of pro-ANP in cardiac myocytes [16].

After the discovery of the cardiac transmembrane serine protease corin, and subsequent characterization of its function indicate that corin is probably the pro-ANP convertase. Corin mRNA was detected in tissues such as heart, kidney, testis, uterus, and bone where pro-ANP and other natriuretic peptides are known to be expressed. Biochemical studies showed that the corin protein had a molecular mass of ~150 kDa and was associated with the cell membrane. In transfected 293 cells, recombinant corin cleaved pro-ANP to produce a small peptide that was indistinguishable from the mature ANP by SDS-PAGE and Western analysis. Mutagenesis analysis showed that the cori-mediated cleavage of pro-ANP was highly sequence-specific. It remained, to show that corin is indeed the endogenous pro-ANP convertase in cardiac myocytes [16].

Processing of pro-BNP to BNP by corin

B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-pro-BNP) are the products of the enzyme-mediated cleavage of their precursor molecule, pro-BNP. The clinical significance of pro-BNP derived peptides as biomarkers of heart failure, whereas little is known about the mechanisms of pro-BNP processing [19].

B-type natriuretic peptide (BNP) is a cardiac peptide hormone mainly expressed by ventricular myocardium in response to volume overload and increased filling pressure. An active BNP hormone comprising 32 amino acid residues (AARs), along with a physiologically inactive N-terminal fragment (NT-pro-BNP) (76 AAR), is formed from the precursor molecule, pro-BNP (108 AAR), by specific enzyme cleavage. BNP and NT-pro-BNP are currently established biomarkers of heart failure (HF) [20, 21] and are routinely used by clinicians for the exclusion of HF and risk assessment in patients with acute coronary syndromes [22,23]. Inspite of the great interest in the products of pro-BNP cleavage as HF biomarkers, the mechanism of pro-BNP processing itself, as well as the enzymes responsible for the conversion of BNP precursor molecules, has not been characterized. However, the comprehensive

assessment of pro-BNP processing mechanisms could be of valuable for better understanding HF development and reliable interpretation of the results of BNP, NT-pro-BNP, and pro-BNP measurements [19].

Several recent studies demonstrated that endogenous pro-BNP and NT-pro-BNP are O-glycosylated. O-glycosylation of the threonine 71 residue, located close to the pro-BNP cleavage site, has a pronounced suppressive effect on the processing efficiency and should be considered when studying pro-BNP processing. In cell-based experiments, corin has been shown to be a specific enzyme responsible for processing of the A-type natriuretic peptide precursor. Corin has also been suggested to be responsible for pro-BNP processing, but its potential involvement in this process has not been supported by convincing experimental data. Thus, the role of corin, in pro-BNP processing should be validated [19]. Despite numerous studies devoted to the assessment of the clinical significance and therapeutic potential of pro-BNP-derived peptides, little is known about the mechanisms of pro-BNP processing itself [19].

Corin is located on the plasma membrane and has been shown to cleave the precursors upon secretion. The potential ability of corin to cleave pro-BNP has been described [24], whereas both the influence of pro-BNP has been glycosylation on corin-mediated processing and the specificity of cleavage have not been previously shown. Experiments on the corin-mediated processing of pro-BNP were performed using HEK 293 cells transfected with the corin expressing plasmid. Observed that corin was able to cleave nonglycosylated pro-BNP (E.Coli), as well as the pro-BNP nonglycosylated at threonine 71 (proBNP-T71A), but failed to process the pro-BNP – WT modified by O-glycans at threonine 71 [19].

Corin is thought to cleave potential substrates with a preference for Arg/Lys residues at the P1 position (toward the N-terminus from the cleavage site), Pro/Phe/Gly at the P2 position, and small neutral amino acids at the P3 position [7]. The appropriate substrate profile is presented twice in human pro BNP sequence close to the known cleavage site, -Ala_{74}-Pro_{75}-Arg_{76}↓Ser_{77}-and–Ser_{77}-Pro_{78}-Lys_{79}↓ Met_{80}-. The cleavage between Arg_{76} and Ser_{77} would give rise to BNP 1-32 [25], whereas the cleavage between Lys $_{79}$ and Met $_{80}$ should be uniquely attributed to the action of corin and is expressed to result in BNP-4-32 production. Gel filtration studies revealed that corin mediated cleavage led to the formation of a

BNP form, shorter than the synthetic one or the one generated by furin-mediated cleavage. According to MS analysis, the pro-BNP cleavage by corin resulted in BNP 4-32 formation, suggesting corin's preference for the –Ser_{77}-Pro_{78}-Lys_{79}↓Met_{80}- profile. Of note, this form was observed only in the case of corin expressing cells and never in nontransfected cells or furin-transfected cells. Corin was not able to process BNP 1-32 to BNP 4-32, possibly because of the absence of additional residues before the N-terminal serine in BNP 1-32 that could be important for substrate recognition by the enzyme [19].

The presence of N-terminal truncated BNP forms, including BNP 3-32, BNP 4-32, and BNP 5-32, in heart failure patients has been reported recently. The formation of BNP 3-32 is attributed to the action of dipeptidyl peptidases, whereas the mechanisms that lead to the formation of other truncated forms has not been characterized. The formation of BNP 4-32 due to the specific processing activity of corin, hereby, presence of BNP 4-32 with possibly reduced hormonal activity in plasma of heart failure patients could be partially explained by corin-mediated processing activity. These findings provide several new insights into human pro-BNP processing mechanisms. The corin-mediated processing of pro-BNP results in the formation of truncated BNP 4-32, suggesting that corin is unlikely to be the primary candidate for the role of pro-BNP processing enzyme [19]. Adequate natriuretic peptide processing is essential for the endogenous natriuretic peptide system (NPS) to function in maintaining cardiovascular homeostasis. [25].

Corin as a candidate gene:

The human corin gene is on chromosome 4p 12-13, which has 22 exons and spans >200kb in length [26]. Genetic studies identified single nucleotide polymorphism (SNPs) in the corin gene, which were present in patients with hypertension and cardiac hypertrophy [27,28]. In cell-based studies, these SNPs were found to alter corin protein structure and impair its biological activity [24]. The results suggest that corin defects may contribute to hypertension and heart disease in humans. Plasma levels of unprocessed pro-ANP and pro-BNP are highly elevated in patients with severe heart failure [29-34], indicating that processing these natriuretic peptides becomes rate-limiting as the disease progresses. It appears, therefore, that low plasma corin levels in heart failure patients may reflect the underlying disease mechanism in the heart [14].

Corin as a candidate gene, impaired corin activity would reduce natriuretic peptide processing and reduce the in vivo function of the endogenous natriuretic peptide system. The human corin gene was sequenced in 33 African-Americans with dilated cardiomyopathy leading to the identification of two previously unreported non-synonymous, non-conservative single nucleotide polymorphisms, T555I and Q568P, each located in exon 11 of the human corin gene. The T555I and Q568P amino acid substitutions are located in the second cysteine-rich, frizzled-like domain of corin. This domain is involved protein-protein interactions and this domain is required for corin catalytic activity. Moreover, these amino acid changes are biochemically non-conservative and change highly conserved amino acid residues increasing the probability that they might alter corin protein function [17,25].

Corin is a transmembrane serine protease that is expressed in cardiomyocytes and cleaves pro-ANP and pro-BNP into biologically active peptide hormones. A minor allele in corin, defined by two coding variants in complete linkage disequilibrium (T555I and Q568P), is common and is expressed. The corin I555 (P568) allele is associated with increased systolic blood pressure, increased risk for systemic hypertension, and an enhanced concentric cardiac hypertrophic response to increased blood pressure. Recently, in vitro experiments have demonstrated that the presence of both the T555I and Q568P amino acid substitution significantly reduce the natriuretic processing activity of mutant I555(P568) corin [25].

Polymorphisms in the corin gene have been associated with increased risk of hypertrophy in the setting of systolic hypertension [27, 28]. These polymorphisms are associated with decreased activation of corin (zymogen) and thereby decreased corin activity [18,24].

Clinical Significance:

Corin is essential for maintaining normal blood pressure. In African Americans, who are known for their high prevalence of cardiovascular disease, corin variants with impaired natriuretic peptide processing activity have been associated with hypertension. Patients with these variants developed severe cardiac hypertrophy and had poor clinical outcomes [35].

Levels of atrial and brain (B-type) natriuretic peptides (ANP, BNP) are elevated in patients with heart failure with fluid retention. However, ANP and BNP should help prevent fluid retention because they

facilitate sodium excretion (natriuresis), cause vasodilatation, and interfere with the renin-angiotensin system. Corin, a heart-specific enzyme, plays an important role in this system by cleaving and activating pro-ANP to ANP. In patients with reduced systolic function and decompensated heart failure, there is a reduced levels of circulating corin and evidence that cleavage of pro-ANP to ANP was impaired [18].

The reduction of plasma corin levels appeared to correlate with the severity of HF. In contrast, no significant changes in plasma corin levels were found in patients with acute myocardial infarction (AMI). These results indicate that low plasma corin levels are associated closely with pathological changes in HF but not AMI.

These data suggest that low plasma corin levels in patients with HF may reflect impaired corin activation in failing hearts. It is possible, therefore, that plasma corin may be used as a biomarker for the diagnosis of HF. Such a biomarker may also be tested in other hypertensive disease.

CONCLUSIONS:

In summary, Corin is a newly-identified protease that is essential for processing natriuretic peptides in the heart. Levels of atrial and brain (B-type) natriuretic peptides (ANP, BNP) are elevated in patients with heart failure with fluid retention. However, ANP and BNP should help prevent fluid retention because they facilitate sodium excretion (natriuresis), cause vasodilation, and interfere with the renin-angiotensin system. Corin plays an important role in this system by cleaving and activating pro-ANP to ANP. Plasma corin levels were reduced significantly in patients with heart failure, low corin levels and impaired processing of natriuretic peptides in the heart, may contribute to the pathogenesis of heart failure and that plasma corin may be used as a biomarker in the diagnosis of heart failure.

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