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Corin in Clinical Laboratory Diagnostics

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Abstract

Corin is a transmembrane serine protease identified in the heart, where it converts natriuretic peptides from inactive precursors to mature active forms. Studies in animal models and patients with hypertension and heart disease demonstrate that corin is critical in maintaining normal blood pressure and cardiac function. Like many proteolytic enzymes, corin expression and activity are regulated. Cell biology experiments indicate that transcriptional control, intracellular protein trafficking, cell surface targeting, zymogen activation and ectodomain shedding are important mechanisms in regulating corin expression and activity in the heart. More recently, soluble corin was detected in human blood and its levels were found to be reduced in patients with heart failure (HF). These findings indicate that corin deficiency may be involved in the pathogenesis of HF and suggest that soluble corin may be used as a biomarker for the disease. In this review, we describe the function and regulation of corin and discuss recent studies of soluble corin in human blood and its potential use as a biomarker for HF.

1. Introduction

Proteolytic cleavage mediated by serine proteases plays an important role in many biological processes, including food digestion, inflammatory response, wound healing, hormone processing, blood coagulation, and fibrinolysis [1]. In the heart, for example, serine proteases such as tissue kallikrein, chymase and urokinase are involved in processing of many bioactive molecules, including bradykinin, angiotension II, interleukin-1β, transforming growth factor-β, stem cell factor, and matrix metalloproteases [2]. These protease-mediated activities are critical in regulating blood pressure and cardiac function, and may contribute to pathological conditions such as hypertension, cardiac hypertrophy and heart failure (HF).

Most trypsin-like serine proteases are secreted proteins. More recently, a new class of type II transmembrane serine proteases (TTSPs) has been identified [3–5], which includes

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enteropeptidase [6–8], hepsin [9–11] and matriptases [12–15]. All these proteases consist of an N-terminal cytoplasmic tail, a single-span transmembrane domain and an extracellular region with a C-terminal trypsin-like protease domain. Corin is a TTSP identified in the heart [16–18]. In this review, we describe the biology of corin and discuss recent findings of soluble corin in human blood and its potential use as a biomarker for the diagnosis of HF.

2. Corin protein and domain structure

Human corin is a protein of 1042 amino acids [18]. It contains an N-terminal cytoplasmic tail of 45 amino acids followed by a single-span transmembrane domain of 21 amino acids. The rest molecule is extracellular and contains several types of domains, including two frizzled-like domains, eight LDL receptor (LDLR)-like repeats, one scavenger receptor-like domain, and a C-terminal trypsin-like protease domain (Fig. 1). These distinct domains serve for specific functions [19, 20]. The transmembrane domain anchors the protein on the cell surface, whereas the protease domain carries out the catalytic function. The other extracellular domains participate in interactions with corin substrates and possibly activator(s). Unlike many membrane receptors whose cytoplasmic tails transduce outside-in signals, the cytoplasmic tail of corin did not appear to have such a function. Instead, it has a role in intracellular trafficking and membrane targeting. A recent study identified a specific amino acid motif, DDNN, in human corin cytoplasmic tail that is important for cell surface expression [21].

Human corin contains 19 predicted *N*-linked glycosylation sites in its extracellular region [18] (Fig. 1). Most of these glycosylation sites are conserved among mammalian species [18, 22], indicating the importance of glycosylation in corin biosynthesis and/or function. Studies with tunicamycin-treated cells and glycosidase digestion have detected abundant *N*-glycans on human, rat and mouse corin, which are critical for corin cell membrane targeting and zymogen activation [23, 24]. To date, no *O*-linked glycans or sialic acids have been detected on corin [24].

Corin is made as a zymogen, which is activated by cleavage at a conserved site, Arg801-Ile802 (Fig. 1). The cleavage induces conformational changes in the protease domain, making it catalytically active [25]. Purified single-chain corin had no detectable enzymatic activity [20]. Substitution of Arg801 with Ala prevented corin activation, thereby abolishing its function [20, 26]. After the Arg801-Ile802 peptide bond is cleaved, the protease domain remains attached to the rest of molecule through a disulfide bond (Fig. 1). The disulfide bond can be broken by reducing agents such as β-mercaptoethanol and dithiothreitol. This method is used to distinguish corin zymogen from the activated form [20, 24]. Based on the Arg801-Ile802 activation sequence, corin activator is predicted to be a serine protease that favors basic residues. To date, however, the corin activator has not been defined.

3. Corin gene and expression

The human *CORIN* gene is located on the short arm of chromosome 4 at p12–13, a region adjacent to the centromere [18]. It has 22 exons and spans >200 kb [27]. The intron-exon junctions correspond to boundaries of corin protein domains. For example, frizzled-like domains are encoded by two exons each whereas each LDLR repeat is encoded by one exon [27]. Such a genomic structure supports that the *CORIN* gene arose from exon duplication and rearrangement during evolution.

The mouse *corin* gene is located on chromosome 5 with an overall structure similar to that of the human gene. One exception is that the first exon, which encodes the cytoplasmic tail, differs in both length and sequence between human and mouse, suggesting that alternatively spliced variants may exist [27]. Indeed, a recent study showed that both human and mouse

corin genes have alternative first exons, encoding two versions of cytoplasmic tails with different membrane targeting efficiencies [21]. It remains to be determined if mechanisms exist to regulate the use of these alternative exons, which in turn regulate corin expression and activity on the cell surface.

Corin is highly expressed in the heart, primarily in cardiomyocytes [16, 18, 28, 29]. This tissue expression pattern is controlled by its promoter that contains conserved binding sites for TBX5, GATA, NKX2.5 and Krüppel-like transcription factors [27]. GATA-4 appears to be a major transcription factor for corin expression in the heart. Mutations at a major GATA-binding site and antibodies again GATA-4 markedly inhibited corin expression in cardiomyocytes [27]. A similar GATA-4-mediated mechanism also is involved in natriuretic peptide expression in the heart [30].

Corin mRNA expression has been detected in other tissues, including kidney [18, 29, 31], skin [32], bone [18], brain [33, 34] and pregnant uterus [18]. In general, expression levels in these tissues were lower than that in the heart. The significance of corin expression in these tissues is not well understood. For example, corin expression is detected in dopaminergic neurons but its function in the brain remains unknown [33, 34]. In mice, corin is expressed in the dermal papilla of the hair follicle [32, 35]. Mice lacking corin have a lighter coat color. It is unclear if the role of corin in regulating coat color provides an advantage for these animals in natural environments. In addition to its expression in normal tissues, corin mRNA is detected in cancer cells, including small cell lung cancer, osteosarcoma, endometrium carcinoma, and leiomyosarcoma [18, 36].

4. Corin in natriuretic peptide processing

Atrial and B-type or brain natriuretic peptides (ANP and BNP) are cardiac hormones that regulate body fluid balance and blood pressure [37, 38]. Upon binding to their receptor, these peptides stimulate intracellular cGMP production, thereby promoting natriuresis and diuresis in the kidney and muscle relaxation in the blood vessel. These peptide hormones are well conserved from primitive vertebrates to humans. In many migratory fish species such as salmon and eels, natriuretic peptides are critical for maintaining electrolyte homeostasis during their life cycles in fresh and salty water environments [39–41].

Like many peptide hormones, natriuretic peptides are made as inactive pro-forms that are converted to active forms by proteolysis. Corin has been identified as the physiological pro-ANP convertase (for reviews see refs. [42, 43]). When pro-ANP is secreted from cardiomyocytes, corin activates it on the cell surface. In mice, knockout the *corin* gene abolished ANP generation [44], indicating that no other enzymes act redundantly for this function *in vivo*. Apparently, the function of corin is not cell membrane-dependent. A soluble corin lacking the transmembrane domain cleaved pro-ANP as efficiently as the membrane-bound corin [20]. Similar findings of cell membrane-independence have been reported in other TTSPs, such as hepsin [45] and matriptase [15, 46]. These data suggest that the primary function of the transmembrane domain in TTSPs is to localize the enzymes at specific tissue sites but not to enhance their catalytic activities [3, 47].

In addition to pro-ANP processing, corin also cleaves pro-BNP [29, 48–50]. The reaction, however, is less sequence-specific and less efficient. To date, several other enzymes such as furin and dipeptidyl peptidase IV have been shown to process pro-BNP [48, 51–53]. Furin also cleaves pro-C-type natriuretic peptide (pro-CNP) but not pro-ANP [54]. Recent studies show that human pro-BNP contains abundant *O*-glycans that are terminally sialylated [55–59]. This posttranslational modification is unusual, because no *N*- or *O*-linked glycosylation was detected in human pro-ANP and pro-CNP [56]. The *O*-glycans were shown to increase pro-BNP stability [56]. In human pro-BNP produced from HEK293 cells, *O*-glycans near

the processing site inhibited furin- and corin-mediated cleavage, indicating that glycosylation may regulate BNP production and activity [59–61]. Currently, pro-BNP and its derivatives are used as biomarkers for HF [62]. It will be important to determine if pro-BNP glycosylation is altered under pathological conditions.

5. Corin shedding from the cell membrane

Ectodomain shedding is an important mechanism in regulating the function of a variety of membrane proteins, including adhesion molecules, enzymes, cytokines, growth factors, and receptors [63, 64]. Many TTSPs have soluble forms. In fact, enteropeptidase was first found in the intestinal juice by Ivan Pavlov, who won a Nobel Prize in 1904 for his discovery of digestive enzymes [5, 47]. What Pavlov found was likely a soluble form of enteropeptidase, which was shown to be released into the small intestine lumen upon bile stimulation [65]. Ectodomain shedding is also a critical mechanism in controlling the activity of matriptases on the cell surface [15, 46, 66–68].

Several forms of soluble corin have been identified in cell culture. In the conditioned medium from transfected HEK293 cells, fragments of recombinant human corin were detected by immunoprecipitation and Western blotting [69]. Three major fragments were of ~180, ~160, and ~100 kDa, respectively. These fragments were generated from proteolytic cleavage but not from alternatively spliced mRNAs that lack the transmembrane domain coding sequence, because the production of these fragments was inhibited when the cells were incubated with protease inhibitors. Similar findings were confirmed in transfected HL-1 cardiomyocytes [69].

In experiments with protease inhibitors, small interfering RNA knockdown and site-directed mutagenesis, the metalloproteinase ADAM10 was found to be responsible for cleaving corin in its juxtamembrane region, producing the ~180-kDa fragment that corresponds to the near entire extracellular region [69] (Fig. 2). Corin also cleaved itself at Arg164 in frizzled 1 domain and Arg427 in LDLR 5 repeat, generating the ~160- and ~100-kDa fragments, respectively (Fig. 2). In functional studies, the ~180-kDa fragment, but not the ~160- and ~100-kDa fragments, was active in processing pro-ANP [69] (Fig. 2). The result was consistent with early structure-function studies, showing that frizzled 1 domain and LDLR repeats are required for corin to process pro-ANP [19].

Physiologically, proteolytic enzymes are tightly regulated to avoid potential hazardous consequences. The ectodomain shedding and autocleavage of corin may represent an important mechanism to regulate its activity in the heart. It is likely that after corin is activated and cleaves natriuretic peptides, active corin molecules are removed to prevent excessive proteolytic activities on the surface of cardiomyocytes. This function appears to be carried out primarily by ADAM10 [69]. Corin inactivates the remaining molecules by autocleavage. This hypothesis was consistent with the finding that the majority of soluble fragments were from activated corin molecules [69]. Once corin fragments are detached from cardiomyocytes, these molecules may enter blood circulation if they are not degraded quickly in the tissue.

6. Detection of soluble corin in human blood

By ELISA-based assays, soluble corin has been detected in human blood [29, 70–73]. The levels in plasma and serum were similar [71, 73], indicating that soluble corin did not interact with activated platelets or clotting proteins. The reported values from five published studies are listed in Table 1. In addition to corin antigen, corin activity in human plasma was detected by pro-ANP or pro-BNP processing assays [29, 72]. To date, molecular forms of

soluble corin in plasma or serum have not been well characterized. Most likely, fragments of various lengths are present, which were detected by antibodies used in the ELISA assays.

Interestingly, plasma corin levels were significantly higher in males than females [29, 70, 71]. It is unclear if this difference reflects different corin expression levels or rates of corin shedding and/or degradation between males and females. Within the same gender group, plasma corin levels were similar among different age groups [71]. One report, however, suggested that plasma corin levels may be slightly higher among older (>60 years) individuals [29]. It was noticed that the levels reported in the Chinese were lower than those from other ethnic groups [29, 70, 71, 73]. Previously, lower levels of plasma pro-BNP were reported in a Chinese population when compared to those in European and American populations [74]. Because soluble corin assays in the reported studies were not standardized, it is unknown if the observed difference was due to specific ethnic backgrounds or simply due to different assay conditions. Values of plasma soluble corin concentration may vary if different types of anticoagulants are used. For example, the values in plasma samples with heparin were found to be significantly higher than that in samples with sodium citrate or EDTA [71].

Many plasma proteases such as blood coagulation factors are unstable in test tubes. In comparison, soluble corin was remarkably stable in plasma or serum. No apparent degradation was observed when plasma samples were left at room temperature for up to 12 hours [71]. If samples were kept at 4°C with or without protease inhibitors, no significant reduction in soluble corin levels was detected within 72 hours [71]. Similar results were obtained if recombinant corin was added to pooled human plasma. If samples were stored below −20°C, soluble corin remained stable for at least one year [73]. In serum or sodium citrate-containing plasma samples, levels of soluble corin remained unchanged after several cycles of freezing-and-thawing [71]. This remarkable protein stability may represent a significant advantage over other unstable plasma proteins or peptides if soluble corin is used as a diagnostic biomarker in clinical settings, where strict time or temperature controls may not be feasible.

7. Plasma soluble corin in patients with HF

Corin is essential for maintaining normal blood pressure. In mice, corin deficiency causes spontaneous hypertension and cardiac hypertrophy [44, 75]. 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 [49, 76]. Patients with these variants developed severe cardiac hypertrophy and had poor clinical outcomes [77, 78]. These data suggest that corin defects may be an important contributing factor in hypertension and heart disease.

Recently, plasma corin antigen levels were found to be significantly lower in patients with HF than that in normal individuals [70]. This finding was supported by another independent study, in which both plasma corin antigen and activity were measured [72]. The reduction of plasma corin levels appeared to correlate with the severity of HF, as indicated by lowest levels in patients with New York Heart Association classes III and IV [70, 79]. In contrast, no significant changes in plasma corin levels were found in patients with acute myocardial infarction (AMI) [70]. These results indicate that low plasma corin levels are associated closely with pathological changes in HF but not AMI.

Natriuretic peptide production is highly elevated in patients with hypertensive disease [62]. The function of this compensatory mechanism is to reduce blood volume and pressure. Many studies detected unprocessed pro-ANP and pro-BNP in patients with severe HF, suggesting that the function to process these peptides is compromised under the pathological

condition [43, 80–82]. In animal models of HF and human failing hearts, corin expression was increased but the activity was not [83–85], indicating that corin zymogen activation may be a rate-limiting step in HF. As reported in cell-based studies, most soluble corin fragments were derived from activated corin molecules [69]. 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.

8. Perspectives

HF is a major disease. Effective managing this life-threatening disease depends on timely and accurate diagnosis. Currently, N-terminal pro-BNP and BNP are used as diagnostic markers to identify patients with HF [62, 86, 87]. The accuracy rates of these diagnostic tests are only ~75–85% in hospital emergency settings [88–91]. Similar results also were reported in patients with chronic HF [92]. Therefore, more sensitive and accurate tests are needed to improve the diagnosis and treatment of HF. Previously, soluble forms of several membrane proteins such as tumor necrosis factor-α and interleukin-1 receptors were found to be increased in patients with HF [93–96]. However, the levels of these proteins were also increased in patients with AMI, indicating that the shedding of these membrane receptors may represent a general inflammatory response in the heart, which is not specific for HF.

Discovery of corin as the long-sought natriuretic peptide convertase has extended our knowledge of the natriuretic peptide system [42, 43]. Many important questions remain regarding the role of corin in the cardiovascular biology and disease. Recent findings of soluble corin in human blood and the reduced levels in patient with HF are intriguing. Given its remarkable stability in plasma and serum, soluble corin could be used as a novel biomarker for HF. Current data are still limited. More prospective and comparative studies are needed with large patient populations to determine how soluble corin levels change in patients with HF and if the changes correlate with the underlying pathology. The results shall help us to understand the role of corin in HF or other heart disease and to determine diagnostic and prognostic values of soluble corin in clinical settings.

Highlights

> Corin is a transmembrane protease that processes natriuretic peptides. > Corin is critical for maintaining normal blood pressure and cardiac function. > Proteolytic shedding is an important mechanism in regulating corin activity. > Soluble corin is detected in human blood and its levels are lower in patients with heart failure. > Soluble corin may be used as a novel biomarker for heart failure.

Abbreviations

AMI	acute myocardial infarction
ANP	atrial natriuretic peptide
BNP	B-type or brain natriuretic peptide
CNP	C-type natriuretic peptide
HF	heart failure
LDLR	LDL receptor
TTSP	type II transmembrane serine protease

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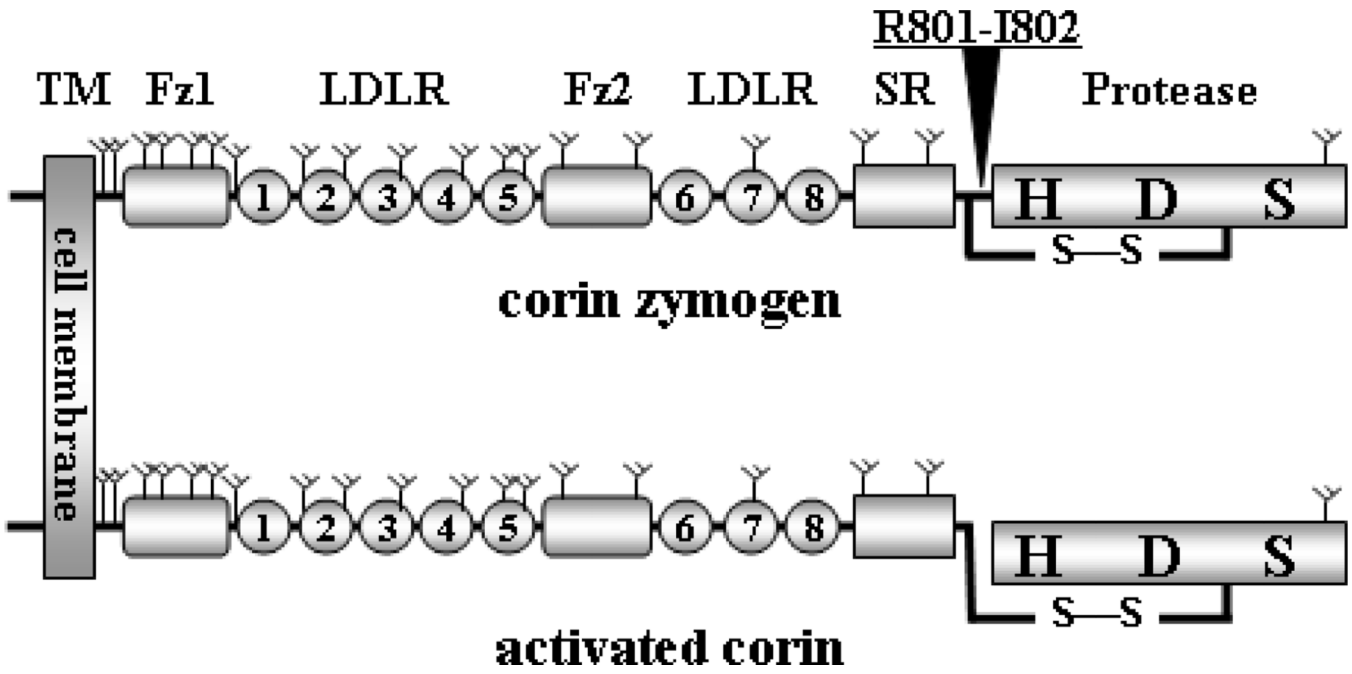

Fig. 1.

Corin protein domain structure. The transmembrane domain (*TM*), frizzled-like domains (*Fz*), LDLR repeats, scavenger receptor-like domain (*SR*), and protease domain (*Protease*) with active site residues histidine (*H*), aspartate (*D*), and serine (*S*) are indicated. Y-shaped symbols indicate predicted *N*-glycosylation sites. An arrow head indicates the activation cleavage site between Arg801-Ile802. A disulfide bond (*S*-*S*) connects the protease domain and the rest of the molecule after corin zymogen (*upper*) is activated (*lower*).

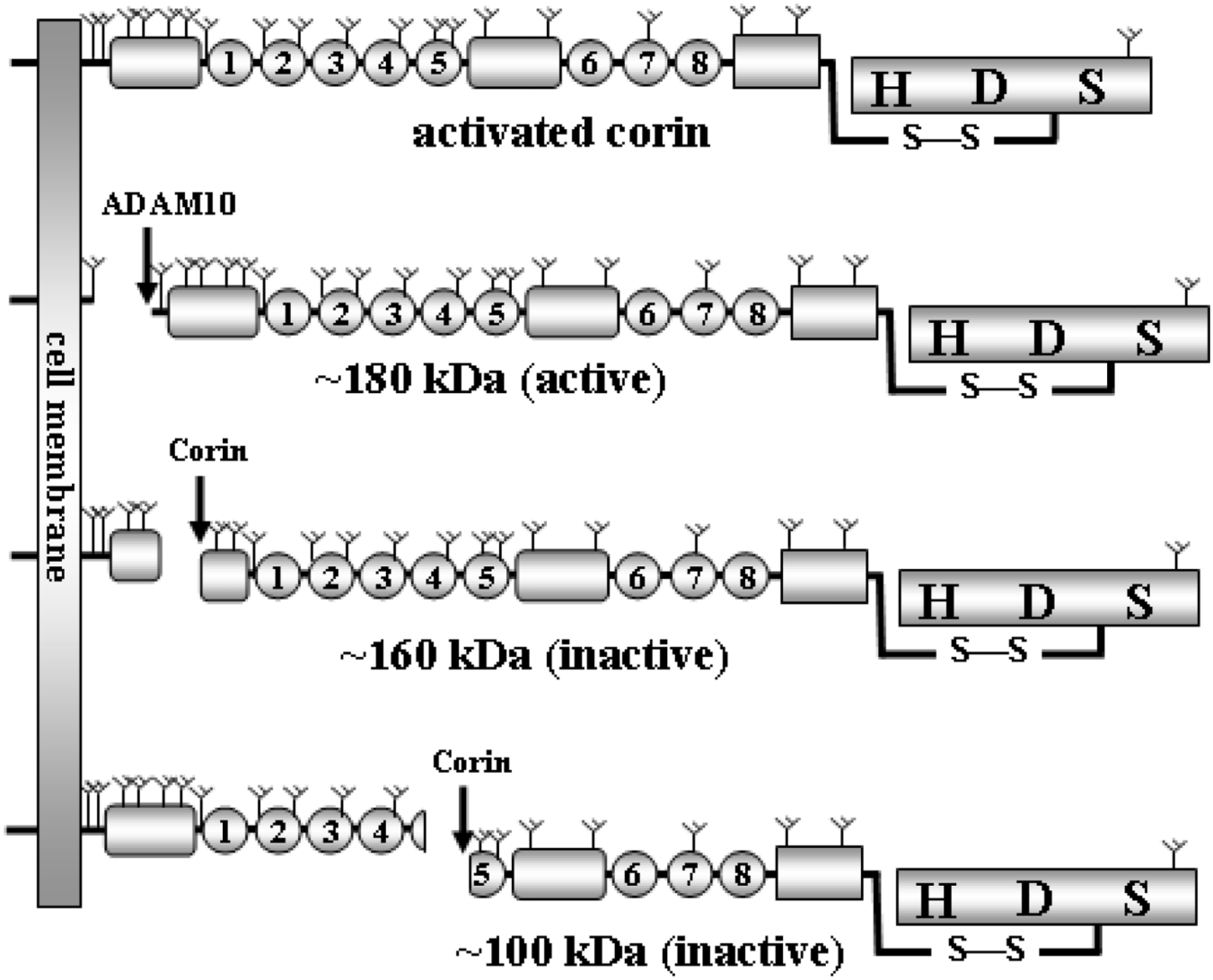

Fig. 2.

Illustration of soluble corin fragments. Activated corin (*top*) on the cell surface is shed by ADAM10 to produce a near full-length extracellular fragment that is active in processing pro-ANP. Corin also cleaves itself in Fz1 domain and LDLR5 repeat, respectively, to produce two shorter but inactive fragments [69].

Table 1

Serum and plasma corin concentrations in healthy individuals.

Study	sample	total	male	female
Peleg *et al.* [73]	serum	296–2590[a] (n=30)	n/a	n/a
Dong *et al.* [70]	plasma	690 ± 260[b] (n=198)	798 ± 285[b] (n=104)	551 ± 224[b] (n=94)
Dong *et al.* [71]	plasma	216–1663[a] (n=348)	842 ± 283[b] (n=182)	569 ± 192[b] (n=166)
Ichiki *et al.* [29]	plasma	889 (587 – 1477)[c] (n=55)	1623 (1187–1827)[c] (n=19)	810 (509–982)[c] (n=36)
Ibebuogu *et al.* [72]	plasma	180[d] (n=16)	n/a	n/a

All concentrations were in pg/mL.

[a] range;

[b] mean ± S.D.;

[c] median (25^{th}–75^{th} quartiles);

[d] median;

n/a, not available.