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Review

Circulating soluble corin as a potential biomarker for cardiovascular diseases: A translational review

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ABSTRACT

Corin is a type II transmembrane serine protease that is highly expressed in the heart and plays a physiological role in the activation of natriuretic peptides. Corin is expressed primarily in myocytes, and it can enter the circulation. Circulating soluble corin has been found to be associated with various cardiovascular diseases, such as hypertension, heart failure, myocardial infarction, preeclampsia, and stroke. All these findings indicate that circulating soluble corin has the potential to be a sensitive and specific biomarker for risk prediction and prognostic assessment of cardiovascular diseases. However, there are certain challenges hindering the incorporation of circulating soluble corin into clinical practice. To provide new ideas based on the use of corin for risk prediction, prognostic assessment, and clinical treatment of cardiovascular diseases and to promote the implementation of corin as a routine laboratory index, we summarize the latest studies of the association between corin and cardiovascular diseases in recent years and offer some prospective proposals for future research on corin in this review.

1. Introduction

Corin is a newly identified transmembrane serine protease in the heart, where it converts atrial natriuretic peptide (ANP) from inactive precursor to active form [1]. This protease plays a key role in maintaining cardiac function and normal blood pressure [1]. Corin is also expressed in other tissues, such as the bone, kidney, pregnant uterus, and brain [2, 3]. In recent years, several studies have reported that corin expression is significantly altered in animal models of cardiovascular diseases [4, 5]. Moreover, in many clinical studies, serum or plasma soluble corin concentrations were assessed in cardiovascular patients to investigate the relationship between corin and cardiovascular disease. It was found that the level of soluble corin in the circulation was associated with the risk and prognosis of cardiovascular diseases, suggesting that this protease might serve as a biomarker for cardiovascular diseases.

Nonetheless, some challenges hinder the use of corin in clinical practice. Overall, the precise mechanisms underlying the relationship between circulating soluble corin and cardiovascular diseases remain unclear. Given that the design of most articles are case-control and nested cross-sectional studies, the causal relationship of corin with cardiovascular diseases cannot be inferred. Furthermore, some recent studies have shown that the level of circulating soluble corin does not reflect the level of corin in tissues [5], and the concrete reason leading to this inconsistency is not clear. Additionally, most epidemiological studies to date have examined only the level of circulating soluble corin, and not its activity, in patients with cardiovascular diseases. Before accepting circulating soluble corin as a clinically useful biomarker, the distribution of the association between circulating soluble corin and demographic characteristics should be studied in the general population. However, there is a lack of population-based evidence for a relationship between corin and many demographic characteristics.

Previous reviews of corin have mainly described the structure, function and regulation of the protease in the myocardium and reported its role in hypertension and heart failure. In recent years, circulating soluble corin levels have been reported to be associated with the risk and prognosis of cardiovascular diseases, such as hypertension, heart failure, myocardial infarction, preeclampsia, and stroke. Here, we summarize all studies on the association of circulating soluble corin with cardiovascular diseases to date and examine the potential of corin as a novel biomarker for cardiovascular diseases. We also note recent population-based studies indicating that mutation of the *CORIN* gene may be an important mechanism in cardiovascular diseases. In addition, we provide detailed information on the structure, function and

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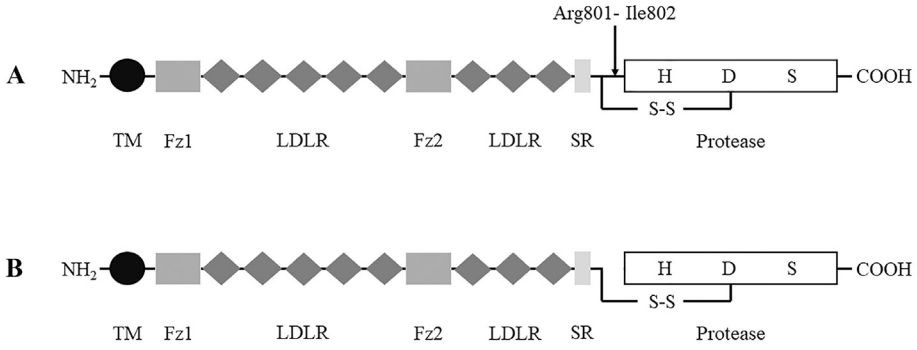

Fig. 1. Domain structure and activation of the corin protein.
A: The corin zymogen. The transmembrane (TM), frizzled-like (Fz), low density lipoprotein receptor (LDLR), scavenger receptor-like (SR), and protease domains are shown. Arg801-Ile802 is the activation cleavage site of the corin zymogen. B: Activated corin. The activated corin fragment still connects with the precursor peptide via a disulfide bond after the peptide bond that connects the 801 arginine (Arg) and 802 isoleucine (Ile) cleavages.

measurement of soluble corin in the circulation. To provide new ideas based on corin for risk prediction, prognostic assessment, and clinical treatment of cardiovascular diseases, this review discusses existing challenges and offers prospective proposals for further studies to promote the incorporation of corin into clinical practice.

2. Corin's structure, activation, and function

2.1. The structure of corin

The *CORIN* gene is located on chromosome 4 at region p12–13, and it spans > 200 kb and includes 22 exons [6]. The intron-exon junctions of the gene are consistent with the corin structural domain boundaries. Corin is a serine protease of 1042 amino acids [7] that contains a transmembrane (TM) domain, an N-terminal cytoplasmic tail and several extracellular domains. The extracellular domains are of a variety of types, including a C-terminal trypsin-like protease domain (protease), one scavenger receptor-like domain (SR), two frizzled-like domains (Fz) and eight low density lipoprotein receptor (LDLR)-like repeats (Fig. 1A). These different domains have their own discrete functions. For example, the transmembrane domain anchors the protease to the cell surface [8]. Rather than functioning in outside-in signal transduction, the intracellular protein domains of corin participate in membrane localization and intracellular migration [9]. The protease domain performs the catalytic function, whereas the remaining extracellular domains are involved in interactions with corin substrates. The extracellular region of corin contains 19 N-glycosylation sites and is essential for corin's biological function of converting pro-ANP to ANP [10].

2.2. The activation of corin

The corin protein is synthesized as an inactive zymogen that must undergo cleavage for activation, and the cleavage site of the human corin protein is located at Arg801-Ile802 (Fig. 1A) [11]. The cleavage process induces structural changes in the protease domain to promote activation. After the peptide bond that connects the 801 arginine (Arg) and 802 isoleucine (Ile) cleavages, the activated corin fragment is still connected to the precursor peptide via a disulfide bond (S—S) (Fig. 1B). Inactivated single-chain corin does not exhibit detectable activity [11]. Mutation at R801A (the conserved activation cleavage site) can abolish corin's function, verifying that activation cleavage is necessary for corin's activity [11].

2.3. The biological function of corin

The main biological function of corin (Fig. 2) is to convert ANP and brain natriuretic peptide (BNP) from inactive precursor to active form [1]. ANP and BNP are cardiac peptide hormones that regulate blood pressure and fluid balance [12]. Binding of ANP and BNP to the natriuretic peptide receptor can increase the synthesis of intracellular cyclic guanosine monophosphate and result in natriuresis, diuresis and vasodilation, thereby reducing blood pressure and improving cardiac function. In pregnant women, this interaction also promotes uterine spiral artery remodelling. Natriuretic peptides are synthesized in an inactive precursor form and are activated by corin at the cell surface during secretion from cardiomyocytes. Studies had found that the synthesis of ANP was blocked and the processing of pro-ANP was restored in *CORIN* gene-knockout mice after intravenous injection of soluble corin [4], indicating that no other enzymes in the body could activate pro-ANP to ANP. In addition to processing pro-ANP, the corin protein can activate pro-BNP through cleavage [1, 2]. However, the efficiency and sequence specificity of this reaction are relatively lower compared to those of pro-ANP activation.

3. The structure and function of circulating soluble corin

Type II transmembrane serine proteases can be shed from the cell surface under physiological or pathological conditions. For example, soluble forms of matriptase and enteropeptidase have been reported [13, 14]. Recent studies found that corin expressed at the cardiomyocyte surface could be shed through corin auto-cleavage and metalloproteinase-mediated hydrolysis [8]. Apparently, shed corin molecules can enter the circulation. Circulating soluble corin is detectable [15] and it have the same activity as membrane-bound corin [11]. Although the source of soluble corin in the circulation remains unclear, it is possible that corin expressed near the vasculature of tissues releases a soluble form into the circulation [2].

Several soluble corin forms have been found in cell culture systems. In cultured medium from transfected HEK 293 cells and HL-1 cardiomyocytes, three soluble corin fragments of ~100, ~160 and ~180 kDa were detected by western blot and immunoprecipitation analyses (Fig. 3) [8]. All three soluble fragments are derived from activated corin and are stable in conditioned medium [8]. Metalloproteinase ADAM10 is found to be responsible for releasing the ~180-kDa soluble corin fragment (Fig. 3A), which corresponds to almost the entire extracellular region. In addition, the ~160-kDa soluble corin fragment (Fig. 3B) arises from corin autocleavage at Arg-164 in the frizzled 1 domain, and the ~100-kDa fragment (Fig. 3C) is the product of auto-cleavage at Arg-427 in the LDLR 5 domain [8].

In transfection experiments, both soluble and membrane-bound corin have similar physiological activities in processing pro-ANP, and soluble corin enzymes that lack the transmembrane domain can also be activated [11]. In addition, the activity of soluble corin in processing natriuretic peptide is not inhibited by plasma [11]. Functional studies have shown that the majority of the observed activity in processing natriuretic peptides can be attributed to the ~180-kDa soluble corin fragment. In contrast, the ~100- and ~160-kDa soluble corin fragments have little biological activity [8]. These findings are consistent with those of another report which finds that the transmembrane domain is not important for the activity of corin but that the LDLR repeats and the frizzled 1 domain are necessary for corin to process natriuretic peptides [16].