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Role of Corin and Atrial Natriuretic Peptide in Preeclampsia

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Abstract

In pregnancy, uterine spiral artery remodeling is an adaptive morphological change at the maternal and fetal interface, which is critical for dilating the artery and promoting blood flow to the fetus. Incompletely remodeled spiral arteries have been recognized as a common pathological feature in preeclamptic patients. To date, the molecular mechanism that controls spiral artery remodeling is not well defined. Corin is a transmembrane serine protease discovered in the heart, where it converts pro-atrial natriuretic peptide (pro-ANP) to active ANP, a cardiac hormone that regulates salt-water balance and blood pressure. Recent studies show that corin is up-regulated in the decidua of the pregnant uterus, suggesting a potential role of corin in pregnancy. In mice lacking corin or ANP, high blood pressure and proteinuria were found at late gestational stages. Histological analysis indicated delayed trophoblast invasion and impaired spiral artery remodeling in the uterus. In humans, *CORIN* gene mutations were identified in patients with preeclampsia. In this review, we discuss the function of corin and ANP in regulating blood pressure and their potential role in preeclampsia.

1. Introduction

Preeclampsia is a serious disease, causing premature births and contributing to maternal and neonatal mortality [1, 2]. To date, the underlying disease mechanism remains poorly understood. Spiral artery remodeling is a major adaptive change in the pregnant uterus, which is critical for decreasing maternal blood flow resistance and increasing uteroplacental perfusion. Failures in remodeling uterine spiral arteries have long been recognized as an important factor in the pathogenesis of preeclampsia [3–6].

In pregnancy, many molecules such as hormones, growth factors, vasodilators, adhesion proteins and proteases act collectively to regulate spiral artery remodeling [4–8]. Defects in signaling pathways mediated by these proteins are likely to prevent a healthy uteroplacental interface, thereby contributing to preeclampsia that is known for its multifactorial nature. Indeed, vascular endothelial growth factor, placenta growth factor, soluble fms-like tyrosine kinase-1 (sFlt1), angiotensin, estradiol, and endoglin have been found to play a role in the disease [9–15].

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Corin is a protease discovered in the heart [16]. Its biological function is to activate atrial natriuretic peptide (ANP), a cardiac hormone that regulates blood pressure and salt-water balance [17, 18]. Interestingly, corin expression was detected in the decidua of the pregnant uterus, suggesting a potential role of corin in pregnancy. Most recently, corin has been shown to have a local function in the uterus to promote trophoblast invasion and spiral artery remodeling [19]. In this review, we briefly describe the biology of corin and discuss a possible role of corin and ANP in preeclampsia.

2. Natriuretic peptides

Natriuretic peptides are evolutionarily conserved hormones present in all vertebrates. Apparently, these molecules were first developed in primitive fish to promote salt excretion in salty water [20]. In eels and salmon, which travel between salty and fresh water, natriuretic peptides are particularly important for these migratory animals to maintain electrolyte homeostasis in environments with drastically different salt levels [21, 22].

Mammals have three types of natriuretic peptides, *i.e.* ANP, B-type or brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) [17, 23, 24]. These peptides are encoded by separate genes but share sequence and structural similarities. Both ANP and BNP are produced in cardiac myocytes to regulate salt-water balance and blood pressure. In a receptor-dependent manner, ANP and BNP promote sodium excretion in the kidney and relax smooth muscles in the artery, thereby lowering blood volume and pressure. CNP is produced in many cell types including endothelial cells, smooth muscle cells and chondrocytes where it regulates vascular remodeling and bone growth [25, 26]. Recent studies show that CNP also functions in the ovary to stimulate follicle development and regulate oocyte maturation [27, 28].

In cells, natriuretic peptides are synthesized as precursor molecules, *i.e.* prepropeptides [17, 24]. To be biologically active, these precursor peptides need to be processed proteolytically. The prepeptide is removed first by signal peptidase to generate propeptides, which are further converted to mature peptides by another round of cleavage. For many years, the proteolytic enzymes responsible for processing natriuretic propeptides remained unidentified.

3. The protease corin

Corin is a trypsin-like serine protease [16, 29]. The protein consists of a string of distinct domains: an N-terminal cytoplasmic tail, a single-span transmembrane domain and an extracellular region that includes two frizzled-like domains, eight LDL receptor (LDLR)-like repeats, a scavenger receptor domain and a C-terminal protease domain (Fig. 1). Similar overall protein domain arrangements have been found in other type II transmembrane serine proteases such as enteropeptidase, matriptases, and hepsin that are involved in diverse biological processes [30–32].

Corin is expressed primarily in cardiac myocytes, where it anchors on the cell surface through its transmembrane domain [33–35]. Amino acid sequences in the cytoplasmic tail and *N*-glycans in the extracellular region regulate corin trafficking to the cell surface [36–38]. Membrane-bound corin can be cleaved by ADAM metalloproteinases and corin autocleavage, producing soluble corin fragments [39] (Fig. 1). Biochemical and cellular experiments have shown that corin converts pro-ANP to mature ANP [40, 41]. In corin-deficient mice, no mature ANP was detected in the heart, indicating that corin is the long-sought physiological pro-ANP convertase [42, 43]. Corin-deficient mice developed spontaneous hypertension. When these mice were fed high salt diets, their renal response to increase sodium excretion was markedly reduced, resulting in worsening hypertension [42,

44]. The mice also exhibited cardiac hypertrophy and had poor cardiac function [42, 45–47]. Overall, the hypertensive phenotype of corin knockout mice is similar to that of ANP knockout mice [48, 49], supporting that corin acts at the top of the ANP pathway to regulate salt-water balance and blood pressure (Fig. 2).

In humans, corin variants (T555I/Q568P) are associated with hypertension and cardiac hypertrophy in African Americans [50, 51]. Studies in cells and mouse models showed that the variant corin had reduced pro-ANP processing activities *in vitro* and *in vivo* [47, 52]. In patients with heart failure, plasma levels of soluble corin protein and activity were lower than those in healthy controls [53, 54]. Moreover, patients who carried the *CORIN* variant allele appeared to have worse clinical outcomes once their heart function deteriorates [55]. These data suggest that corin defects may contribute to hypertension and heart disease in patients.

In addition to pro-ANP, pro-BNP is another possible corin substrate. Recombinant corin, either expressed in transfected cells or in purified forms, converted human pro-BNP to BNP [41, 56–58]. Apparently, other proteases including furin and dipeptidyl peptidase IV also were capable of processing pro-BNP [58–62]. In contrast, pro-CNP is unlikely a corin substrate, despite its sequence and structural similarities to pro-ANP and pro-BNP. Studies showed that pro-CNP was processed intracellularly by furin but not corin [63]. To date, no other physiological corin substrates have been identified.

4. Corin expression in the pregnant uterus

Corin was identified as a cardiac enzyme with abundant expression in atrial and ventricular myocytes [16, 64]. In addition to the heart, low levels of corin mRNA or protein were identified in other tissues, including epithelial cells in renal distal tubes [16, 56, 65], prehypertrophic chondrocytes in developing bones [16], dopaminergic neurons in the brain [66, 67], hair follicles in the skin [68], and small cell lung cancers [69]. The corin function in the kidney is expected to promote salt excretion. In mice, corin expression in hair follicles appears to regulate coat color in an agouti-dependent pathway [68]. The functional significance of corin expression in the bone and brain remains unclear.

Serendipitously, high levels of corin expression were found in the decidua of the pregnant uterus. By *in situ* hybridization, corin mRNA was detected in decidual cells in the mouse pregnant uterus [16]. Subsequent experiments, including PCR, immunostaining and cDNA array, confirmed corin mRNA and protein expression in mouse and human pregnant uteruses [19, 70]. The result was intriguing, because corin expression was not detected in the non-pregnant uterus in previous studies [16]. This finding suggested that corin expression may be up-regulated in the decidua as a specific physiological mechanism to regulate blood pressure in pregnancy.

5. Hypertension and proteinuria in pregnant corin knockout mice

If corin plays a role in preventing hypertension in pregnancy, one would expect high blood pressure when corin knockout mice become pregnant. Indeed, highly elevated blood pressure was detected in pregnant corin knockout mice [19, 42]. Once the mice delivered pups, their blood pressure dropped to the pre-pregnant level. In addition, the mice had late gestational proteinuria, which was absent in non-pregnant corin knockout mice [19, 42]. Histological examination also detected glomerular damages in pregnant corin knockout mice, which probably was caused by high blood pressure. The mice also had placental cell necrosis and calcium deposits [19]. Thus, the phenotype in these mice resembled the pathological changes in preeclamptic patients, supporting a specific function of corin in maintaining normal blood pressure in pregnant mice.

These results led to the question of whether the anti-hypertensive function in pregnancy is mediated by cardiac or uterine corin. A new set of transgenic mice were created to distinguish these two possibilities [19]. First, a mouse line was generated to express corin specifically in the heart under the α -myosin heavy chain promoter. Then the mice were crossed into a corin null background to create knockout/transgenic (KO/Tg) mice that expressed corin in the heart but not uterus. In these KO/Tg mice, recombinant corin expression restored pro-ANP processing in the heart and normalized blood pressure [19]. Interestingly, the mice, which were normotensive, also developed gestational hypertension and proteinuria [19]. The results indicate that in these mice, hypertension in pregnancy was not due to pre-existing high blood pressure and that uterine, but not cardiac, corin is required to counter hypertension in pregnancy. Compared to wild-type mice, corin knockout and KO/Tg mice also had smaller litter sizes [19].

If corin acted locally in the pregnant uterus, was this function mediated by pro-ANP as its substrate? Many trypsin-like serine proteases have multiple substrates. Thrombin, for example, cleaves fibrinogen and activates protein C and thrombin receptors [71]. Earlier studies reported pro-ANP mRNA and protein expression in different cell types including decidual cells, myometrial cells, trophoblasts and natural killer cells in mouse, rat and human uteroplacental tissues [72–77]. ANP receptor expression was also detected in the pregnant uterus [78–82]. In animal models and cultured human cells, ANP antagonized the contractile effect of angiotensin II and endothelin-1 on uteroplacental vessels and promoted myometrial relaxation [78, 83–87]. If corin function in the uterus is mediated by ANP, mice lacking pro-ANP were expected to have a similar phenotype to that of corin knockout mice in pregnancy. Non-pregnant ANP knockout mice were known to be hypertensive [48]. When these mice became pregnant, their blood pressure elevated further at late gestational stages [19]. The mice also had gestational proteinuria. Thus, phenotypes in pregnant corin and ANP knockout mice were strikingly similar, indicating that the uterine corin function is likely mediated by its pro-ANP processing activity.

6. Impaired trophoblast invasion and spiral artery remodeling in corin knockout mice

Insufficient trophoblast invasion and impaired uterine artery remodeling are common pathological features in patients with preeclampsia [3–6]. These structural changes are expected to reduce vessel size and diminish uteroplacental perfusion, thereby causing placental hypoxia. Consistently, endothelial dysfunction, oxidative stress, and inflammatory cytokines are well-recognized contributing factors in preeclampsia [88–93].

In addition to its function in promoting renal salt excretion, ANP is known to relax arteries and inhibit vascular smooth muscle cell proliferation [94, 95]. ANP also regulates endothelial cell growth and migration [96, 97] and promotes endothelial regeneration in angiogenic processes [98, 99]. Apparently, this pro-angiogenic function was mediated by a downstream cyclic GMP-dependent protein kinase [100]. It is possible, therefore, that locally produced ANP by corin in the pregnant uterus may promote spiral artery remodeling.

This hypothesis was supported by immunohistochemical studies in corin and ANP knockout mice, which were found to have smaller uterine spiral arteries than those in wild-type mice [19]. In these knockout mice, spiral arteries retained more endothelial cells in the lumen and more smooth muscle cells in vessel walls, indicating an incomplete vascular remodeling process. Moreover, in these mice there was an apparent delay of trophoblast invasion, both interstitially and endovascularly [19]. Similar findings of impaired spiral artery remodeling and trophoblast invasion were found in corin KO/Tg mice that expressed corin in the heart but not uterus [19]. In cell-based experiments, ANP stimulated human trophoblasts in

invading matrigels [19]. These results support a role of locally produced ANP by corin in the decidua to promote trophoblast invasion and uterine spiral artery remodeling (Fig. 3). The results also provide mechanistic insights into possible underlying causes for the hypertensive phenotype in pregnant corin and ANP knockout mice.

7. Corin mutations in preeclamptic patients

Mouse models are important tools to study human disease. To date, several mouse models of preeclampsia have been reported [101–104]. Significant differences, however, exist between mouse and human uteroplacental structures [105, 106]. In mice, for example, trophoblast invasion and uterine spiral artery remodeling are less profound than in humans. Consistent with this, observed pathological changes in pregnant corin and ANP knockout mice appeared less severe than those in patients with severe preeclampsia [19]. The mice did not exhibit the HELLP syndrome-like signs that often appear in preeclamptic patients [107]. In this regard, the phenotype in corin and ANP knockout mice is similar to other mouse models of preeclampsia, which usually had a mild phenotype [101–104]. It was unclear, therefore, if the findings in pregnant corin and ANP knockout mice were relevant to the pathology underlying preeclampsia in patients.

More studies were done with human cells and tissues to address this question. By PCR and ELISA, levels of corin mRNA and protein were found low in uterus samples from non-pregnant women but markedly higher in normal pregnant women. In preeclamptic patients, uterine levels of corin mRNA and protein were significantly lower than those in normal pregnant women [19]. These results were consistent with the mouse studies, indicating that corin expression also is up-regulated in the decidua of the human pregnant uterus, and that reduced uterine corin expression may contribute to preeclampsia in patients.

Previously, corin was shown to be shed from the cell surface and soluble corin was detected in human blood [39, 53, 108–110]. Paradoxically, plasma levels of soluble corin were found higher in preeclamptic patients than normal pregnant women [19, 111]. It appears that plasma soluble corin was probably derived from the heart, which produced more corin in response to high blood pressure in preeclamptic patients. Increased corin expression was reported previously in hypertrophic mouse and human hearts [34, 112]. These data indicate that plasma corin levels may not reflect the levels in uterine tissues. Similarly, elevated plasma levels of pro-ANP and ANP were reported in preeclamptic women [113–116]. It is possible that the detected plasma pro-ANP and ANP in patients may also be derived primarily from the heart.

The human *CORIN* gene has 22 exons and spans ~244 kb, making it one of the biggest protease genes [117]. In principle, naturally occurring mutations are more likely to occur in large genes. Interestingly, two *CORIN* gene mutations were found in preeclamptic patients; one mutation changed amino acid Lys317 to Glu in LDLR2 domain and another changed amino acid Ser472 to Gly in frizzled 2 domain [19]. In previous studies, both LDLR2 and frizzled 2 domains were found important for corin to process pro-ANP [118]. In functional experiments, both corin mutants Lys317Glu and Ser472Gly exhibited markedly reduced pro-ANP processing activities, indicating that these mutations may impair corin function in the patients, thereby contributing to preeclampsia [19].

8. Perspectives

Preeclampsia is an ‘old’ disease. “*After more than a century of intensive research, preeclampsia and eclampsia remain an enigmatic set of conditions*” [1]. Currently, medical options for this disease are still limited. In many cases, the only cure is to terminate pregnancy by early labor induction or Cesarean deliveries. Impaired uterine spiral artery

remodeling has long been identified as a major pathological feature in preeclampsia, but the underlying cause remains poorly understood.

Many scientific discoveries started with some seemingly trivial observations. Corin is a cardiac enzyme that activates pro-ANP [17, 40]. The importance of corin in maintaining normal blood pressure has been shown in animal models and human genetic studies. Most recent efforts to pursue a chance finding of uterine corin expression led to identifying a novel local function of corin and ANP in regulating spiral artery remodeling and preventing hypertension in pregnancy [19]. Previous studies showed that corin variants with a reduced activity are more common in African Americans than Caucasians [47, 50, 52]. Interestingly, African Americans also are known to be a high-risk population for preeclampsia. It will be important to examine if the corin variants contribute to preeclampsia in African Americans.

Pregnancy brings about tremendous changes in body fluid volume and distribution. Fundamentally, preeclampsia is a disease that reflects an underlying failure in regulating vascular and hemodynamic changes in pregnancy. The disease is expected to involve many genes. The latest findings of corin and ANP function in the uterus are exciting, but many questions remain to be answered. It is unclear, for example, how corin and ANP expression is up-regulated in the pregnant uterus and why such up-regulation failed in some preeclamptic patients. It is unclear how ANP regulates spiral artery remodel at the molecular level. It is unclear how impaired spiral artery remodeling leads to maternal hypertension and proteinuria. Studies to answer these and many other questions about the role of corin and ANP in the pregnant uterus should help to identify additional molecules that act at the uteroplacental interface and may help to develop new therapeutic approaches to prevent and treat preeclampsia.

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Abbreviations

ANP	atrial natriuretic peptide
BNP	B-type or brain natriuretic peptide
CNP	C-type natriuretic peptide
LDLR	LDL receptor
TTSP	type II transmembrane serine protease

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Fig. 1.

Illustration of corin protein domain structure. Corin is expressed on the cell surface. The protein consists of an N-terminal cytoplasmic tail, a single-span transmembrane domain (TM), two frizzled-like domains (Fz), eight LDL receptor (LDLR) repeats, a scavenger receptor (SR) domain, and a C-terminal trypsin-like protease domain (PR). Proteolytic cleavage sites by ADAM metalloproteinases and corin autocleavage to generate soluble corin fragments are indicated by arrows.

Fig. 2. Corin-mediated pro-ANP activation. Corin cleaves pro-ANP, converting the propeptide to active ANP. ANP binds to its receptor, natriuretic peptide receptor A (NPRA), which promotes natriuresis, diuresis, and vasodilation, thereby lowering blood volume and pressure.

Fig. 3.

Proposed role of corin and ANP in spiral artery remodeling. In pregnancy, corin expression is up-regulated in the uterus. Locally produced ANP by corin promotes trophoblast invasion and spiral artery remodeling, which increases uteroplacental perfusion. The figure is taken from [19].