Brief Review

Human Prorenin

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Human prorenin is the enzymatically inactive biosynthetic precursor of renin. Recent interest has focused on the posttranslational sorting and processing of prorenin to renin since markedly increased levels of circulating prorenin have been associated with both physiological and pathological changes. These observations raise the question of whether prorenin processing may be a regulatory event in renin production in the kidney. In the juxtaglomerular cells of the kidney, prorenin can be sorted to either of two pathways: 1) the regulated pathway, which is mediated by secretory granules, where a thiol protease resembling cathepsin B processes prorenin to renin by cleavage of the amino terminal 43-amino acid prosegment, which allows exposure of the active site of renin, or 2) the constitutive pathway, which is not regulated and does not involve conversion of prorenin to renin. Studies in which segments of prorenin are modified by site-directed mutagenesis suggest that the prosegment and glycosylation are not required for sorting, although they may influence or participate in sorting, or both. Certain areas in the prosegment are important determinants of enzyme activity and ability to cleave the prosegment. Further structural analysis of prorenin will be useful to assess details of its sorting and processing. In addition, a number of extrarenal tissues such as uterine lining, ovarian theca, corpus luteum, pituitary, and adrenal, express the renin gene. These tissues have different capabilities to sort and process prorenin compared with kidney, and some tissues secrete only prorenin. Whether prorenin-to-renin conversion is necessary to activate these local renin-angiotensin systems is a key issue. Understanding mechanisms involved in prorenin-to-renin conversion will help to dissect the potential regulatory role of this step in renin secretion, to define the physiological importance of extrarenal prorenin and renin production, and to determine whether the prorenin processing step could be a site for therapeutic intervention. (Hypertension 1991;17:469-479)

Renin is rate limiting for the generation of angiotensin II (Ang II) in the renin-angiotensin-aldosterone cascade. This cascade is known to regulate blood pressure and sodium-potassium homeostasis, but it has also been implicated to play a role in growth, angiogenesis, reproduction, drinking behavior, anti-diuretic hormone production, and catecholamine release from nerve endings (for review see References 1 and 2). Whereas renin of renal origin appears to be predominantly responsible for the generation of Ang II in the circulation, some of the effects listed above may be mediated by local renin-angiotensin systems.1-4 Extrarenal sites expressing the renin gene are seemingly ubiquitous.5-12 However, some extrarenal tissues produce primarily prorenin6,7,10; in normal humans, the kidney is also a source of prorenin.13,14 In certain body fluids such as that in the ovarian follicle, vitreous fluid in diabetics with proliferative retinopathy, or amniotic fluid, prorenin concentrations can approach 100 times the levels found in plasma.5,9,15-18 In recently developed transgenic rats harboring the mouse Ren 2 gene, fulminant hypertension is associated with high plasma prorenin and aldosterone levels and enhanced adrenal renin activity, whereas plasma and kidney renin levels are low and renal renin gene expression is essentially undetectable.19 These examples raise the question of whether prorenin is activated locally and whether it could contribute to the variety of effects that are attributed to Ang II. It is also unknown whether the conversion of prorenin is regulated; for example, some patients with diabetes mellitus have elevated plasma prorenin levels with low active renin.20 Do these observations reflect a defect in prorenin-to-renin conversion in the kidney20 and indicate that prorenin conversion to active renin is regulated, or does the prorenin in these patients come from nonrenal sources?21 These considerations underscore the need to define renal and extrarenal mechanisms involved in activation and posttransla-
tional processing of prorenin to renin, as these events potentially impact on a variety of physiological activities throughout the body.

Since the initial identification of human inactive renin by Lumbers in 1971, much progress has been made in understanding the relation between prorenin and renin. This progress is largely the result of purification of native human renin with generation of antibodies against renin and of cloning human renin gene sequences. These events made it possible to study renin gene expression and to produce recombinant prorenin and renin and to provide knowledge of their complete amino acid sequences. Evidence confirming the identity of human inactive renin as prorenin stems from the observations that 1) antibodies developed against peptide sequences of the prosegment of prorenin cross-react with human inactive renin purified from plasma, tumor, kidney, and amniotic fluid; 2) inactive renin and human recombinant prorenin share multiple biochemical similarities including molecular weight, kinetics of enzyme activity on angiotensinogen, reversible acid activation and the capability to be enzymatically activated, and 3) the amino terminal sequence of human inactive renin purified from chorion decidua is identical to the amino acid sequence deduced from human inactive renin complementary DNA (cDNA).

This review will focus on prorenin with respect to: 1) its intracellular processing, trafficking, and sorting to different secretory pathways; 2) activation by proteolytic cleavage of its 43-amino-acid prosegment and other mechanisms; 3) its three-dimensional structure with assessment of the mechanisms by which the prosegment inactivates the enzyme; and 4) its clinical implications in physiological and pathological states.

**Cellular Processing and Secretion of Prorenin and Renin**

Preprorenin is the primary translation product of renin messenger RNA (mRNA). A 23-amino-acid signal, or "pre" sequence, directs insertion of the protein into the lumen of the rough endoplasmic reticulum, which is associated with its rapid cleavage to form prorenin. In this inactive state, prorenin traverses the rough endoplasmic reticulum and Golgi apparatus where it is glycosylated at Asn and Asn (numbering with respect to the amino terminus of renin). The extent of glycosylation of these sites and the overall carbohydrate content is variable, both in the renin produced by the kidney and that produced by extrarenal sources. This contributes to heterogeneity of secreted forms of renin and prorenin that may affect its uptake by peripheral tissues and its clearance. From the Golgi apparatus, prorenin can be sorted to one of three compartments, which include two secretory pathways (regulated and constitutive) and lysosomes.

Prorenin has been demonstrated to bind to mannose 6-phosphate receptors, which appear to facilitate its entry into the lysosomal compartment, where it is degraded. This binding results from the addition of mannose 6-phosphate to the carbohydrate moieties of prorenin. In contrast, mouse renin is not glycosylated and does not appear to enter the lysosome. The percent of cellular renin that enters this compartment is unknown. It appears to be relatively small (approximately 5%) in mammalian L cells but is higher in frog oocytes. This could be a significant pathway in some renin-producing cells. However, the role of the lysosome in determining the amount of renin secreted by cells that produce it endogenously is unknown. Paul et al. treated AtT-20 cells transfected with a preprorenin expression vector with tunicamycin to block glycosylation and found an increase in the ratio of secreted to cellular renin, and they suggested that glycosylation prolongs intracellular transit time. In the same cell line transfected with a preprorenin expression vector in which the glycosylated amino acids were mutated, Chu et al. found that prorenin was not only processed to renin, but the cells actually processed more of the prorenin to renin, implying that the sugar moieties actually retard prorenin processing in the regulated pathway. Thus, the sugar moieties may have some effect on prorenin processing, although they are not essential.

Active renin is the primary product of the regulated secretory pathway. This pathway stores secreted proteins, acutely releases them after stimulation by a secretagogue, and is mediated by dense secretory granules, which also serve as the site of prohormone-to-hormone conversion. Prorenin-to-renin conversion appears to occur in the secretory granule. Taugner et al. demonstrated that antibodies directed against the carboxy terminal third of the renin prosegment detect prorenin in immature secretory granules but not in mature granules of human juxtaglomerular cells. Gene transfection studies also suggest a role for the secretory granule. Chinese hamster ovary cells do not have secretory granules. When transfected with a human preprorenin expression only vector, inactive prorenin is produced and released. In contrast, AtT-20 cells from a mouse pituitary tumor line contain abundant secretory granules and, when transfected with the same vector, these cells cleave the 43-amino-acid prosegment and release renin in response to a secretagogue such as 8-bromo cyclic AMP.

Prorenin is the secretory product of the constitutive pathway. This pathway is not regulated acutely and delivers prohormone to the cell surface at a constant rate. Electron microscopy studies in AtT-20 cells indicate that hemagglutinin, a protein destined for constitutive secretion, is concentrated in clear vesicles. We have identified two human tissues that primarily secrete prorenin; an ovarian leiomyosarcoma and the decidua of pregnant women. Electron microscopy studies with antisera to human renal renin (which cross-reacts with both prorenin and renin) demonstrated that, in contrast to renal juxtaglomerular cells where renin was concentrated in dense core secretory granules, renin immunoreactivity was localized to amorphous clear membrane-
bound vesicles in these tissues (Figure 1). An antibody directed against the prosegment of prorenin (which cross-reacts with only prorenin) confirmed that these vesicles contained prorenin (unpublished results from our laboratory). Furthermore, forskolin, which activates adenylate cyclase, did not stimulate acute release (within 2 hours) of either prorenin or renin in cultured human decidual cells.49 These studies suggest that prorenin is the primary form of renin in the membrane-bound vesicles, and that prorenin is released constitutively in these tissues.

It is unknown what factors determine whether the Golgi sorts prorenin to either the regulated or the constitutive pathway. Using site-directed mutagenesis of a human preprorenin expression vector transfected into AtT-20 cells, elimination of either the glycosylation sites or the entire prosegment or exchange of the signal peptide sequence for that of a protein that is secreted constitutively does not prevent renin from being secreted by the regulated pathway.41 Moreover, if the cleavage site Arg-1 at the carboxy terminus of the prosegment is mutated to Gin, prorenin is not cleaved but is still sorted to the secretory granules in AtT-20 cells.40 These results suggest that sequences in the body of renin can participate in sorting and that sorting is independent of processing. Elimination of the prosegment of insulin similarly does not prevent packaging of this protein into secretory granules, whereas fusion of the prosegment of prosomatostatin to constitutively secreted lactoglobin resulted in regulated secretion of lactoglobin.51,52 A "sortase" from canine pancreas binds to hormones destined for regulated secretion but not to constitutively secreted proteins and may be involved in sorting to secretory granules.53 However, the specific structural features responsible for binding to this sortase are unknown. In addition, renin expressed from a vector encoding renin without its propeptide was secreted from myeloma cells, which do not have a regulated pathway.54 Thus, the propeptide is also not necessary for constitutive secretion.

Prorenin is processed to renin in cells that contain a regulated pathway of secretion (i.e., kidney, AtT-20 cells). However, tissues with regulated secretory pathways can vary in how they process a given protein. For example, proopiomelanocortin is processed differently in the anterior lobe compared with the posterior lobe of the pituitary.55 Nevertheless, the identification of dense core secretory granules in a tissue that can express the renin gene may provide a clue that prorenin is processed to renin in that tissue. Renin immunoreactivity has been localized to secretory granules in the kidney, pituitary, adrenal, and certain renin-secreting tumors,46,56–58 and renin activity has been detected in extracts of these tissues. The kidney processes prorenin to renin and is the major source of circulating renin in humans, since plasma renin activity decreases markedly and remains low after bilateral nephrectomy.14 In the pituitary and adrenal, a local renin-angiotensin system has been implicated to have paracrine/autocrine effects.56,58 In other tissues, such as decidua, ovary, and some tumors, as described above, prorenin is the primary form of renin secreted, which presumably occurs via a constitutive mechanism. Whether the prorenin secreted by this pathway is subsequently activated extracellularly or is taken up by other tissues and then activated remains to be determined. In addition, under certain conditions cells can be stimulated to produce secretory granules49 and thus, may change their pathway of hormone processing and secretion.

**Activation of Prorenin**

**Cleavage of the Prosegment**

Amino terminal sequencing of pure human renal renin indicates that the kidney cleaves the prosegment after two dibasic residues (Lys-Arg') to yield a Leu at the one position of active renin.21 This prosegment cleavage site is similar to those in other polypeptide hormone systems, which occur after a pair of basic amino acids, particularly Lys-Arg.60 However, since there are 10 pairs of dibasic amino acids in prorenin, it remains to be determined why this site and not the others are recognized. That structural features outside this dibasic peptide are critical for the recognition by the prorenin processing enzyme is suggested by the finding that mutation of Pro-47 of the prosegment to Gin impairs processing.41 It is likely that a specific enzyme is involved in this process. Current evidence suggests that requirements for the renal prorenin processing enzyme include 1) activation of prorenin, 2) correct cleavage of the prosegment, 3) lack of activity to degrade renin, and 4) colocalization to renin secretory granules.

We sought to identify the predominant enzyme in the kidney that satisfied the first three of these criteria and isolated a thiol protease from human renal cortical homogenates that both activated human recombinant prorenin and correctly cleaved the complete 43–amino-acid prosegment.61 This 25,000 molecular weight protease had a pH optimum of 6, which is consistent with that inside a secretory granule,62 and when incubated with pure native human renal renin at that pH, did not destroy active renin. Further identification of this candidate prorenin processing enzyme awaits its complete purification and localization to secretory granules of the juxtaglomerular cell.

The enzyme described above resembles cathepsin B, a thiol protease that is abundant in lysosomes of the kidney and liver.53 Indeed, cathepsin B has been demonstrated to activate prorenin and to decrease its molecular weight,54–56 but the exact site of cleavage of prorenin by this enzyme has not been demonstrated. Cathepsin B has also been colocalized to renin-containing secretory granules in rat juxtaglomerular cells67 and in human pituitary lactotrophs.56 In addition to its endopeptidase activity that cleaves after dibasic amino acids, cathepsin B has exopeptidase activity that cleaves dipeptides from the carboxy terminal of proteins.68 However, it does not cleave peptide bonds involving proline; this may prevent
active renin from being degraded by cathepsin B, since renin has surface loop proline residues at its carboxy terminal. Because of their content of acid hydrolases, it has been suggested that renin secretory granules are modified lysosomes, which could explain the involvement of a lysosomal enzyme in prorenin processing. However, sorting to secretory granules is not dependent on binding to mannose-6-phosphate receptors or glycosylation.

Trypsin, plasmin, pepsin, kallikrein, and other proteases can also activate prorenin. However, when the yeast kex2 and POMC genes were cotransfected, POMC was accurately cleaved, suggesting that the expression of a processing enzyme in the cell could induce prohormone processing enzymes. Trypsin and pepsin are not found in the kidney and with time, degrade active renin. Kallikrein, although present in the kidney, does not appear to reside directly in the juxtaglomerular cells.

At present, the identification and regulatory role of prohormone processing enzymes remain elusive. Thus far, several different proteases have been implicated as potential processing enzymes, rendering some tissue specificity to this mechanism. For example, a calcium-dependent serine protease has been isolated from insulin secretory vesicles; a paired dibasic residue-specific (POMC) aspartyl protease has been identified in pituitary intermediate lobe secretory vesicles, and a calcium-dependent thiol protease, kex2, which processes proalbumin, has been isolated in yeast. When the POMC gene was transfected into cells that do not process this prohormone, POMC was synthesized but not cleaved. However, when the yeast kex2 and POMC genes were cotransfected, POMC was accurately cleaved, suggesting that the expression of a processing enzyme gene in the cell could induce prohormone processing and regulate the form of hormone released. To date, there has been no demonstration that processing enzymes are regulated. That secretory granule formation could play a role in regulating hormone production is suggested by the recent finding that synthesis of SGM 110, a secretory granule component in normal pancreatic islets, as well as insulin, is enhanced by glucose.

Extrarenal tissues not only produce prorenin locally but can also take it up from the circulation. However, the extent to which they process prorenin is not resolved. For example, prorenin has been reported to be extracted by the rodent vascular wall and human heart and might be activated in these tissues for local Ang II generation. In primates, the liver and kidney take up circulating prorenin and convert it to renin without secreting renin back into the circulation. Neutrophils produce abundant enzymes that could activate prorenin and enhance local Ang II levels during the inflammatory process. However, the presence of moderate levels of prorenin in the circulation does not appear to lead to significant Ang II effects. Infusion of large amounts of recombinant prorenin into primates did not result in any detectable Ang II responses, and infusion of radiolabeled human prorenin into primates did not result in significant conversion of prorenin to renin. Patients have had tumors that resulted in high circulating levels of prorenin without associated hypertension or other stigmata of Ang II excess. In addition, some patients with diabetes mellitus have hyporeninemic hypoaldosteronism and high circulating levels of prorenin.

**Alternate Proteolytic Activation**

Cleavage of the prosegment at sites other than the classical one can also generate active renin. The classical one can also generate active renin. Heinrichson et al found that cleavage of prorenin between residues 34 to 30 of the prosegment yields an active enzyme. Plasmin clips prorenin between Lys-Arg to generate active renin; trypsin cleaves prorenin at Arg-Leu as well as between Arg-Leu to generate active renin. We purified recombinant prorenin by a procedure involving acid precipitation and found that a substantial portion of the prorenin was activated with cleavage of 32 amino acids of the prosegment. An active "prorenin" of similar size was also found in extracts of chorion decidua. Thus, it is conceivable that these alternative cleavages could occur in vivo to activate prorenin, although there is currently no evidence that this occurs.

**Nonproteolytic Activation**

Prorenin can be activated in the absence of cleavage of the prosegment by acid or cold temperature. These maneuvers result in reversible activation and are presumably due to effects on the conformation of the prosegment that removes it from a position in which it inhibits the activity of the enzyme (discussed below). Activation without cleavage has been suggested to be an intermediate step in prorenin processing; however, the thiolytic protease we isolated cleaved both inactive and active prorenin similarly at 37°C. The activity of prorenin in vivo appears to be quite low or negligible, in situations where prorenin levels are quite high (for example, in ovarian follicular fluid), there is a potential to have significant renin activity of prorenin. In addition, it is possible that other cellular effects on prorenin might activate it locally without the need for...
proteolytic cleavage of the prosegment, although there is no direct evidence for this.80

Three-Dimensional Structure of Prorenin

Renin is a member of a family of aspartyl proteases that includes pepsin and penicillopepsin. These proteases are similar in their amino acid sequences, active sites, mechanisms of catalysis, and zymogen precursors.89-91 Their genes probably arose from a common ancestral precursor gene. In humans, a single gene encodes for both renal and nonrenal renin.92 This gene structure is similar to that of human pepsinogen in terms of size, homology in the coding regions, positions of introns, and sizes of the exons.25-27 The aspartyl proteinases also have similar three-dimensional structures. The structures of pepsinogen, Rhizopus pepsin, and penicillopepsin were previously reported and that of recombinant human renin was recently reported at 2.5 Å resolution.93 The structural core and active sites of renin are highly conserved with other aspartyl proteases. However, there are variations in the surface residues that are critical for the differences in substrate specificity. These include the “flap” areas84; the carboxy terminal domains that may affect the pH profile (Ala304), allowing renin to have activity at a relatively high pH of 5.5-7.595; and the carbohydrate moieties at the glycosylation sites, which may affect intracellular transit time,40 metabolic clearance rate of renin from the circulation,37 and stability of prorenin.96

From these structural comparisons, it can be inferred that the structure of prorenin will resemble that of pepsinogen (Figure 2). Cleavage of the prosegment of pepsinogen is followed by an enormous conformational change in the molecule in which the amino terminus moves by about 40 Å.89 The prosegment originally extends from the amino terminus of pepsin into the active site with a lysine forming ionic interactions with the aspartate groups of the active site. The prosegment then forms a loop that is followed by sequences containing α-helical structures and then a β-strand that is fitted into a hydrophobic groove on the back of the molecule and that forms part of a β-pleated sheet. The amino terminus of the prosegment extends from the β-strand. It is likely that the prosegment of prorenin assumes an overall similar configuration.

Knowledge of prorenin’s structure provides a framework for studies examining how the prosegment inactivates prorenin. It appears most likely that the physical occupancy of the active site of the enzyme by the prosegment prevents the substrate of renin, angiotensinogen, from reaching the active site of the enzyme. But how is the prosegment held in this position? Are the interactions between the prosegment and renin around the active site or those between the β-sheet of the prosegment and the hydrophobic groove most important? Peptide fragments of the prosegment of rat prorenin and human prorenin have been demonstrated to bind to the active site of the pure enzyme and to inhibit generation of angiotensin I, although large concentrations are required for this.97 The segment from Phe32 to Pro37 in human prorenin inhibits human renin with a Ki of 10^-4 M. This observation suggests that the middle portion of the prosegment might also block angiotensinogen access to the active site. The data cited earlier in which removal of as few as 9-13 amino acids of the prosegment activates prorenin85 suggests that the amino terminal amino acids of prorenin also contribute to holding the prosegment in place. Thus, the interactions of the β-sheet that are fitted into the hydrophobic groove are probably important for stabilizing the prosegment in a configuration that keeps prorenin inactive. This model further implies that the portion of the prosegment that is cleaved lies in a cleft so that it is accessible to the prorenin processing enzyme.

Clinical Implications

Absolute levels of plasma prorenin vary with physiological changes and under pathological conditions (Table 1). Measurement of plasma prorenin may provide insight into its relation with renin when the
TABLE 1. Clinical States Associated With Elevated Plasma Prorenin

<table>
<thead>
<tr>
<th>Plasma source</th>
<th>Active renin (ng Ang 1/ml/hr)</th>
<th>Prorenin (ng Ang 1/ml/hr)</th>
<th>Prorenin/renin ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal patients</td>
<td>2–15</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>Hypertensive patients</td>
<td>Low to elevated</td>
<td>&lt;50</td>
<td>Slight variations</td>
</tr>
<tr>
<td>Diabetic patients with nephropathy</td>
<td>Low to normal</td>
<td>50–200</td>
<td>High</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Normal to slightly elevated</td>
<td>50–200</td>
<td>High</td>
</tr>
<tr>
<td>Women undergoing in vitro fertilization</td>
<td>Normal</td>
<td>100–200</td>
<td>High</td>
</tr>
<tr>
<td>Patients with renin-secreting tumors</td>
<td>Normal</td>
<td>300–1,000</td>
<td>High</td>
</tr>
</tbody>
</table>

Elevated plasma prorenin levels are commonly found in patients with diabetes mellitus (Types I and II) and have been implicated as a potential marker of nephropathy. In Type I diabetes mellitus, Luetscher and colleagues have found that elevated prorenin levels are a predictor of microvascular complications. However, these same workers also reported that some hypertensive diabetic patients may have normal plasma prorenin despite the presence of complications and suggested that hypertension may suppress plasma prorenin levels. We found that 95% of patients with Type II diabetes mellitus, hypertension, and occult renal disease defined by normal blood urea nitrogen, serum creatinine, negative urine dipstick, and microalbuminuria have elevated plasma prorenin concentrations (P. Anderson and W. Hsueh, unpublished observations). However, we also found that 40% of hypertensive Type II diabetic patients with no evidence of renal disease and normal albumin excretion also have elevated plasma prorenin levels. Thus, this relatively early rise in prorenin may also be a predictor of complications in Type II diabetes mellitus.

Somewhat paradoxically, diabetic nephropathy is also the most common cause of hyporeninemic hypoaldosteronism. This is usually associated with other stigmata of renal disease and with modest or marked elevations of plasma prorenin concentrations. It is likely that the kidney contributes at least in part to the elevated prorenin levels in patients with diabetic nephropathy; prorenin has been identified in extracts from kidneys of diabetic subjects. Although the eye could contribute to the elevated plasma prorenin, since the vitreous fluid of diabetics is the most common cause of hyporeninemic hypoaldosteronism. This is usually associated with other stigmata of renal disease and with modest or marked elevations of plasma prorenin concentrations. It is likely that the kidney contributes at least in part to the elevated prorenin levels in patients with diabetic nephropathy; prorenin has been identified in extracts from kidneys of diabetic subjects. Although the eye could contribute to the elevated plasma prorenin, since the vitreous fluid of diabetics may have elevations of plasma prorenin levels. An impaired conversion of prorenin to renin in the kidney in diabetes has been postulated to cause the rise in circulating prorenin. This hypothesis implies that prorenin processing is abnormal in the diabetic kidney due to either defective storage granule formation or impaired proteolytic processing. Consistent with this hypothesis, defective prokallikrein-to-kallikrein conversion and decreased cathepsin B levels have been found in the streptozotocin diabetic rat.
The female reproductive tract is another important source of prorenin. High levels of prorenin in ovarian follicular fluid and amniotic fluid bathe the unfertilized and fertilized ovum. This active peptide has been postulated to regulate growth and maturation, angiogenesis, steroidogenesis, and vasoconstriction and blood flow in the ovum and fetus, since Ang II can induce all of these effects in other tissues. Specific high affinity Ang II receptors have been identified in these areas, as well as on granulosa cells in the rat ovary. Ang II may affect progesterone production in the human ovary. Ovarian prorenin production appears to be modulated by gonadotropin. Follicle-stimulating hormone stimulates renin mRNA expression in the rat ovary; human chorionic gonadotropin induces a profound rise in circulating prorenin in women undergoing in vitro fertilization, whereas endogenous lutetizing hormone appears to induce a smaller, less sustained rise in plasma prorenin. Taken together, these data suggest prorenin may mediate some of the effects of gonadotropins in the ovary.

Pregnant women have twofold to fivefold elevations of circulating prorenin. The ovary contributes to the early rise in prorenin, since ovariotomized pregnant women do not display the normal rise in circulating prorenin. As pregnancy progresses, the utero-fetal-placental unit also contributes to circulating prorenin. Renin immunoreactivity has been identified in human chorionic membranes; however, studies of renin mRNA expression suggest that the decidua is the major source of renin in the uterus and placenta. Renin gene expression was not detected in amnion, basal plate chorion, myometrium, or the placental villi. Thus, decidua as well as fetal kidney may contribute to the high levels of prorenin in amniotic fluid. The lack of renin gene expression, but positive immunostaining in chorion, suggests that this membrane does not produce prorenin but may take up prorenin synthesized by the decidua and transport it into amniotic fluid. An analogous situation exists for decidual prolactin. Endometrium, uterine lining in the nonpregnant state, also expresses the renin gene, but gene expression and prorenin production by cultured endometrial cells is much less than in decidua. Estrogen and progesterone do not appear to induce the rise in prorenin production by the uterine lining that occurs with decidualization (unpublished results from our laboratory). Whether human chorionic gonadotropin or growth factors are involved in this process remains to be determined.

Patients with renin-secreting tumors have the largest known elevations of circulating prorenin. These tumors typically arise from the kidney, but can be extrarenal. When these tumors secrete both prorenin and renin, they are generally associated with hypertension and hypokalemia. A high prorenin associated with elevated blood pressure in the absence of pregnancy or diabetic nephropathy may suggest a renin-secreting tumor, so that elevated prorenin levels may serve as a tumor marker. Fifteen cases of extrarenal renin-secreting tumors have been reported in the literature; 14 of these were in women and seven were located in the reproductive tract. All of the extrarenal tumors have been malignant. Processing of prorenin to active renin may be variable in the extrarenal tumors, since an elevated prorenin can occur in the absence of hypertension. In a retrospective study of eight ovarian malignancies, four well-differentiated tumors contained immunoreactive renin and four undifferentiated tumors did not. Only one of the positive-staining tumors was associated with hypertension and a high prorenin; one normotensive subject had a high plasma prorenin level. In certain tumors, local production of renin may contribute to angiogenesis or growth of the tumor. In a series of 24 pulmonary carcinomas, upon immunostaining the walls of tumor vessels, 80% demonstrated renin. Although the Ang II receptor has been identified as the protein product of the mas oncogene, this result has not been confirmed.

In summary, high plasma prorenin levels serve as a marker for rare renin-secreting tumors, abnormalities in the diabetic patient with and without overt nephropathy, and for physiological changes during the menstrual cycle and pregnancy. Whereas the importance of renal prorenin to renin conversion is clear, the role of extrarenal prorenin activation is not understood. Nevertheless, these clinical observations provide a stimulus for further investigation of the molecular, cellular, and biochemical mechanisms that control posttranslational processing and activation of prorenin. Understanding these mechanisms may provide novel insights into the regulation of the renin-angiotensin system.

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