On the Pathophysiologic Implications of an Intracellular Renin Receptor

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The renin angiotensin system plays an important role on the regulation of arterial pressure, blood volume and cardiac function. Both a circulating and several tissue-localized systems have been identified and able to cleave angiotensinogen by renin to form angiotensin I which is converted to angiotensin II (Ang II) by angiotensin converting enzyme. The presence of local Ang II generation, which has been supported by the beneficial effects of Ang II AT1 receptor blockers and ACE inhibitors independently of their effects on arterial blood pressure, certainly requires that renin, angiotensinogen and ACE be synthesized locally or taken from the plasma.

Concerning the presence of the different components of the RAS in different tissues evidence is available that in nephrectomized rats, the renin levels in the heart, for instance, are extremely low what indicates that intracellular renin in cardiac myocytes of normal animals, would need to come from plasma. However, rats transgenic for the mouse ren-2 renin gene develop severe hypertension and cardiac remodeling and incubation of cardiac myocytes from these animals with prorenin (the precursor of renin) leads to intracellular appearance of angiotensin I and II what suggests prorenin internalization. Moreover, an alternative transcript for a nonsecreted renin has been described in brain and heart. The transfection of a nonsecreted form of angiotensinogen into hepatoma cells that expressed this renin transcript, increased proliferation by a process that is sensitive to renin antisense, indicating that the renin transcript has functional properties. Indeed, the alternative renin transcript is upregulated in adult rats with MI suggesting its contribution to intracellular Ang II generation under pathological conditions. Regardless of whether intracellular renin or Ang II is the result of intracellular synthesis or internalization, evidence exists that intracellular renin is able to increase the inward calcium current in myocytes from the failing heart. In addition, transgenic overexpression of the intracellular nonsecreted form of renin and angiotensinogen in the brain leads to an increase in drinking volume and mean arterial pressure. The work of Schefe et al indicated that the primary localization of the human renin/prorenin receptor (RER) is in the perinuclear zone what conflicts with previous studies indicating its localization in the plasma cell membrane. The intracellular localization was confirmed using different constructs and studies of mutagenesis and colocalization. Indeed, mutagenesis of the atypical C-terminal ER-retention signal strongly reduced the perinuclear localization of the renin receptor. Furthermore, a transcription factor promyelocytic zinc finger protein (PLZF) was identified as a direct protein interaction partner of the C-terminal domain of the renin receptor and following the activation of RER by renin, PLZF is translocated from the cytoplasm to the nucleus providing positive or negative regulation of target genes. Renin stimulation also increased PI3-K-85α messenger RNA whereas small interfering RNA against PLZF abolished this effect. Moreover, experiments performed on PLZF knockout mice supported the view that PLZF is an upstream regulator of RER. Interestingly, renin stimulation in rat H9c2 cardiomyoblasts not only increased the cell number but elicited a decrease of apoptosis.

Although further studies will be needed to rule out the existence of more than 1 renin receptor, Schefe et al did not rule out the possibility that very small amount of RER within the plasma cell membrane might be sufficient to initiate a RER signal transduction cascade despite its intracellular localization. In this case, other receptors like mannose-6 phosphate receptors could internalize renin and prorenin and the intracellular Ang II formation elicited by renin internalization, might explain the severe cardiac damage seen in transgenic rats expressing the mouse ren-2 renin gene.

The question remains whether renin is able to work by itself or depends on the formation of Ang II. Tissue accumulation of plasma prorenin results in angiotensin generation but could also, through binding to a recently cloned prorenin/renin receptor, lead to angiotensin-independent effects including p42/p44 mitogen-activated protein kinase (MAPK) activation and plasminogen-activator inhibitor (PAI-1) release. In mesangial cells, renin increases transforming growth factor-β1 and matrix proteins also independently of Ang II mechanisms whereas in cardiomyocytes isolated from the failing heart, intracellular renin increments the inward calcium current, an effect suppressed by intracellular losartan. These apparent discrepant results lead us to think that the activation of RER has multiple functions some related to the activation of the RAS and other not (see Figure). Here caution must be exercised because variations of species or type of preparations used in the experiments might influence the results.

The intracellular localization of the renin receptor described in Schefe’s article certainly reactivates the tantalized question whether an intracellular renin angiotensin system is involved on the regulation of tissue function in different pathophysiological conditions. Activation of this receptor by enhanced expression of renin gene elicited by cell stretch for instance, might be in part responsible for cardiac remodeling and changes in electrical properties. On the other hand, increased internalization of

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Angiotensin generation. It is, intracellular renin reduces cell communication in the heart, an interaction and increasing the inward calcium current.

The diagram also shows the possible generation of Ang II inside the cell and its effect decreasing gap junctional communication and increasing the inward calcium current.

renin can result in intracellular degradation or intracellular angiotensin generation. The clinical implications of these findings are several: 1) inhibition of prorenin binding attenuates the development and progression of cardiac fibrosis and inhibits the development of diabetic nephropathy in animal models; 2) RER messenger RNA can be detected in human glioblastomas and renin inhibitors decreases the number of cells in glioblastoma cell lines; 3) a mutation of the renin receptor gene causes the X-linked mental retardation and epilepsy in humans; and 4) intracellular renin reduces cell communication in the heart, an effect drastically reduced by intracellular enalaprilat. It is, then, conceivable that stimulation of RER by overexpression of the renin gene might impair impulse propagation and facilitates the generation of cardiac arrhythmias.

As it can be seen, the intricacies of the RER activation and possible consequences are barely realized. The widespread implications of RER in different pathological conditions as described above, support the view that the biological relevance of this receptor goes beyond the RAS. Cytoplasmic compartmentalization and the activation of a variety of intracellular signal pathways as well positive or negative regulation of target genes might be responsible for the diverse pathophysiological implications related to the activation of RER. Future research in this area promises to bring far more penetrating insights into the intracellular renin receptor and it implications.

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