Letter

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Proposed interaction between angiotensinogen and retinoblastoma tumor suppressor protein: Potential molecular origin of hypertension

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Summary: *Hypertension ranks among the most important disease challenges on a global scale. Here, a novel hypothesis is presented which implicates angiotensinogen, i.e. the precursor protein for the hypertensive peptide angiotensin II, as a key culprit in the pathogenesis of hypertension. This hypothesis more precisely entails that intracellular angiotensinogen binds and thereby inactivates the retinoblastoma tumor suppressor protein (RB), consequently leading to an inflammatory and hyperproliferative state that significantly contributes to pathologically increasing blood pressure. Accordingly, a conceivable antihypertensive strategy could comprise RB-derived compounds that neutralize angiotensinogen.*

Cardiovascular disorders are still the most common cause for morbidity and mortality in industrialized countries. Within this major group of diseases, hypertension plays a leading role. Similar to other important pathologies such as cancer, the prevalence of hypertension increases with aging (*1*). Currently, among the principal treatments for hypertension are calcium-channel blockers, β-adrenergic antagonists and substances interfering with the renin-angiotensin system such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (*1*). However, it is also known that the therapy of hypertension needs further improvement since it is not infrequent that polypharmacy by means of several different antihypertensive agents is needed to control certain forms of hypertension and, moreover, other (malignant) variants of hypertension are refractory to antihypertensive drug treatment.

As a result, the present investigation has aimed for identifying novel antihypertensive drug targets. In this context, I have focused on the potential pathogenetic role of angiotensinogen, *i.e.* the precursor protein for the hypertensive peptide angiotensin II, that has previously been described to occur in the intracellular compartment of human astrocytes (*2*) and of human dopaminergic neurons of the substantia nigra compacta (*3*).

Discovery and hypothesis: In the course of analyzing the amino acid sequence of human angiotensinogen, I have now discovered that it harbors the LXFXE amino acid motif (Figure 1) that has previously been defined as a retinoblastoma tumor suppressor protein (RB) binding motif in the viral oncoprotein Tax (*4*).

Leu Leu **Phe** Glu **Glu**
HTLV-I Tax oncoprotein residues 306-310

Leu Asp **Phe** Thr **Glu**
Human angiotensinogen residues 239-243

Figure 1. Alignment of LXFXE amino acid motifs in HTLV-1 Tax oncoprotein and human angiotensinogen. The crucial residues of the LXFXE motif have been highlighted in bold letters.

This novel finding suggests that intracellular angiotensinogen physically interacts with RB and thereby inactivates it, thus leading to cellular hyperproliferation and tissue inflammation both of which ultimately contribute to pathologically increasing blood pressure.

This new hypothesis on a potential involvement of angiotensinogen in the pathogenesis of hypertension is consistent with several reports on the inflammation-hypertension connection (*5-7*) along with data showing that the pro-inflammatory cytokine interleukin 6 increases the (plasma) level of angiotensinogen (*8*) and, moreover, that the angiotensinogen gene is a target for the intracellular pro-inflammatory protein NF-κB (*9*). In this context, it is worth noting that NF-κB inactivates RB (*10*) and, conversely, intact RB inhibits the gene regulatory activity of NF-κB through the conformational induction of a transcriptionally inactive NF-κB-DNA complex (*11*).

Given this now proposed candidate role for angiotensinogen in the etiology of hypertension, it should be promising to target the above-described angiotensinogen LXFXE RB-binding motif by means of antiproliferative

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RB-derived peptides such as those (anticancer) RB peptides that have previously been reported to recognize and neutralize the related LXCXE RB-binding motif (*12-16*).

This potential therapy of hypertension is in line with previous concepts on the inhibition of vascular smooth muscle cell proliferation, which is a crucial process in the pathology of hypertension, by means of an antiproliferative RB isoform (*17*) and the α_1-adrenergic receptor antagonist doxazosin (*18*).

Moreover and interestingly, the presently proposed treatment of hypertension by previously validated anti-cancer compounds such as MCR peptides (targeting the LXCXE motif) resembles the activity spectrum of naturally occurring substances such as quercetin that is *e.g.* a component of apples. Accordingly, quercetin has been shown to both block cancer cell growth (*19*) and to reduce blood pressure in hypertensive subjects (*20*).

If effective, the presently advanced therapeutic approach would once again underscore the previously recognized importance of *intracellular* targets and pathways for the successful treatment of human diseases (*21-24*). Last not least, this proposed (quercetin-like) strategy has the potential to additionally validate the likely effectiveness of both bionic and epigenetic interventions towards solving long-standing and important medical challenges.

Acknowledgments

The aim of the present hypothesis is both to stimulate research into a fundamentally new direction in the field of hypertension and to commemorate the 20th anniversary of the foundation of *Molecular Concepts Research* (*MCR*).

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