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Elucidation of Novel Molecular Signaling between Salt-Loading and Cardiovascular Diseases Based on a Genetic Approach

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Summary

The stroke-prone spontaneously hypertensive rat (SHRSP) is a representative disease model of essential hypertension and cerebral stroke. Our genetic approach using a series of congenic strains between SHRSP and SHR (a stroke-resistant hypertensive strain) have identified that two major quantitative trait loci (QTL) responsible for a salt-induced stroke in SHRSP were located on chromosome (chr) 1 and 18. Recently, we showed that an approximately 3 Mbp fragment on the chr1 QTL had possible candidate genes. In the present study, we focused on the *Cblc* (Cas-Br-M (murine) ecotropic retroviral transforming sequence c), coding an E3 ubiquitin ligase, as a promising candidate because it was computationally predicted that its 3D structure would be different between SHRSP and SHR due to variations of amino acids sequence. CBLC belongs to Cbl family and is thought to participate various signaling pathways through its E3 ubiquitin ligase activity and phosphorylated tyrosine binding domain SH2. Because it was reported that CBLC had a suppressive role in fibrotic changes induced by TGF-β1 in human lung fibroblasts, we hypothesized that CBLC would play a role in fibrotic changes of renal tubular cells as well.

TGF-β1 induced *Col1a1* (a fibrotic marker gene) mRNA and protein expression in NRK-52E cells, a rat renal proximal epithelial cell line. Interestingly, transfection of *Cblc* siRNA reduced COL1A1 protein expression with no change in mRNA level. This result suggested that CBLC may regulate COL1A1 stability. TGF-β1 also induced α-SMA protein expression, a fibrotic/EMT marker, while the expression level was not affected by *Cblc* knockdown.

In conclusion, the present results raised a possibility that CBLC causes excess accumulation of COL1A1 resulting renal fibrosis. Therefore, CBLC may play a pathophysiological pivotal role in salt-induced stroke of SHRSP by accelerating renal injury under salt-loading.