Tubuloglomerular Feedback and Hypertension: Possible Role of Abnormal Function of Glomerular Mesangial Cell. Toshihiro Okuda, Yoji Inishi, and Kiyoshi Kurokawa. 1st. Department of Internal Medicine, Tokyo University and 3rd. Department of Internal Medicine Toho University, Tokyo 113

It is now established that Cl^- transport by macula densa, the most distal part of thick ascending limb of Henle, is the first step of signal transduction mechanism of tubuloglomerular feedback (TGF), the regulation of glomerular filtration by distal tubular flow. There lie extraglomerular cells between macula densa and glomerulus. Using cultured mesangial cells, we previously reported that vasoactive agents-induced signaling and cell contraction were attenuated in mesangial cells via prostaglandin (PG) production when ambient Cl^- concentration ($[\text{Cl}^-]_o$) was reduced. Based on these observations, we proposed the modulation of extraglomerular mesangial cell function by change in $[\text{Cl}^-]_o$ according to macula densa Cl^- delivery and transport has an important role in the mediation of Cl^- signal from distal tubule to glomerulus when TGF is activated. TGF is thought to be the intrinsic mechanisms to maintain the appropriate water and electrolyte balance and resetting of this balance might lead to the development of hypertension through increased volume of the body. Indeed, abnormal TGF activities are reported in SHR and this suggests the possibility that abnormal TGF activities are causally related to the development of hypertension in SHR. In the present study, we examined if modulation of mesangial cell function by $[\text{Cl}^-]_o$ is altered and different from normal in SHR. We used cultured mesangial cells obtained from 4week and 8week old rats. In mesangial cells obtained from control Wistar Kyoto rat (WKY), angiotensin II- and vasopressin-induced Ca^{++} signal and cell contraction was attenuated when the cells were pretreated with solution containing decreased $[\text{Cl}^-]_o$, as we reported previously in mesangial cells from normal Wistar rat. In contrast, this attenuation was absent or diminished in SHR mesangial cells. Also, Enhanced PGE2 production caused by decrease in $[\text{Cl}^-]_o$ observed in WKY mesangial cells was absent in SHR mesangial cells. However, angiotensin II increased PGE2 production and exogenous addition of PGE2 attenuated Ca^{++} signaling and cell contraction both in WKY and SHR mesangial cells, indicating that angiotensin II induced PG production and modification of cell function by PGE2 is normal in SHR mesangial cells. The alterations observed in the present study in SHR are thought to be genetically determined since similar results were obtained in mesangial cells obtained from rats both 4weeks and 8weeks of age, i.e., before, and after the development of hypertension. Therefore we conclude that modulation of mesangial cell function by $[\text{Cl}^-]_o$ is specifically disturbed in SHR mesangial cells. We suggest the possibility that insensitivity of SHR mesangial cell to change in $[\text{Cl}^-]_o$ might be one of the causes of TGF abnormalities present in SHR and this may lead to the development of hypertension.