論文内容の要旨

論文題目　Regulation of actin dynamics and cell motility of glomerular mesangial cells.

−Role of epithelial protein lost in neoplasm (EPLIN)

(Epithelial protein lost in neoplasm (EPLIN)によるメサンギウム細胞の

アクチン細胞骨格と運動性の制御)

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Migration of mesangial cells is crucial in the repair process following glomerulopathy or during glomerular development, and is regulated by several growth factors. Directional migration requires the establishment of a polarized cytoskeletal arrangement, a process regulated by coordinated actin dynamics at the peripheral lamellipodia in migrating cells. Here, I demonstrate that the actin binding protein epithelial protein lost in neoplasm (EPLIN) is highly expressed in mesangial cells, proximal and distal tubular cells, and extraglomerular endothelial cells, it was associated with the mesangial cytoskeleton and regulates mesangial migration. EPLIN was localized in an area where mesangial cells are contiguous with endothelial cells, and in the mesangial cell–cell adhesion sites. It was also expressed in the mesangial extensions consisting of actin-containing microfilaments underneath the capillary endothelium close to the mesangial angles where they were attached to the glomerular basement membrane. In Thy-1.1 nephritic rats, the expression of EPLIN in injured glomeruli was dramatically decreased after anti-thy1 antibody injection. In cultured mesangial cells, EPLIN was colocalized with peripheral actin bundles and paxillin. PDGF induced membrane ruffling in mesangial cells and translocalization of EPLIN to the peripheral ruffles. Knockdown of EPLIN in mesangial cells altered the stability of focal adhesion and enhanced PDGF-induced cell migration, but not proliferation. These observations shed light on the role of coordinated actin remodeling in mesangial cells during restorative remodeling. Changes in the expression and localization of cytoskeletal regulators are responsible for the phenotypic changes of mesangial cells in glomerulonephritis.