論文の内容の要旨

Studies on the role of Cep169, a centrosome protein, in primary cilium formation

（中心体タンパク質 Cep169 の一次繊毛形成制御機構の研究）

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Abstract

The primary cilium is an immotile antenna-like organelle that arises from the mother centriole. Recent accumulating lines of evidence have shown that the primary cilium functions as a signal sensor on the surface of quiescent cells and that its dysfunction is tightly associated with a class of human diseases collectively called ciliopathies. Despite its biological and clinical importance, the mechanism by which the formation of primary cilia is repressed in proliferating cells remains elusive. Cep169 is a recently identified microtubule plus-end tracking and centrosome protein. Although the roles of Cep169 in microtubule dynamics and stability have been studied, its potential involvement in the regulation of primary cilia formation remains to be determined. In this thesis, using proteomic and cell

biological approaches, I have comprehensively investigated the mechanism by which Cep169 regulates primary cilium formation.

The mass spectrometry-based analysis identified hundreds of novel Cep169-interacting proteins in human HeLa cells. Remarkably, they included several centrosome and cilium proteins. Many posttranslational modifications, such as cell cycle-dependent phosphorylation, methylation, and ubiquitination, were also identified. These results raised the possibility that Cep169 participates in primary cilium formation. Therefore, I attempted to gain further insight into the relationship between Cep169 and the primary cilium. The siRNA-mediated depletion of Cep169 from proliferating human RPE1 cells induced untimely primary cilium formation. The resultant ciliated cells eventually entered a quiescent state. Cep169 depletion also caused a marked increase in the amounts of the TTBK2 kinase, which was previously implicated in ciliogenesis, consequently promoting the dissociation of Cep97 and CP110 from the mother centrioles. Remarkably, neither untimely ciliogenesis nor Cep97 dissociation was observed in cells simultaneously depleted of Cep169 and TTBK2. Taken together, these results strongly suggested that Cep169 plays a central role in the inhibition of untimely primary cilium formation in proliferating cells, by preventing the TTBK2-mediated dissociation of Cep97.