



Title	SRC-1, a non-receptor type of protein tyrosine kinase, controls the direction of cell and growth cone migration in <i>C. elegans</i>
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学位論文名	SRC-1, a non-receptor type of protein tyrosine kinase, controls the direction of cell and growth cone migration in <i>C. elegans</i> (線虫SRC-1は細胞移動と軸索伸長の方向を制御する)
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論文内容の要旨

Src family tyrosine kinase (SFK) has been implicated in the regulation of cell adhesion and migration during animal development. Here I show that SRC-1, an orthologue of SFK, plays an essential role in directing cell migration in *Caenorhabditis elegans*. The mutation in the *src-1* gene results in defective distal tip cell (DTC)-directed gonad morphogenesis in an activity-dependent and DTC cell-autonomous manners. In the *src-1* mutants, DTCs fail to turn and continue their centrifugal migration along the ventral muscles. The effect of the *src-1* mutation is suppressed by mutations in genes that function in the CED/Rac pathway, suggesting that SRC-1 in DTCs is an upstream regulator of a Rac pathway that controls cytoskeletal remodeling. In the *src-1* mutant, the expression of *unc-5*/netrin receptor is normally regulated, and either the precocious expression of UNC-5 or the mutation in the *unc-5* gene does not significantly affect the DTC migration defect. These data suggest that SRC-1 acts in the netrin signaling in DTCs. The *src-1* mutant also exhibits cell-autonomous defects in the migration and growth cone path finding of Q neuroblast descendants AVM and PVM. However, these roles of SRC-1 do not appear to involve the CED/Rac pathway. These findings show that SRC-1 functions in responding to various extracellular guidance cues that direct the cell migration via disparate signaling pathways in different cell types.

論文審査の結果の要旨

申請者は、Src family kinase (SFK) の線虫 orthologue である SRC-1 の機能を解析し、細胞移動と軸索伸長の制御に不可欠な働きをしていること明らかにした。線虫 *src-1* mutant は、生殖巣形成を導く distal tip cell (DTC) の移動に異常が観察され、正常な DTC 移動には SRC-1 の kinase 活性が必須であることを見いだした。さらに、*src-1* mutant では神経細胞の移動や、軸索伸長方向の異常も確認され、SRC-1 が細胞移動の方向の制御を指揮していることを明らかにした。また、SRC-1 に結合する分子のスクリーニングを行い、Wnt シグナル関連因子である PRKL-1 を同定しており、SRC-1 と Wnt シグナルとの関連性を十分に考察しており、本審査を受けるに値すると考える。

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学位授与の要件 学位規則第4条第1項該当

生命機能研究科生命機能専攻

学位論文名 Roles of C-terminal Src Kinase in Epithelial Construction and Maintenance
(表皮組織構築における SFK/Csk の生理的機能解析)

論文審査委員 (主査)

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論文内容の要旨

Carboxy-terminal Src kinase (Csk) is a negative regulator of Src family tyrosine kinases (SFKs) which play pivotal roles in controlling cell adhesion, migration and cancer progression. To elucidate the *in vivo* role of Csk in epithelial tissues, I conditionally inactivated Csk in squamous epithelia using the keratin-5 promoter/Cre-loxP system in mice. The mutant mice developed apparent defects in the skin, esophagus and forestomach, with concomitant chronic inflammation and epithelial hyperplasia. Analysis of primary keratinocytes showed that the expression of mesenchymal marker proteins, matrix metalloproteinases (MMPs) and the proinflammatory cytokine TNF- α were elevated in the mutant cell. These aberrant gene expressions could be suppressed by anti-inflammatory reagent FK506 through inactivation of Calcineurin and NF- κ B pathway. Furthermore, treatment with the anti-inflammatory reagent FK506 rescued hyperplasia in the mutant epidermis, indicating that epidermal hyperplasia was associated with inflammation. Analysis of the susceptibility of Csk hetero-mutant mice to two-stage skin carcinogenesis revealed that papillomas arose earlier and in greater numbers compared with those of wild-type littermates did. It suggested that SFK activity was strictly regulated by Csk and deregulation of them promoted papilloma formation. Histology of the mutant epidermis revealed delayed differentiation and impaired cell-cell adhesion in the basal cell layers. Primary cultured keratinocytes also showed defects in formation of cell-cell adhesion and cytoskeletal remodeling. Defective cell-cell adhesion observed in mutant keratinocytes was found to be accompanied with irregular cytoskeletal remodeling by altered Rac1/RhoA activity. In addition, mitotic defects were caused by downregulation of RhoA activity in the mutant keratinocytes. Fluorescent resonance energy transfer analysis also showed that Rac1/RhoA was activated at multiple places of cell periphery in the mutant keratinocytes, which might account for the loss of cell polarity by Csk inactivation. These observations suggest that the SFK/Csk circuit plays crucial roles in development and maintenance of epithelia by controlling cellular cytoskeletal organization, cell polarity as well as phenotypic conversion linked to inflammatory events.

論文審査の結果の要旨

申請者は、非受容体型チロシンキナーゼファミリーSFK の抑制因子 Csk を表皮組織特異的にノックアウトしたマウスを作製し、その表現型発現機構の解析を行なった。その結果、Csk ノックアウト表皮角化細胞から分泌される TNF- α や MMP9 によって誘導される表皮下の炎症によって表皮の過形成が生じること、さらには活性化された Rac1 によって細胞骨格形成のバランスが変化し、細胞間接着形成不全を引き起こすことを明らかにした。そして、多段階的発がんモデル実験によって、SFK/Csk のシグナルががんの形成促進に寄与し得ることを示した。

以上、申請者による研究は、未解決とされる SFK/Csk シグナルとがんとの関わりの理解につながるものであり、学位の授与に値すると考えられる。