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Form 3

Abstract of Thesis

Name (NGUYEN QUYNH MAI)	
Title	A novel function of LAR clustering in cytoneme-like membrane protrusions formation （ＬＡＲ分子によるサイトネーム様突起形成に及ぼすクラスター化の意義）

Abstract of Thesis

Intercellular communication between cells distally located from each other can be assured by the formation of membrane protrusions that elongate from one cell to its target and function as conduits for the trafficking of various signaling factors. One type of the membrane protrusions called “cytonemes” – defined as thin, close ended protrusions enriched in actin filaments – is receiving more attentions in regards to its formation in many types of cells supporting numerous events like: establishment of the morphogen gradients, pattern formation, directed morphogenesis, and maintenance of the stem cell niche. Despite their crucial roles in cell signaling, the molecular mechanism by which cytonemes are established and maintained, however, remains elusive. In this study, I showed that the leukocyte common antigen-related (LAR) protein tyrosine phosphatase receptor plays an important role in cytoneme-like membrane protrusions formation. Exogenous expression of LAR in the human derived cell line induced formation of actin rich thin membrane protrusions, some of which exceed lengths of 200 μm and displayed a complex morphology with branches. To address how LAR functions in the cytoneme-like protrusions formation, I focused on the regulation of LAR dimerization/oligomerization by the extracellular matrix components: heparan sulphates (HS), chondroitin sulphates (CS) and the resulting regulatory effects on LAR phosphatase activity. Longer and more branched LAR-induced cytoneme-like membrane protrusions were observed with HS application compared to vehicle or CS treatments. These results were supported with the fact that a newly established rapamycin-induced LAR dimerization system also displayed significant increase in the formed longest protrusion length and complexity. Interestingly, although the truncated form of LAR entirely lacking the phosphatase-related domains D1 and D2 (LAR_ΔD1D2) resulted into promotion of cytoneme-like protrusions formation, the phosphatase-inactive forms did not show clear changes suggesting that LAR clustering triggers formation of a molecular assembly that activates the formation of cytoneme-like protrusions in a phosphatase-independent manner. Altogether with the fact that axon (a well-known type of membrane protrusion formed in neurons) and cytonemes formation machineries share common cytoskeletal regulating factors like Arp2/3, Ena/VASP, Rac1, the current study results hint on the existence of a common molecular mechanism for membrane protrusions establishment in the cell-to-cell contact formation, the one in which LAR is a key player.

様式７

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

申請者Nguyen Quynh Maiは、軸索側枝形成における受容体型チロシンホスファターゼの一つであるLARの機能解明を研究する過程で、同分子が培養細胞において細く長い突起を誘導する現象を見出した。誘導される細く長い突起は、一般にサイトネームと呼ばれる突起に類似した形態をとり、突起内はアクチンを主成分とすることを見出した。さらに、同分子が二量体を形成することがこのサイトネーム様突起形成に重要であり、細胞外マトリックスを構成するヘパラン硫酸が同分子の二量体形成を促し、かつこの突起形成を促す役割を持つことを明らかにした。いまだその形成に関わる分子機構が完全には解明されていないサイトネームを含む細く長い突起の形成に対し、独自に系を組み立て、その性質を特定の分子の存在様式と合わせ解明をすすめたことは意義が大きく、新たな生命現象の解明となる可能性を秘めた研究成果として評価できる。ゆえに、論文は博士の学位を授与するに値するものと認める。