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# 学位論文抄録

HIV-1 Nef-induced activation of the Src kinase Hck and its altered trafficking to the Golgi apparatus affecting the protein glycosylation process
（HIV-1 NefによるSrc kinase Hck の活性化とゴルジ体での局在がタンパク質の糖鎖付加過程に影響を及ぼす）

ハッサン　ラニヤ

Hassan, Ranya

熊本大学大学院医学教育部博士課程病態制御学専攻予防開発学

指導教員

岡田　誠治教授
熊本大学大学院医学教育部博士課程医学専攻予防開発学

**Abstract of the thesis**

[Background]

Human immunodeficiency virus type 1 (HIV-1) Nef accelerates the progression to AIDS by binding with and activating a Src tyrosine kinase Hck, but underlying molecular basis is not understood. A recently reported specific output of Nef-Hck binding was the inhibition of the function of a macrophage-specific cytokine M-CSF through inhibition of glycosylation maturation/intracellular trafficking of its receptor Fms, a possible trigger of uncontrolled immune system.

[Purpose and methods]

In this study, we attempted to clarify the underlying molecular mechanism of the new function of HIV-1 pathogenetic protein Nef, i.e. the inhibition of host cell protein trafficking and glycosylation machinery, by using mutants of Nef and Hck, and chemicals, in particular, a newly-identified Nef-targeting small-molecule compound.

[Results and discussions]

A striking change in Hck induced by Nef other than activation was its skewed localization to the Golgi due to predominant Golgi-localization of Nef. Studies with different Nef alleles and their mutants showed a clear correlation among higher Nef-Hck affinity, stronger Hck activation, severe Golgi-localization of Hck and severe Fms maturation arrest. Studies with a newly-discovered Nef-Hck binding blocker 2c more clearly showed that skewed Golgi-localization of active Hck was indeed the cause of Fms maturation arrest. 2c blocked Nef-induced skewed Golgi-localization of an active form of Hck (Hck-P2A) and Fms maturation arrest by Nef/Hck-P2A, but showed no inhibition on Hck-P2A kinase activity. These results indicated that aberrant dual regulation of Hck, activation/localization at Golgi, was the direct cause of Fms maturation arrest by Nef. Our finding also establishes an intriguing link between the pathogenesis of Nef and a newly emerging concept that the Golgi-localized Src kinases regulate the Golgi function.