学位論文内容の要旨

（Summary of dissertation）

博士の専攻分野の名称　博士（医　学）　氏名　ラニア ハッサン モハメド ハッサン

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学位論文題名

（Title of dissertation）

The *SKINT1*-like Gene Is Inactivated in Hominoids But Not in All Primate Species: Implications for the Origin of Dendritic Epidermal T Cells

（ヒト及び類人猿で不活化している SKINT1 様遺伝子の旧世界ザルでの機能残存と樹状表皮 T 細胞の由来に関する検討）

Background: The $\gamma\delta^+$ dendritic epidermal T-cells (DETCs) are the residential T-cells in mouse epidermis expressing the invariant Vγ5Vδ1 TCR and have a critical role for skin immunosurveillance and homeostasis. DETCs are generated by positive selection in the fetal thymus during the narrow period from embryonic day 14.5 to 18.5, after which they migrate to the skin. *Skint1* gene is composed of 7 coding exons expressing an immunoglobulin protein exclusively in thymic epithelial cells and keratinocytes at embryonic day 15 and continue to adulthood. *Skint1* duplicated in mice to form *Skint* family which is in turn considered as a member of butyrophilin (*BTN*) family. Skint-1 protein is suggested as the first and indispensible component for selection of the invariant DETC. Rat and cow have Skint1 orthologs with protein topology and structure similar to that of mouse, in addition, they have high population of DETC-like cells expressing γδ TCR with limited variability. In contrast, Skint1 has multiple in-frame premature termination codons in both human and chimpanzee, moreover, humans don't posses neither high population nor monomorphic epidermal γδ T cells. It is noteworthy that the presence of Skint1 is correlated with presence of a restricted cutaneous T cell population. It will be of particular interest to determine when Skint1 rendered inactive in the mammalian phylogeny and concomitantly DETCs are lost.

Methods: To detect at which stage in primate evolution *Skint1* inactivation took place, we analyzed the predicted SKINT1L sequences in primate species. We called here *Skint1* of all mammalian species other than mice as *SKINT1L*. Cloning and sequencing were done to characterize the *SKINT1L* of cynomolgus

macaque as a representative of Old World Monkeys (OWM). Using RT-PCR and immunohistochemical staining, we also examined the epidermal γδ T cell population in cynomolgus macaque investigating the functionality of SKINT1L. To better understand the evolution of the *Skint1/SKINT1L* gene family, and more generally the entire *SKINT* gene family, we extended our bioinformatics to mammals other than primates.

Results: We found that all hominoids *SKINT1L* has a common inactivating mutation, but that Old World monkeys have apparently functional *SKINT1L* sequences and the epidermal resident γδ T cells in cynomolgus macaques contains a population of dendritic-shaped γδ T cells expressing an invariant Vγ10Vδ1 T-cell receptors. We demonstrated also that *SKINT1L* emerged in an ancestor of placental mammals, but was inactivated or lost multiple times in mammalian evolution.

Discussion and conclusions: *SKINTL* family and in turn *SKINT1L* are highly evolved through the mammalian evolution, They have been emerged in an ancestor of eutheria and lost or inactivated multiple times in the mammalian phylogeny which suggest a concomitant loss of the skin-resident γδ T cells in the orders lacking in consequence to *SKINT1L* deficiency.