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Title	Essential role of CARD14 in murine experimental psoriasis
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Citation	大阪大学, 2017, 博士論文
Version Type	
URL	https://hdl.handle.net/11094/69259
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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

乾癬とは日本人にはあまり馴染みのない慢性の皮膚角化疾患であるが、白色人種では人口の1-2%を占めると言われ、近年、日本においても食生活や環境の変化に伴い患者数の増加が報告されている。また、生物学的製剤の開発により、新たな治療法と発症メカニズムにも注目を浴びている。しかしながら、病因の解明には未だ不明な点が多く、更なる解明が望まれている。本発表では病態関連因子として挙げられているCARD14分子の新規ノックアウトマウスを使用し、乾癬病態解明の新たな手掛かりを見出した。

特にCARD14KOマウスではイミキモド誘導性乾癬モデルに抵抗性を示し、それらは炎症時に表皮に移行してくるgd T細胞が産生するIL-17とIL-22の産生に関与していることを明らかとした。

これらの研究成果は学位の授与に値すると考えられる。

論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	田中　麻優里
論文題名 Title	Essential role of CARD14 in murine experimental psoriasis (乾癬マウスモデルにおけるCARD14の重要な役割)

論文内容の要旨

〔目　的(Purpose)〕

Psoriasis is a chronic inflammatory skin disorder that is predominantly characterized by sharply demarcated chronic erythematous plaques. Although its etiological mechanisms are largely unknown, recent evidence suggests that the topical application of imiquimod (IMQ) cream causes psoriasis-like skin inflammation in humans and mice. Recently, caspase recruitment domain family member 14 (CARD14), encoded at the psoriasis susceptibility locus 2 (PSORS2) located in human chromosomal region 17q25.3, was shown to have carry unique gain-of-function mutations associated with psoriasis. Because little is known about the immunological role of CARD14 in psoriasis-form skin inflammation *in vivo*, we evaluated its immunological function in murine psoriasis-like models. In this study, we examine pathophysiological role of CARD14 in IMQ-induced psoriasiform skin inflammation by generating *Card14*$^{-/-}$ mice.

〔方法ならびに成績(Methods/Results)〕

We examined the role of CARD14 in murine experimental models of psoriasis induced by either IMQ cream or recombinant IL-23 injection. The psoriasiform skin inflammation was abrogated in *Card14*$^{-/-}$ mice in both models, however *Tlr7*$^{-/-}$*Tlr9*$^{-/-}$ mice were failed to prevent IL-23-induced psoriasis model. Next, we examined whether IL-23p19 production or characteristic gene signatures induced by IL-23 are affected in *Card14*$^{-/-}$ and *Tlr7*$^{-/-}$*Tlr9*$^{-/-}$ mice by IMQ treatment. We analyzed the gene expression profile of the treated skin at 4 h after IMQ cream treatment by microarray and found that the gene expression profiles of the *Card14*$^{-/-}$ and *Tlr7*$^{-/-}$*Tlr9*$^{-/-}$ mice were similar, but distinct from other control groups such as WT, *Tlr7*$^{-/-}$ or *Tlr9*$^{-/-}$ mice. Furthermore, we sorted the potential IL-23p19-producing cells from the ear skin of mice after IMQ cream treatment for 4 h. These data indicate that IL-23p19-producing Langerin^{+} LCs are a characteristic feature of psoriasis, but their levels differ in the early responses between *Card14*$^{-/-}$ and *Tlr7*$^{-/-}$*Tlr9*$^{-/-}$ mice. We have confirmed IL-17-producing dermal γδ T cells and found that the number of Vγ4^{+} T cells producing IL-17 and IL-22 in the IMQ cream treated skin were increased predominantly in the epidermis, which is the most importantly prevented in *Card14*$^{-/-}$ mice. Our results suggest that CARD14 is necessary for the IMQ-mediated production of IL-17 and IL-22 by γδ T cells.

〔総　括(Conclusion)〕

Comparison of early gene signature of the skin between IMQ cream-treated *Card14*$^{-/-}$ mice and *Tlr7*$^{-/-}$*Tlr9*$^{-/-}$ mice revealed not only their similarity, but also distinct gene sets targeted by IL-23. Cell type specific analysis of these mice identified skin Langerin^{high} langerhans cells as a potent producer of IL-23, which was dependent on both TLR7 and TLR9, but independent of CARD14, suggesting that CARD14 is acting downstream of IL-23, not TLR7 or TLR9. Instead, bone marrow chimera study suggested that CARD14 in radio-sensitive hematopoietic cells were required for IMQ-induced psoriasiform skin inflammation, controlling the number of Vγ4^{+} T cells producing IL-17 or IL-22 infiltrating through dermis to the inflamed epidermis. These data indicate that CARD14 is essential and a potential therapeutic target for psoriasis.