Isao Matsuura et al., J Clin Exp Dermatol Res 2017, 8:4 (Suppl)
DOI: 10.4172/2155-9554-C1-060

Evaluation of familial primary cutaneous amyloidosis (FPCA)-derived mutation in the OSMRβ subunit of IL-31 receptor

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Primary cutaneous amyloidosis (PCA) is an itchy skin disorder that is relatively common in South America and South east Asia. The disease is not life threatening, but chronic itch and unsightly appearance of the skin affect patients' quality of life. There are multiple forms: Macular, lichen and nodular amyloidosis, but amyloid deposition in the papillary dermis is the cardinal feature of the disease. The amyloid deposition is thought to be caused by cellular debris from apoptosed keratinocytes. Most of PCA cases are sporadic, but autosomal dominant inheritance has also been identified (familial PCA, FPCA). The mechanism being unknown, there is no radical cure of the disease. Genetic analyses of FPCA patients have revealed a link between the disease and the missense mutations in the interleukin-31 (IL-31) receptor subunits. We previously reported the same mutations from FPCA patients in sporadic cases, suggesting the significant contribution of these mutations in the skin disease. The IL-31 receptor consists of two subunits, OSMRβ and IL-31RA. All the mutations found in FPCA localize in the membrane proximal fibronectin III (FNIII) domain of either subunit. Several mutations have been identified in the OSMRβ subunit that is also engaged with other IL-6-type cytokine receptors, while only one mutation has been reported in IL31RA that is specific to the IL-31 receptor. We have previously shown that the FPLCA-derived mutation S521F in the IL-31RA subunit of the receptor impacts monocyte chemotactic protein-1 (MCP-1) production from HaCaT, a human keratinocyte cell line. In the current study, we introduced FPCA-derived mutations in OSMRβ in HaCaT by CRISPR/Cas9-based gene editing. We observed impaired production of MCP-1 from the cells harboring all the mutations tested. This result demonstrated that the impaired MCP-1 production is a common consequence with the mutated receptor subunit of the IL-31 receptor in PCA. Since MCP-1 plays a key role in attracting innate immune cells to keratinocytes to clear cellular debris, the impaired MCP-1 production by the IL-31 receptor mutations may be an important part of the pathogenesis of the skin disease.

Biography

Isao Matsuura has been working on signal transduction studies for most of his career. His current research interests include transforming growth factor-b (TGF-b) and Interleukin-31 (IL-31) signaling in diseases. The former signaling pathways are involved in cancer development and metastasis, while the latter in an itchy skin disease called primary cutaneous amyloidosis (PCA) that is relatively common in Taiwan.

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