学 位 論 文 の 要 旨

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学 位 論 文 名　Role of interleukin-15 in development of the mouse olfactory nerve

発 表 雑 誌 名（巻，初頁～終頁，年）　Congenital Anomalies (in press)

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論 文 内 容 の 要 旨

INTRODUCTION

Interleukin (IL)-15 is a cytokine that shares biological activities and receptor components with IL-2. IL-2 and IL-15 bind their unique respective receptor subunits, IL-2 receptor alpha and IL-15 receptor alpha (IL-15Rα). *IL-15* and *IL-15R* mRNAs are expressed in various cell types and tissues including nerve cells and the brain. Both IL-15 and IL-15Rα are expressed throughout the central nervous system of fetal mice and humans. IL-15 expression in mouse brain including olfactory bulb (OB) and olfactory nucleus was reported, while a role of IL-15 in the olfactory nervous system remains unknown. Here, we provide evidence for a novel role of IL-15 in the mouse olfactory nervous system.

MATERIALS AND METHODS

The expression of *IL-15* and *IL-15Rα* mRNAs and proteins were examined by RT-PCR and immunohistochemistry. We compared the IL-15 and

IL-15Rα expression with olfactory neurons marker, growth-associated protein (GAP)-43, a marker of immature neuron, and olfactory marker protein (OMP), a marker of mature olfactory neurons, at embryonic day (E) 14.5 and 18.5. We counted the total number of cells as well as OMP-positive, single-stranded DNA (ssDNA)-positive and proliferating cell nuclear antigen (PCNA)-positive cells within the olfactory epithelium (OE) for comparison with IL-15Rα knock out (IL-15Rα$^{-/-}$) and wild-type mice. We also measured the area of the olfactory neuron bundle in the lamina propria. Data were statistically analyzed using Scheffé's post hoc test and $P < 0.05$ was regarded as significant.

RESULTS AND DISCUSSION

We found by RT-PCR that *IL-15* and *IL-15Rα* mRNAs were expressed in the OE and OB. Immunohistochemistry showed that IL-15 and IL-15Rα were expressed in the OE. At E14.5, IL-15 staining was detected in the axons of olfactory neurons, and was colocalized with GAP-43. Like IL-15 staining, IL-15Rα immunostaining was co-localized with GAP-43 in olfactory neuron axons, besides it was detected in the OE. At E18.5, IL-15 and OMP stainings were overlapped in bundles of olfactory neurons and the OE. Likewise, IL-15Rα immunostaining was co-localized with OMP. To understand the role of IL15 in olfactory neurogenesis, we first compared the number of OMP-positive cells and the area of OMP-positive olfactory nerve bundles in the lamina propria between adult IL-15Rα$^{-/-}$ and wild-type mice. OMP-positive cells and the area of OMP-positive olfactory nerve bundles were fewer in IL-15Rα$^{-/-}$. We next counted PCNA-positive cells in the OE, since PCNA is a marker of the early G1 and S phases of the cell cycle. Male IL-15Rα$^{-/-}$ mice contained significantly fewer PCNA-positive cells than male wild-type mice, whereas female IL-15Rα$^{-/-}$ and wild-type mice did not significantly differ in PCNA-positive cell number. The

distinctive profiles between males and females suggest that compensatory mechanisms for IL-15 signaling function in female mice. The number of ssDNA-positive cells did not significantly differ. Thus, IL-15 is an important factor for olfactory neurogenesis and it might be related with involved in the pathogenesis of neurological disorders involving cytokine dysregulation.

CONCLUSION

The present results have demonstrated the evidence for a role of IL-15 in olfactory neurogenesis. IL-15 and IL-15Rα were expressed in neuronal precursor cells by RT-PCR and immunohistochemistry. In adult IL-15Rα$^{-/-}$ mice, numbers of mature olfactory neurons, but not non-neuronal or proliferating cells, in the olfactory epithelium were less than those in wild-type mice. These results suggest that IL-15 plays an important role in regulating neuronal proliferation during olfactory neurogenesis.