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Article / Book Information

題目(和文)	Trpm5陽性化学感覚細胞における転写因子Skn-1a/Pou2f3の機能解析
Title(English)	
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論 文 要 旨

THESIS SUMMARY

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学生氏名： Student's Name	山下　純平	指導教員（主）： Academic Supervisor(main)	廣田　順二
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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

The transient receptor potential channel M5 (Trpm5) was first identified in sweet, bitter, and umami taste cells, and plays a critical role in taste signaling as a non-selective monovalent cation channel. Interestingly, Trpm5-expressing cells have been also identified in several specialized cells in the extraoral tissues. For example, solitary chemosensory cells in the nasal respiratory epithelium and brush cells in the tracheal epithelium characterized by an apical tuft of microvilli exhibit taste cell-like molecular characteristics by expressing taste receptors and their downstream signaling molecules such as Gnat3, Plcb2, and Trpm5. These cells respond to classical bitter substances and bacterial signaling molecules, inducing protective respiratory reflexes and a neurogenic local proinflammatory response. Recent works show that intestinal tuft cells expressing Trpm5 release interleukin-25 to initiate type II immune response and clear the gut from the parasites such as helminthes and protozoa. These findings suggest that Trpm5-expressing cells function as a gatekeeper of biophylactic reactions.

Skn-1a is required for the generation of Trpm5-expressing taste cells (sweet, umami, and bitter taste cells). Its loss-of-function mutation expanded the sour taste cells population at the expense of Trpm5-expressing taste cells. Thus, Skn-1a functions as an early determinant of the differentiation to Trpm5-expressing taste cells. Given the similarity of molecular characteristics and cellular morphology among Trpm5-expressing cells in the multiple tissues, I hypothesized that Skn-1a is also involved in the generation of Trpm5-expressing chemosensory cells in the multiple tissues other than taste buds. In this study, I examined the expression and function of Skn-1a in Trpm5-expressing cells in multiple tissues to test this hypothesis.

First, I investigated the expression of Skn-1a in the main olfactory epithelium (MOE), because a population of microvillous cells in MOE expresses Trpm5. In situ hybridization analyses revealed Skn-1a is expressed mainly in Trpm5-expressing microvillous cells. To examine the impact of Skn-1a deficiency on Trpm5-expressing microvillous cells, I examined the expression of marker genes (Trpm5, villin and ChAT) for these cells in the Skn-1a-deficient mice. The expression of Trpm5, villin and ChAT was completely absent in Skn-1a-/- MOE, but observed in Trpm5-positive cells in the MOE of wild-type mice. These results showed that Skn-1a is required for the generation of Trpm5-microvillous cells.

Next, I extended our expression and functional analyses of Skn-1a to the multiple tissues, including nasal respiratory epithelium, trachea, auditory tube, urethra, thymus, pancreatic duct, stomach, small intestine and large intestine. Two-color ISH analysis revealed that Skn-1a was expressed in almost all Trpm5-expressing cells in all tissues examined. Immunostaining using antibodies against Trpm5 and villin showed that Trpm5 and villin-double positive cells observed in wild-type mice were completely absent in Skn-1a-/- tissues. Additionally, expression of other marker genes for Trpm5-expressing cells is also absent in Skn-1a-/- tissues. These results show that Skn-1a is required for the generation of Trpm5-expressing cells in these tissues.

Thus, I propose that Skn-1a functions as an essential regulator for the generation of Trpm5-expressing cells. The functions of Trpm5-expressing cells in auditory tube, thymus, pancreatic duct, stomach, and large intestine are currently not well understood. However, considering commonalities of molecular characteristics of Trpm5-expressing cells, it is conceivable that Trpm5-expressing cells in these tissues may also function as a gatekeeper of biophylactic reactions. Because Skn-1a-/- mice lack the Trpm5-expressing cells, further studies of Skn-1a-/- mice would elucidate the physiological roles of Trpm5-expressing cells in mice.