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| Title        | Granzyme A-Producing Type 1 Innate Lymphoid Cells Promote Salivary Secretion in the Aged Submandibular Gland                                          |
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| Citation     | 大阪大学, 2026, 博士論文                                                                                                                                      |
| Version Type |                                                                                                                                                       |
| URL          | <a href="https://hdl.handle.net/11094/105684">https://hdl.handle.net/11094/105684</a>                                                                 |
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論文内容の要旨  
Synopsis of Thesis

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| 氏 名<br>Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 阿部洋章                                                                                                                                                  |
| 論文題名<br>Title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Granzyme A-Producing Type 1 Innate Lymphoid Cells Promote Salivary Secretion in the Aged Submandibular Gland<br>(加齢顎下腺におけるグランザイムA産生1型自然リンパ球による唾液分泌促進) |
| 論文内容の要旨<br>〔目 的(Objective)〕<br>Salivary gland function declines with age, contributing to periodontitis and aspiration pneumonia. However, the cellular mechanisms that preserve secretion during aging remain unclear.<br><br>〔方法ならびに成績(Methods/Results)〕<br>Mice were stratified by aging stage, and saliva output and tissue histology were assessed. To infer cell–cell communication, regions surrounding lymphocyte clusters were microdissected and subjected to site-specific single-cell RNA sequencing. Epithelial cell responses were evaluated in a coculture system using a neutralizing antibody. Finally, physiological relevance was assessed by <i>in vivo</i> depletion, followed by quantification of changes in saliva secretion.<br>Saliva production was maintained or modestly increased during early aging stages and coincided with the emergence of lymphoid cell clusters. Single-cell and interactome analyses identified <i>Gzma</i> <sup>+</sup> ILC1 subsets enriched in aged lymphoid cluster regions and predicted crosstalk with epithelial cells via a GZMA–Pard3 axis. Upregulation of epithelial <i>Aqp5</i> expression was confirmed <i>in vitro</i> . <i>In vivo</i> depletion of ILC1s in aged mice significantly reduced stimulated saliva output, indicating that local ILC1-derived GZMA supports secretory capacity.<br><br>〔総 括(Conclusion)〕<br>Aged submandibular salivary glands accumulated ILC1s that promote epithelial function through a GZMA-dependent pathway and increased AQP5 expression, thereby maintaining salivary secretion during early aging. These findings identify ILC1s as regulators of salivary gland homeostasis and highlight the GZMA–Pard3 axis as a potential therapeutic target. |                                                                                                                                                       |

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

一般に加齢によって唾液腺の機能が低下すると考えられてきた中で、マウスを用いて初期の老化段階では唾液分泌が増加することを明らかにした。解析の結果、老化に伴って唾液腺内にリンパ球クラスターが形成され、その周囲に存在するILC1という免疫細胞が唾液産生上皮細胞と相互作用していることを見出した。特にGZMAという分子をILC1が分泌することで唾液産生に必要なAQP5の発現を高めていた。マウス生体においてILC1を減少させると唾液分泌量が低下し、GZMAを直接唾液腺に投与すると唾液量が増加することがわかった。

以上より、本研究は老化初期においてはILC1が唾液分泌機能を促進し、口腔の健康維持に寄与していることを示したものであり、博士(医学)の学位授与に値する。