様式３

論　文　内　容　の　要　旨

氏　名　（　Xu Lin　）	
論文題名	Diminished retinoid signaling transforms the murine frontonasal mesenchyme into maxillary components. （低下したレチノイドシグナリングがマウスの前頭鼻突起中胚葉の遺伝子発現プロファイルを上顎の成分に変換する.）

論文内容の要旨

Vertebrate facial development depends on the correct specification of embryonic facial prominences, a process known to be governed by region-specific reciprocal signaling pathways between the craniofacial ectoderm and mesenchyme. This process is further modulated by transcriptional and epigenetic mechanisms that regulate the expression of essential genes in mesenchymal progenitors derived from cranial neural crest cells. Retinoid signaling plays a critical role in facial development, and its disturbance results in a wide spectrum of facial defects, including orofacial cleft. In this study, we identified retinoid signaling as a critical regulator of cranial neural crest cell specification toward a frontonasal process identity in mice. Eliminating *Rdh10*, which encodes a rate limiting enzyme required to produce all-trans retinoic acid, resulted in the ectopic formation of whisker pad - a derivative of maxillary process - within the frontonasal process region. This transformation was mediated by the mis-activation of maxillary specific transcription factors including MEIS2 and LHX6 which also exhibited increased chromatin accessibility at their consensus binding sites following the reduction of retinoid signaling in the frontonasal cranial neural crest cells. These results indicate that retinoid signaling acts as a master regulatory signaling pathway in specifying cranial neural crest cells into the frontonasal process, and its elimination could alter the molecular profile of these cells to maxillary process. These results not only advance our understanding of frontonasal prominence specification and the evolutionary development of craniofacial structures, but also offer valuable insights for addressing craniofacial malformations such as orofacial cleft.

様式７

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

本研究はマウス胎生期の前頭鼻突起の運命決定に胎生時期特異的なレチノイン酸シグナルが重要である事を示した。またレチノイン酸シグナルの不足は前頭鼻突起間葉の遺伝子発現プロファイルが上顎突起に類似したものに転換する事を示した。

以上より、本研究は胎生期の顔面発生メカニズム、特に前頭鼻突起の運命決定機構の一端を明らかにした。よって博士（歯学）の学位論文として価値のあるものと認める。