Form 3

# Abstract of Thesis

| Name ( WANG QI ) | |
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| Title | Disturbed cranial neural crest cell development caused by reduced sonic hedgehog signaling underlie the pathogenesis of retinoic-acid-induced cleft palate (レチノイン酸の過剰投与による口蓋裂はソニックヘッジホッグシグナルの低下による頭部神経堤細胞の細胞死により引き起こされる) |


Abstract of Thesis

Cleft palate is one of the most common congenital craniofacial anomalies in humans which is caused by genetic and environmental factors. Excessive intake of retinoic acid (RA) or its precursor, vitamin A, during early pregnancy is associated with increased incidence of cleft palate in offspring. However, the pathogenetic mechanism of cleft palate caused by excess RA is not fully understood. In order to investigate detailed cellular and molecular mechanism of retinoic-acid-induced cleft palate, we gave all-trans RA to ICR pregnant mice by gastric intubation from embryonic day 8.5 to 10.5 (E8.5 – E10.5). In RA treated group, we found disturbed expression pattern of *Sox10*, which marks cranial neural crest cells (CNCCs) in the trigeminal region at E9.5. This disruption of CNCCs also existed at the maxillary component of the first branchial arch at E10.5 which is known to give rise into secondary palatal shelves. Moreover, we found significant elevation of apoptotic cell death in *Sox10* positive CNCCs at E9.5 in RA treated group. For investigating possible molecular mechanism underlies this pathogenesis, we focused on Sonic hedgehog (*Shh*) signaling pathway from our previous RNAseq result. Interestingly, *Shh* and its downstream genes *Ptch1* and *Gli1* were perturbed in the developing face at E9.5 of RA-treated embryos. Consistently, the incidence of cleft palate and CNCC apoptosis due to overdose RA was reduced by administration of SAG (*Shh* signaling agonist). Altogether, our results suggest that one of the critical mechanism of retinoic-acid-induced cleft palate associate with elevated cell death of CNCCs through the down-regulation of *Shh* signaling pathway.

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

本研究は口蓋裂発症の原因として、レチノイン酸シグナルとソニックヘッジホッグシグナルの相互作用が関与する事を明らかにしたものである。本研究結果は口蓋裂の発症メカニズムの一部を解明し、新たな診断法や治療法を開発する上で重要な知見を与えるものであり、博士（歯学）の学位を授与するに値するものと認める。