［課程－２］

審査の結果の要旨

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The H3K27me3 modification is erased by two similar members of the lysine demethylase family namely. Ubiquitously transcribed tetratricopeptide repeat, X chromosome (UTX) and Jumonji domain- containing 3 (JMJD3). H3K27 demethylases are known to activate gene expression by removing the repressive H3K27me3 mark from chromatin which leads to an open chromatin conformation allowing transcription factors to have access to genes. Through positively regulating gene expression, H3K27 demethylases have been found to have various roles including in development. In this study, Ms. Daisy aimed at examining the role of Utx in the development of the mouse retina and her results were as follows:

1. By co-immunostaining the proliferation marker Ki67 and Utx marker; Ms. Daisy found that Utx was expressed in the neuroblastic layer (containing retinal progenitor cells and differentiating neurons) and the ganglion cell layer in early retinal developmental stages. As development progressed, Utx was expressed in post-mitotic cells of the inner neuroblastic layer and in the mature retina it was expressed in the inner nuclear and ganglion cell layers.

2. On RT-qPCR, Utx was stably expressed from developmental to adult stages. This is unlike its counterpart Jmjd3 which was shown in another study to be expressed highly in mid postnatal development but was expressed less in early developmental and adult stages.

3. Loss of function experiments in vitro and in vivo showed a significant decrease in the number of PKCα-expressing rod bipolar cells as well as a reduction in pan bipolar cell number.

4. Other bipolar subtypes which are cone ON and cone OFF bipolar cells were not affected by the loss of Utx. Also, other retinal cell types were not affected by the loss of Utx.

5. Staining Utx conditional knockout (Utx cKO) retinae with the Ki67 and active caspase-3 markers of proliferation and apoptosis respectively, did not show any difference from wild type retinae.

Ms. Daisy therefore revealed that Utx is expressed stably at all mouse retinal stages unlike Jmjd3. Also, that Utx is important in the differentiation of rod bipolar cells of the mouse retina which has not been studied before. As Utx did not decrease proliferation of retinal progenitor cells it may be involved in terminal differentiation or maturation of rod bipolar cells.

This information provides a foundation for examining the molecular mechanisms of Utx in regulating rod bipolar cell differentiation in future. In another study done by members of her lab, Jmjd3 was also found to regulate differentiation of bipolar cells by derepressing bipolar specific genes through H3K27 demethylation. It is important to find out whether the phenotype of Utx was caused by H3K27 demethylase-dependent mechanisms as was the case of Jmjd3 or demethylase- independent mechanisms. In addition, there is a plan to examine the functional interactions of Utx and Jmjd3 in regulating rod bipolar cell development using conditional Utx/Jmjd3 double knockout mice.

よって本論文は博士(医学)の学位請求論文として合格と認められる。