論文の内容の要旨

Elucidation of cell types of maternal microchimeric cell population in mice fetus

（胎児に移入する母由来細胞の細胞種の解明）

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During pregnancy in placental mammals, small numbers of maternal cells (maternal microchimeric cells, or MMc cells) migrate into the fetus and persist decades, or perhaps for the rest of their lives. Given this inheritance, microchimerism can also be regarded as cell-level epigenetics. While migration of MMc cells into fetus is considered to occur in all pregnant cases, higher frequencies of MMc cells are reported in variety of phenomena, such as immune tolerance, tissue repair, and autoimmune diseases. However, it is not known what makes MMc cells involved in such a variety of phenomena. One possibility would be that number of MMc cells may differ among different individual embryos, however, no study so far has verified this possibility. Alternatively, it is also possible that repertoire of cell types and distribution of MMc cells differ in each individual embryo.

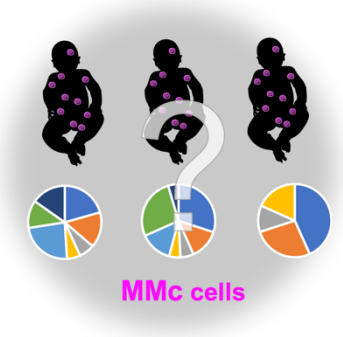

Figure 1 What kind of cell population (number and cell type) is MMc cells in fetus?

Here, for the first time, I developed a whole embryonic detection method for MMc cells using transgenic mice and counted live MMc cells in each individual embryo. Using this technique, I found that the number of MMc cells was comparable in most of the analyzed embryos; however, around 500 times higher number of

MMc cells was detected in one embryo at the latest developmental stage. This result suggests that the number of MMc cells could largely differ in rare cases with unknown mechanisms.

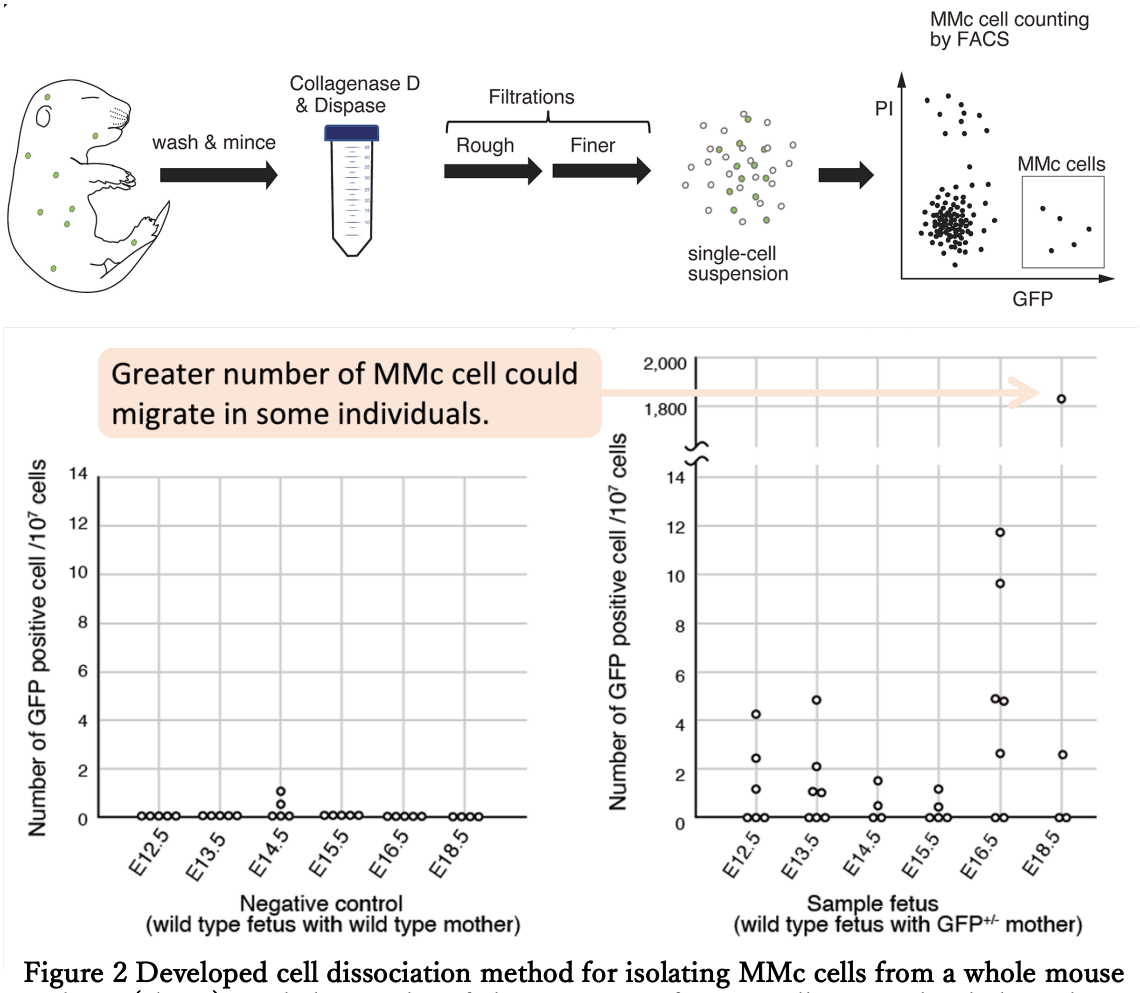

Figure 2 Developed cell dissociation method for isolating MMc cells from a whole mouse embryo (above), and the results of the counting of MMc cells on each whole embryo (below).

In addition, I also revealed repertoire of MMc cell types in whole embryos of early phase of MMc cell migration, namely E14.5 in mice, and estimated the cell types using single cell RNA-seq, gene expression profiling technique. In addition to the immune cell types which were often reported in previous studies, I found that there are other cell types such as cells that are considered to be terminally differentiated, and under proliferation. These imply that embryos receive variety of non-inherited maternal antigens (NIMAs) through MMc cells, and could be contributing to immunological tolerance against maternal antigens. In addition, terminally differentiated maternal cell reported in some case of patients could directly be contributed by these differentiated cells, rather than differentiation from undifferentiated stem MMc cells. Furthermore, I found that all the isolated MMc cells commonly expressed genes of two

transmembrane proteins that are known to be involved in cell migrations. This provides possible basis for understanding how MMc cells migrate from maternal side to fetal side. These data provide a hint toward understanding the biological roles of MMc cells and mechanisms underlying the variety of apparently inconsistent MMc-related phenomena.

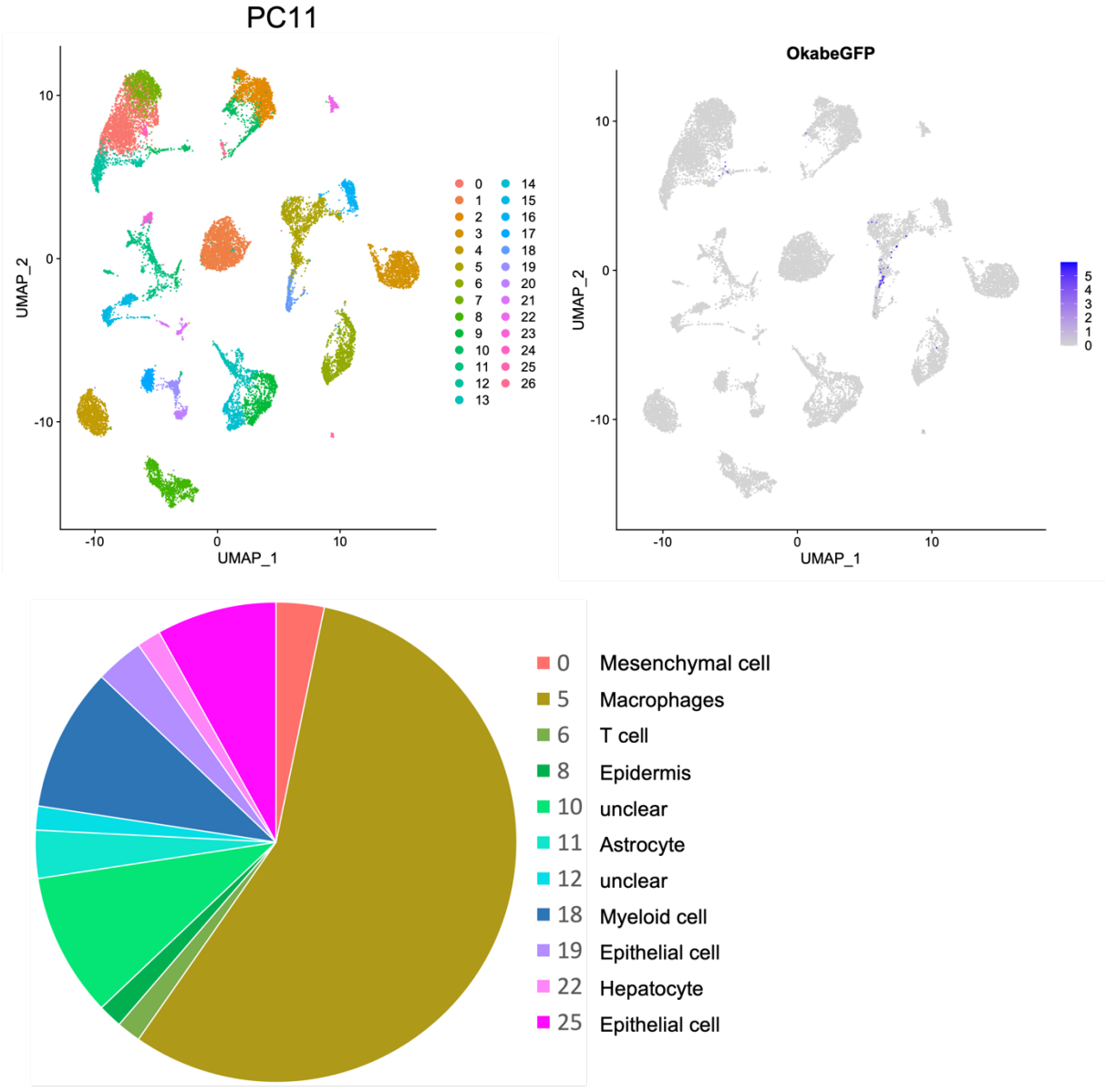

Figure 3 Clustering MMc cells and Tabula Muris data for MMc cell type estimation (above). The position of MMc cells in the clusters were shown as OkabeGFP because all isolated cells were expressed OkabeGFP. Pie chart showing the ratio of each estimated cell type in the isolated cell popultaion (below), suggesting the whole population of MMc cells.