学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Essential roles of cholesterol-binding membrane protein TSPO2 in maturation and proliferation of erythroblasts in mice
（マウス赤芽球の成熟と増殖におけるコレステロール結合蛋白質 TSPO2 の役割）

Erythropoiesis is an essential process that produces sufficient numbers of the enucleated red blood cell (RBC) from the erythroid precursor cell. Previous studies have revealed the mechanisms for various morphologic and biochemical changes during erythropoiesis. However, the factors implicated in regulation of maturation and proliferation in erythroblasts remain yet to be fully defined. Based on an unexpected finding that the HK (high K^+) trait characterized with immature RBC phenotypes in dogs is associated with the TSPO2 gene (TSPO2) mutations, we previously examined erythropoiesis in HK dogs and found morphological abnormalities in late-stage erythroblasts, suggesting some important roles of TSPO2 in erythropoiesis. TSPO2 (translocator protein 2) is a cholesterol-binding transmembrane protein specifically expressed in late erythroblasts. The purpose of the present study was to investigate the function of TSPO2 in erythropoiesis. To do this, Tspo2 knockout ($Tspo2^{-/-}$) mouse models including $Tspo2^{-/-}$ mice and $Tspo2^{-/-}$ mouse ES cell-derived erythroid progenitor (MEDEP) cells were generated and the effects of Tspo2 on erythropoiesis were analyzed. $Tspo2^{-/-}$ mice consistently showed impaired cytokinesis with increased binucleated erythroblasts, resulting in compensated anemia and their red cell membranes had increased Na, K-ATPase, resembling the HK phenotype in dogs. Tspo2-deficient mouse ES cell-derived erythroid progenitor (MEDEP) cells exhibited similar morphological defects associated with a cell-cycle arrest at the G2/M phase followed by apoptotic cell death, resulting in decreased cell proliferation. $Tspo2^{-/-}$ MEDEP cells also exhibited a profound reduction in intracellular unesterified and esterified cholesterol, suggesting the Tspo2 aberration caused cholesterol depletion in erythroblasts. When the terminal maturation was induced, $Tspo2^{-/-}$ MEDEP cells showed delays in hemoglobinization, maturation-associated

phenotypic changes in CD44, CD71, and TER119 expression, and cell-cycle progression with no reduction in the number of cell division prior to enucleation. These findings imply that TSPO2 is essential for coordination of maturation and proliferation of late-stage erythroblasts during normal erythropoiesis possibly through regulation of cholesterol availability in erythroblasts. Although TSPO2 has been suggested to have a role in cholesterol redistribution in erythroblasts, the functional sequela of this observation was not defined. The present findings therefore have implicated a major functional role for TSPO2 in erythropoiesis.