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Characterization of progenitors for mouse fetal Leydig cells

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（胎仔ライディッヒ前駆細胞の解析）

区　　分　：甲

論　文　内　容　の　要　旨

Fetal Leydig cells (FLCs) appear in the interstitial space of fetal testes, and play pivotal roles for masculinization of fetuses through testosterone synthesis. Over the past two decades, the molecular mechanisms of FLC differentiation have been studied primarily with genetically modified animals. As the consequence, many transcription factors and growth factors implicated in FLC differentiation have been identified. However, to comprehend the mechanisms for FLC differentiation, functional correlation among the factors identified by those studies remains to be investigated. To investigate it, identification of progenitor cells for FLCs were essential. EGFP transgenic mice previously established in our laboratory provided us with two cell populations, one of which was strongly EGFP-labeled FLCs (S-EGFP cells) and the other was weakly EGFP-labeled interstitial cells (W-EGFP cells). By in vitro testis reconstruction studies using these EGFP-labeled cell populations, I showed for the first time that the interstitial W-EGFP cells differentiated to S-EGFP (FLCs), indicating that the progenitor cells for FLCs are included in the W-EGFP cell population. Comparison of the transcriptomes of the purified FLCs (S-EGFP cells) and the W-EGFP cells including the progenitors reveled expectedly an elevated expression of the steroidogenic genes in the former cells. Interestingly, the genes involved in other metabolic pathways such as energy production (glycolysis, TCA cycle, and oxidative phosphorylation) and syntheses for lipid and cholesterol were found to be activated in FLCs. Indeed, elevated oxygen consumption and ATP production were observed in FLCs. Investigation of W-EGFP progenitors by single cell transcriptome analyses revealed the presence of a unique fraction of cells, which were as if differentiating into FLCs. A few genes such as Thymosin □10 (Tmsb10) were identified as a transiently expressed gene in the cell population. As for metabolic genes, several glycolytic gene expressions were elevated in these particular cells. A nuclear receptor, Ad4BP/SF-1, has been known to be critical for FLC differentiation, and thus the expression is elevated in FLCs. Investigation of an FLC-specific enhancer of Ad4BP/SF-1 gene demonstrated that GLI transcription factors activate the gene expression at the downstream of hedgehog (HH) signaling. Functional investigation with in vitro testis reconstruction demonstrated that Tmsb10 potentially regulates FLC differentiation possibly through modulating HH signaling. Although additional studies are required to comprehend how Tmsb10 modulates the HH signaling, the present study advances our understanding of the molecular mechanisms underlying HH dependent FLC differentiation.