Abstract of Thesis

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Title	Single cell transcriptomics reveals a fate transitioning factor of cardiomyocytes in mitochondrial cardiomyopathy (1細胞発現解析により見出したミトコンドリア心筋症の病態進行因子の同定)

Abstract of Thesis

Mitochondrial diseases (MDs) are complicated disorders caused by mutations in genes essential for mitochondrial function and have a high prevalence, the most prevalent of which are mutations in complex I of the electron transport chain. OXPHOS dysfunction is a tightly regulated process that activates cascades of cellular regulatory machineries that often fail to sustain due to constant metabolic perturbation. Previous research on MDs focused on late stages or more severe tissue malfunction phenotypes, which made it difficult to identify factors switching off endogenous maintenance pathways and committing cells to malfunction. In addition, CI dysfunction has not been studied and the underlying mechanisms involved in the pathogenesis are not well understood, especially in the context of cardiomyopathy. The aim of this study was to identify such factors and how they contribute to cellular-specific switching to maladaptive state. Therefore, I utilized single cell transcriptomics on hearts of CI *Ndufs6* deficient (FS6KD) female mice, showing cardiac specific phenotype worsening with age, then analyzed using ScanPY analytical platform to perform integration, clustering, differential gene expression analysis, gene ontology, and finally PAGA pseudotime trajectory. The results showed CI-dysfunction in the heart promotes *Pgc1a* upregulation to act as the initial endogenous adaptation response, regulating mitochondrial biogenesis and glucose metabolism. Suppression of *Pgc1a* expression was found to be a crucial point for tissue transitioning to malfunction. In cardiomyocytes, I was able to capture the dynamic transcriptional reprogramming underlying this transitioning within subclusters of young FS6KD, modulated by transient expression of a key transcription factor acting as a repressor. Adaptive mechanisms were found to be activated following shutdown of this early response, suggesting the role of the repressor as a fate determining factor. Early endogenous *Pgc1a* upregulation followed by shutdown was shared among cardiac cellular populations but was not modulated by the same factors identified in cardiomyocytes. In conclusion, these findings support the importance of cellular resolutions in understanding heterogeneous disorders such as MDs, and in identifying targets for therapy.

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

カコラ氏を中心とする研究メンバーは、ミトコンドリア病の治療法開発を目的として研究を開始した。まずミトコンドリア病モデル動物の心臓を病態の各期において採取し、一細胞に分離した後、次世代シークエンサーを用いた発現解析を行った。そこでカコラ氏は、病態の前期に心筋細胞において特定の遺伝子Ａの発現が増加し病態の進行に伴って低下することを発見した。さらに、Aの下流の遺伝子Bを介したシグナルがミトコンドリア病の病態形成に重要であることを証明した。一細胞シークエンスの実施から解析および特定病因遺伝子の特定、さらにそのシグナル解析のための生化学的確認など複数の観点からミトコンドリア病の病態を解明した。新規の病態関連因子の同定につながった研究であり、ミトコンドリア病の新たな治療法の開発にもつながる可能性のある質の高い研究であると評価された。博士の学位を授与するに値するものと認める。なお、チェックツール“iThenticate”を使用し、剽窃、引用漏れ、二重投稿等のチェックを終えていることを申し添えます。