学位論文審査結果の要旨

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（学位論文審査結果の要旨）

MicroRNA Profiles in Intestinal Epithelial Cells in a Mouse Model of Sepsis

【主論文審査結果の要旨】

Sepsis is a systemic inflammatory disorder that leads to the dysfunction of multiple organs. In the intestine, the deregulation of the epithelial barrier contributes to the development of sepsis by triggering continuous exposure to harmful factors. However, sepsis-induced epigenetic changes in gene-regulation networks within intestinal epithelial cells (IECs) remain unexplored. In this study, we analyzed the expression profile of microRNAs (miRNAs) in IECs isolated from a mouse model of sepsis generated via cecal slurry injection. Among 239 miRNAs, 14 miRNAs were upregulated, and 9 miRNAs were downregulated in the IECs by sepsis. Upregulated miRNAs in IECs from septic mice, particularly miR-149-5p, miR-466q, miR-495, and miR-511-3p, were seen to exhibit complex and global effects on gene regulation networks. Interestingly, miR-511-3p has emerged as a diagnostic marker in this sepsis model due to its increase in blood in addition to IECs. As expected, mRNAs in the IECs were remarkably altered by sepsis; specifically, 2248 mRNAs were decreased, while 612 mRNAs were increased. This quantitative bias may be possibly derived, at least partly, from the direct effects of the sepsis-increased miRNAs on the comprehensive expression of mRNAs. Thus, current in silico data indicate that there are dynamic regulatory responses of miRNAs to sepsis in IECs. In addition, the miRNAs that were increased with sepsis had enriched downstream pathways including Wnt signaling, which is associated with wound healing, and FGF/FGFR signaling, which has been linked to chronic inflammation and fibrosis. These modifications in miRNA networks in IECs may lead to both pro- and anti-inflammatory effects in sepsis. The four miRNAs discovered above were shown to putatively target LOX, PTCH1, COL22A1, FOXO1, or HMGA2, via in

silico analysis, which were associated with Wnt or inflammatory pathways and selected for further study. The expressions of these target genes were downregulated in sepsis IECs, possibly through posttranscriptional modifications of these miRNAs. Taken together, our study suggests that IECs display a distinctive miRNA profile which is capable of comprehensively and functionally reshaping the IEC-specific mRNA landscape in a sepsis model.

以上のように、敗血症における腸管上皮細胞マイクロRNAネットワークの重要性を明らかにした論文であり、学術上極めて有益であり、学位論文として価値あるものと認めた。

Cells 2023, 12, 726.
Published: 24 February 2023
doi: 10.3390/cells12050726

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