博士論文（要約）

Glutamine induced NRF2 signaling in cancer cells

（癌細胞におけるグルタミン誘導性 NRF2 シグナル経路）

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Cancer cells are often exposed to harsh microenvironments such as hypoxia, acidic pH and nutrient starvation. They tend to adapt to these conditions by rewiring their metabolism. Here we examined how cancer cells adapt to nutrient starvation conditions by utilizing glutamine as their only source of nutrients. We performed gene expression profiling with cancer cells under control, nutrient starvation with or without the compensation of amino acids. We found that upon compensation of glutamine, not other amino acids, to nutrient starvation, the up- and downregulated genes are closely clustered with control. By examining histone modification data, we found a CNC-family transcription factor is activated upon glutamine supplementation to nutrient starvation. The integrated analysis of transcriptomic and epigenomic data suggested that a subset of target genes was upregulated as a result of this transcription factor binding. Furthermore, we found that upregulation of these genes involves another member of CNC-family transcription factor. These two transcription factors common binding sites regulate sub-set of genes that play important roles in cellular redox homeostasis and drug metabolism. We also found the presence of heterodimeric protein partner of these factors were present in cancer cells under control, NS and NS+Gln conditions. Therefore, we propose a model glutamine that regulates these CNC-family transcription factors activation in the specific gene locus interacting with each other, suggesting the inhibition of these transcription factors could be utilized for disrupting their activation in cancer cells. In conclusion, targeting interaction of these transcription factors under microenvironmental situations, such as glutamine being the main source of nutrients in cancer cells, can be a potent cancer treatment.