論文の内容の要旨

論文題目　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 that transcription factor NRF2 is activated upon glutamine supplementation to nutrient starvation. The integrated analysis of transcriptomic and epigenomic data suggested that a subset of NRF2 target genes were upregulated as a result of NRF2 binding. Furthermore, we found that upregulation of these genes involves another transcription factor BACH1 which shares the same motif as NRF2. NRF2 and BACH1 common binding sites regulate sub-set of genes that play important roles in cellular redox homeostasis and drug metabolism. We also found sMaf (MAFF, MAFG, and MAFK) presence in cancer cells under control, NS and NS+Gln conditions. Therefore, we propose a model glutamine where regulates NRF2 activation in the specific gene locus interacting with BACH1 and sMAFs, suggesting the inhibition of NRF2 and small MAFs could be utilized for disrupting NRF2 activation in cancer cells. In conclusion, targeting interaction of NRF2/BACH1 and Small MAF under microenvironmental situations, such as glutamine being the main source of nutrients in cancer cells, can be a potent cancer treatment.