NRF2 addiction of cancer cells

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KEAP1-NRF2 system is a major inducible defense mechanism against redox disturbance. While increased NRF2 activity is principally beneficial for our health, outcome of NRF2 activation in cancer cells is detrimental which is observed in almost 15% of non-small cell lung cancer (NSCLC). Multiple lines of evidence suggest that aberrantly activated NRF2 in cancer cells drives their malignant progression and that the cancer cells consequently develop “NRF2 addiction.” NRF2 enhances survival of cancers by activating cytoprotective genes. NRF2 also redirects glucose and glutamine into anabolic pathways by activating metabolic genes, which are advantageous for cancer cell proliferation. Under the influence of microenvironment, NRF2 strongly promotes tumorigenesis by helping cancer cells to evade anti-cancer immunity. To explore new therapeutic targets for NRF2-activated cancers, we conducted an unbiased approach by investigating NRF2-dependent transcriptome in NSCLC cell lines with NRF2-activated NSCLCs, and in those with NRF2-normal NSCLCs. We identified a battery of genes that are regulated by NRF2 specifically in NRF2-activated NSCLCs and found that these genes are accompanied by unique NRF2-dependent enhancers. CEBPB accumulation in NRF2-activated NSCLCs is found to be one of the prerequisites for the establishment of the unique enhancers, in which NOTCH3 enhancer is critical for the promotion of tumor-initiating activity. In addition, genes involved in drug metabolism and detoxification were found to be coregulated by NRF2 and CEBPB. These results suggested that enhanced activities of stem-like phenotype, drug metabolism and detoxification are achieved by the cooperative function of NRF2 and CEBPB in NRF2-activated NSCLCs.