IS01-4 **Targeting Oxidative Stress Defense System in Cancer**

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Transcription factor NRF2 is an important modifier of cellular response to oxidative stress. Although its cytoprotective effects were firmly established, there is considerable evidence suggesting the involvement of NRF2 signaling in cancer pathobiology. Here we suggest novel roles of NRF2 in cancer biology using two models, tumor angiogenesis and tumor sphere growth. In mouse xenografts study, a stable knockdown of *NRF2* in cancer cells from the colon (HT29 and HCT116) strongly suppressed tumor growth. As an underlying mechanism, it was observed that a vessel formation and vascular endothelial growth factor expression were repressed in *NRF2* silenced colon cancer tumors. The mechanism studies showed that NRF2-inhibited colon cancer cells failed to accumulate HIF-1α protein under hypoxia; therefore HIF-1α target gene expression for angiogenesis was limited in these cells. Further experimental demonstrations revealed that *NRF2* knockdown cancer cells accompanied miRNA expression changes and in particular, elevated miR181c1 was shown to affect the expression of mitochondrial cytochrome c oxidase subunit 1, resulting in the reduction of mitochondrial respiration rate. Additionally, we provide evidence that NRF2 signaling can be implicated in cancer stem cell survival. The levels of NRF2 and target gene expression were significantly higher in the MCF7 mammospheres than in the monolayer. Whereas, *NRF2* knockdown mammospheres showed an increased cell death and retarded sphere growth, and did not develop anticancer drug resistance in contrast to the control mammospheres. Collectively, these results indicate that NRF2 may be an effective target to control cancer cell survival and growth under stressful tumor microenvironment.

Key words: NRF2, HIF-1α, angiogenesis, mitochondria, mammosphere, colon cancer, breast cancer