IL-11 contribution to tumorigenesis in an NRF2 addiction cancer model

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The KEAP1-NRF2 system, originally identified as a critical defense mechanism against oxidative stress, is often dysregulated in various human cancers forming solid tumors, resulting in the aberrant activation of NRF2. Increased accumulation of NRF2 in cancers is strongly associated with the poor prognoses of cancer patients, including those with lung and breast cancers. 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. We recently found a significant correlation between NRF2 and IL-11 status in breast cancer patients. Based on a previous report demonstrating that IL-11 is induced downstream of NRF2, we examined the significance of IL-11 in NRF2-driven tumorigenesis with a newly established NRF2 addiction cancer model. Expression of Il11 was elevated during the tumorigenesis of the NRF2 addiction cancer model, but intriguingly, it was hardly detected when the cancer model cells were cultured in vitro. These results imply that a signal originating from the microenvironment cooperates with NRF2 to activate Il11. To the best of our knowledge, this is the first report showing the influence of the microenvironment on the NRF2 pathway in cancer cells and the contribution of NRF2 to the secretory phenotypes of cancers. Disruption of Il11 in the NRF2 addiction cancer model remarkably inhibited the tumorigenesis, suggesting an essential role of IL-11 in NRF2-driven tumorigenesis. Thus, this study suggests that IL-11 is a potential therapeutic target for NRF2-addicted breast cancers.