

Hijacking stress response in cancer

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(Medical Xpress)—Cancer cells have alteration in metabolic pathways as a result of oncogenes that promote tumor growth. NRF2 (nuclear factor erythroid-derived 2-related factor 2) works as a "master gene" that turns on stress response by increasing numerous antioxidants and pollutant-detoxifying genes to protect the lungs from variety of air pollutants such as diesel exhaust and cigarette smoke. However, researchers at the Johns Hopkins Bloomberg School of Public Health and others have found for the first time that NRF2 signaling also plays a role in the growth of tumor cells by altering metabolic pathways. The study is published in the July issue of the *Journal of Clinical Investigation*.

"Previously, we had reported that [lung cancer cells](#), due to mutation in inhibitors of NRF2, hijack the stress response pathway to cause chemoresistance," said Shyam Biswal, PhD, lead investigator of the study and professor in the Department of Environmental Health Sciences at the Bloomberg School of Public Health. "With our latest study, we show how the NRF2 pathway reprograms glucose metabolism, leading to increased energy production and tumor cell proliferation. A better understanding of this process could lead to potential cancer treatments."

The Johns Hopkins study demonstrated an important and previously unrecognized role for the NRF2 transcription factor in regulating [cell metabolism](#). Specifically, NRF2 regulates genes miR-1 and miR-206 to "reprogram" [glucose metabolism](#) through PPP (pentose phosphate pathway) and the TCA (tricarboxylic acid) cycle, and [fatty acid synthesis](#). The study demonstrated that these enzyme pathways, working together in specific patterns, stimulated tumor growth. The researchers validated

their findings through a series of in vitro experiments and studies involving mice.

"Although Nrf2 has been extensively studied as a target for chemoprevention, recent work from our group and others have highlighted the idea of developing inhibitors of Nrf2 to inhibit cancer " said Anju Singh, PhD, lead author of the study and assistant scientist in the Bloomberg School's Department of Environmental Health Sciences. Using an integrated genomics and ¹³C-based metabolic flux system wide association analysis, we demonstrate that Nrf2 modulates glucose flux through PPP and TCA cycles in cancer cells. Biswal concludes that "This study reinforces the idea that targeting Nrf2 with small molecule inhibitors will starve the cancer cells by affecting [metabolic pathways](#) as well as decrease antioxidants and detoxification genes to intervene in therapeutic resistance." Biswal's group has been working with the National Center for Advancing Translational Sciences at NIH to develop Nrf2 inhibitors for cancer therapy.

More information: "Transcription factor NRF2 regulated miR-1 and miR-206 to drive tumorigenesis" *Journal of Clinical Investigation*, 2013. www.jci.org/articles/view/66353

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