

# Review: Nrf2, a multi-organ protector?

by Glen Thomson - NRF2.com on May 3, 2013

A classic NRF2 study entitled, “Nrf2, a multi-organ protector?” predates many of the latest studies regarding NRF2. It was however one of those landmark studies that paved the way for later studies.

The study states, “Nrf2 may serve as a master regulator of the ARE-driven cellular defense system against oxidative stress.” and then goes on to investigate whether multiple organs in the body are protected from the activation of NRF2.

The researchers conclude their abstract with the following statement, “The widespread nature of Nrf2 may have an important therapeutic potential, allowing prevention of carcinogenesis and neurodegenerative diseases.”

The paper claims that humans are bombarded by wide variety of toxic insults each and every day. Toxins such as carcinogens, electrophiles, reactive oxygen species, diesel exhaust, inflammation, calcium disturbance, UV light, and cigarette smoke. They also state that “many studies have shown that NRF2 is crucial in protecting a variety of tissues such as lung, liver, kidney, stomach, small intestine, central nervous system, splenocytes, macrophages, erythrocytes, and retinal epithelia.”

Why is it important to protect these multiple organs from the toxins? Well, the research goes on to state that “Reactive oxygen species (ROS) and electrophiles cause cellular damage leading to many diseases including cancer, autoimmune disease, and neurodegenerative disease; such toxic insults are normally detoxified by phase II detoxification enzymes and antioxidant proteins”.

Studies have shown that the following organs have benefited from NRF2 activation. (read the full study to obtain references for studies relating to these findings below).

## **Lung and liver**

Nrf2 has been shown to protect the lungs from butylated hydroxytoluene-induced acute respiratory distress syndrome, hyperoxic injury, and bleomycin-mediated pulmonary fibrosis. It does so by detoxifying pathways and antioxidant potentials. Smokers and those impacted by second hand smoke will be interested to know that studies demonstrate Nrf2 protection against cigarette smoke-induced emphysema and COPD.

Nrf2 also assists in protecting the liver, through increased sensitivity to acetaminophen-induced centrilobular hepatocellular necrosis and hepatotoxicity.

## **GI tract**

The article further states that additional studies have demonstrated that “Nrf2 protects GI tract from carcinogenesis, implying a role for Nrf2 in cell cycle regulation and cancer prevention... Thus, constitutive and inducible expression of phase II enzymes through the Nrf2-ARE pathway can modify the susceptibility of GI tract to carcinogenesis.”

## **Nervous system**

The Nrf2-ARE pathway also assists in neuroprotection. Neuroblastoma cells received protection from oxidative glutamate toxicity and H<sub>2</sub>O<sub>2</sub>-induced apoptosis (cell death).

## **Others**

The protective effects of Nrf2 are not limited to the organs previously mentioned but have proved key to protecting other cell types as well. Sulforaphane was shown to protect retinal pigment epithelial cells from photo-oxidative damage. Macrophages and epithelial cells were protected from diesel exhaust chemicals. Nrf2 protects gallstone genes and is very beneficial in wound healing. Lastly, NRF2 has been shown to benefit against the progression of autoimmune diseases like lupus, MS and Parkinson’s disease.

The researchers state “Our hypothesis for Nrf2-conferred multi-organ protection phenomenon is that Nrf2 protects multiple tissues by coordinately up-regulating classic ARE-driven detoxification and antioxidant genes as well as cell type-specific targets that are required for basic defense in each unique environment.”

A wide variety of cells are impacted positively by NRF2 activation such as lung, liver, kidney, stomach, small intestine, central nervous system, splenocytes, macrophages, erythrocytes, and retinal epithelia. Common to all these organs is the fact that each cell utilizes the Nrf2-ARE pathway as a protector.

In conclusion, the paper presents evidence supporting the hypothesis that Nrf2 is central to multi-organ protection within the body. To quote the authors further, “As numerous studies have demonstrated the great potential for the Nrf2-ARE pathway as a therapeutic target in preventing cancer, autoimmune disease, and neurodegenerative disease, it is important to identify ways to modulate cell-specific Nrf2 activity so as to facilitate the development of novel therapeutic strategies for treatment of these diseases.”

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