in support of WORLD CANCER RESEARCH DAY

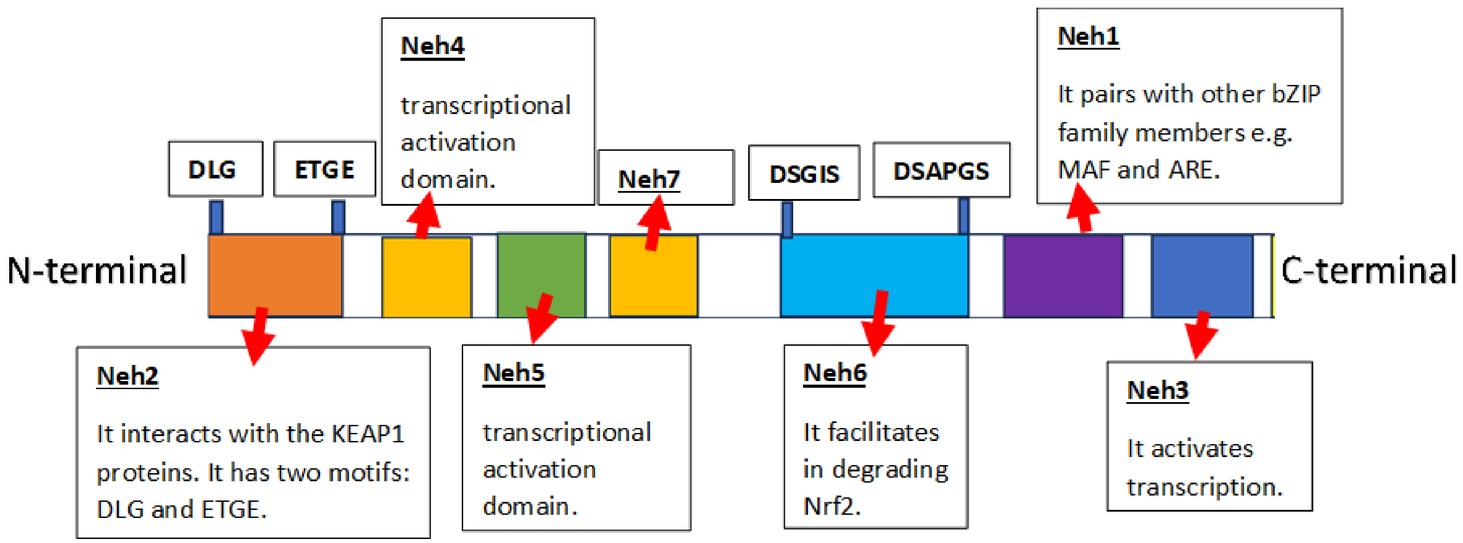
September 24th

2024 Campaign

INNOVATION IN CANCER RESEARCH DRIVES PROGRESS TOWARDS HEALTH EQUITY

NRF2 signalling and cancer

By Dr Hafsa Waseela Abbas



Structure of Nrf2 (Abbas, 2024)

What is Nrf2 and how does its structure look like?

It is a protein that is encoded by a gene called Nfe2l2.

A protein is made of building blocks called amino acids.

There are 589 amino acids that make up the Nrf2 protein.

Nrf2 is a member of a Cap'n'collar (CNC) transcription family that functions as transcription factors.

There are three types of Nrf2 proteins: (Nrf1. Nrf2 and Nrf3)

Location: placenta

White blood cells (B cells, monocytes)

Key Definitions

- **Transcription factor: A protein that helps transcribing genes by affecting an enzyme called RNA polymerase. Transcription is the first step involved in making a protein.**
- **Amino acids: The building blocks that make proteins.**
- **Gene: A short section of DNA that helps determine characteristics of an organism.**
- **Protein: A large molecule containing amino acids and functions for growth and repair.**
- **Mutation: A random change in the DNA that affects that particular gene or chromosome.**

Farah With Me Cancer Project is part of Farah Saeed Trust, a voluntary organisation that aims to inspire, educate and help others. Farah With Me aims to raise public awareness on cancer through virtual and in-person event. World Cancer Research Day is not affliiated with FST, however, FST enjoys partaking in its annual research initiatives.

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NORMAL FUNCTION

1) **Regulates transcription for more than 200 genes** that are involved in such as:

- Immune system
- Production of energy via mitochondria – an organelle or part of a cell. A cell is the smallest unit of a living organism
- Regulating tissue homeostasis
- Metabolism - a series of reactions that occur in cells to support life.
- Transcription of other genes.

2) **Cytoprotection**: Protecting cells from oxidative stress

(Pouremamali *et al.* 2022; Judge and Dodd, 2020)

WHEN NRF2 IS MUTATED

- **Deactivation of Nrf2**
- **Increase of Nrf2 gene in the nucleus** of cancer cells. This increases oxidative stress which can damage cells, mutates genes that suppressor tumours and increase in cancer progression (Shibata *et al*., 2008)
- **Cancer progression** can cause the cancer cells to survive and spread to other parts of the body and resist to chemotherapy.

(Zhao, Gao and Qu, 2010; Basak *et al.*, 2017; Kuzniak, Paluszczak and Baer-Dubowska, 2016; Song ET AL., 2021; Sporn and Libv, 2012)

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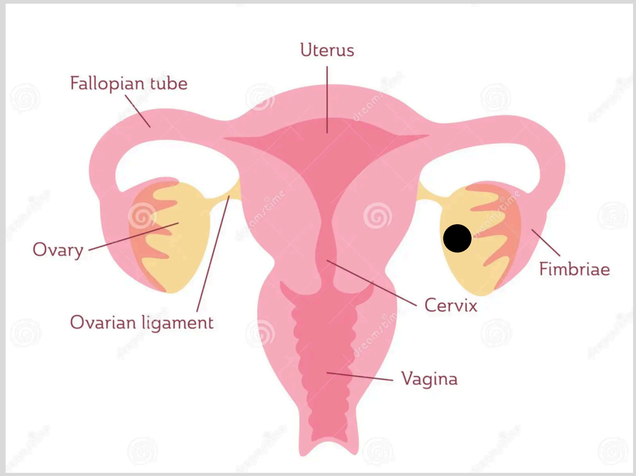
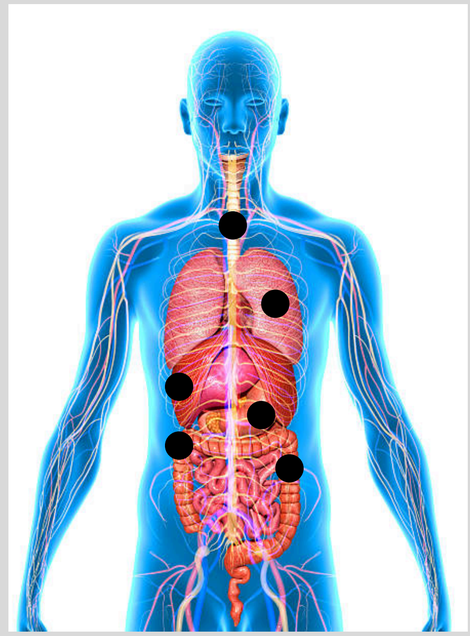
CANCERS ASSOCIATED WITH NRF2 SIGNALLING PATHWAY

Cancers caused by Keap1 mutations:

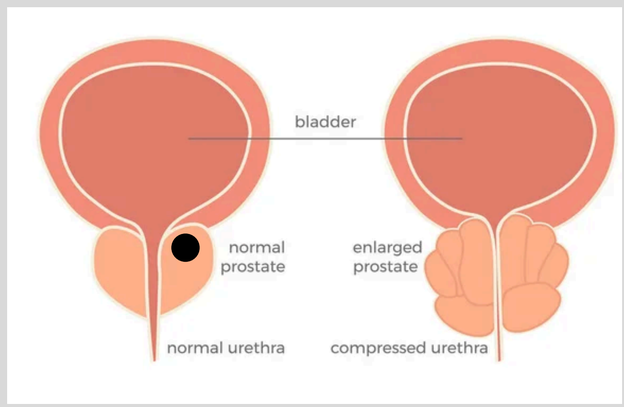
- Lung cancer (second most common)
- Ovary (19% of cases)
- Gastric (11% of cases)
- Liver (9% of cases)
- Colon (8% of cases)
- Prostate (8% of cases)
- Breast cancer (2% of cases)





Cancers caused by Nrf2 mutations

- Oesphageal carcinoma (food pipe)
- Lung cancer
- Head and Neck cancer



Cancers caused by Cul3 mutations

- Sporadic papillary renal cell carcinoma type-2 (kidney cancer)

All four images are stock photos on this poster with exception of the black dots

(**Singh *et al*., 2006; Lawrence *et al*. 2014; Konstatinopoulos *et al.*, 2011; Zhang *et al;* 2010; Pouremamali *et al.* 2022; Ooi *et al.* 2013; Mitsuishi, Motohashi and Yamamato, 2012)**

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HINGE AND LATCH MODEL PROCESS

Nrf2 protein is found in the cytosol – inside the cell.

The Neh2 domain that contains the ETGE/DLG motifs in the Nrf2 protein connects with the KEAP1 Kelch domain in the KEAP1 protein. This is known as open conformation.

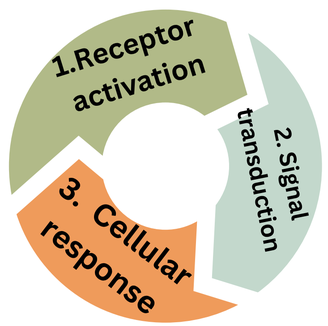
This promotes ubiquitination of Nrf2 by the Cul3-Rbx10-E3 ligase complex to breakdown the protein (proteolysis) by a structure called proteosome.

KEAP1 regulates Nrf2 to increase interaction with other transcription activators, other signalling pathways and increase its function.

However, when KEAP1 is exposed by reactive oxygen species (ROS) and other stresses, it can cause a change in the KEAP1/Cul3/RBX/Nrf2 complex. This prevent ubiquitination of Nrf2 and leads to a change in the structure of KEAP1

Nrf2 separates from KEAP1 and enters the nucleus.

Here, at Neh1 domain, it can dimerise with small MAF proteins and then to the antioxidant response elements (ARE) region located in Nrf2 target genes.



Key Definitions

- **ARE**: It is found in the promoter region of a gene that control gene expression.
- **Nucleus**: It is an organelle that contains genetic information to control the cell.
- **Cytosol:** A short section of DNA that helps determine characteristics of an organism.
- **Proteolysis:** The breakdown of proteins by peptide bonds.
- **Proteosome**: An organelle where proteins are destroyed
- **Ubiquitination:** A reversible process where proteins are directed by ubiquitin that attaches to target protein for addition changes (post-translational modification)
- **Dimerize:** The union of two molecules.

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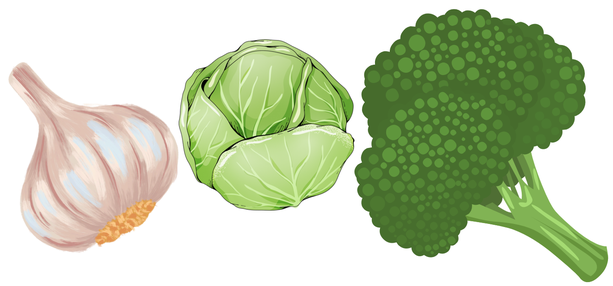
New research on the role of Nrf2 (Pouremamali *et al*. 2022)

NRF2 INDUCERS

They are commonly found in plants.



- **Diallyl trisulfide (DATS):**

This is found in garlic oil and in some of cruciferous vegetables e.g. cabbage, watercress and broccoli. Experimental studies present it can modify Keap1 to stimulate Nrf2 and promote expression of several enzymes and drug metabolism.

- **Curcumin:**

This is extracted from an Indian spice called turmeric. It prevents oxidative stress and inflammation.
Low concentrations of curcumin can increase the expression of Nrf2 and its target genes. According to clinical trials, it is quite safe to use and can increase sensitivity for chemotherapy and radiotherapy to work e.g. in prostate, ovarian and colorectal cancers.
It has inhibitory effects on Notch1, mitochondrial and NF-kappa B signalling pathways

- **Sulforaphane [1-isothiocyanato-4-(methylsulfonyl)-butane] (SFN)**

It is found in broccoli and Brussel sprouts and has shown to prevent oxidative stress in cells, increase sensitivity of chemotherapy, promote cancer cell death (apoptosis), decrease formation of blood vessels (angiogenesis) and increase cell cycle progression.

- **Epigallocatechin-3-gallate (EGCG):**

It is found in green tea extract and has shown to decrease the regulation of several enzymes e.g. nitric oxide synthase to increase anti-oxidative stress and anti-inflammatory responses.
It also decreases matrix metalloproteinanases to decrease the invasion and spread of cancer.

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New research on the role of Nrf2 NRF2 INHIBITORS

(Pouremamali *et al*. 2022)

- **Luteolin:**

Luteolin can be found in peppers, celery, broccoli and parsley.
Some studies consider it an Nrf2 activator, others consider it an Nrf2 inhibitor
It increases sensitivity to chemotherapy drugs e.g. doxorubicin, oxaliplatin and bleomycin to prevent the growth of cancer cells by inhibiting the cell-cycle and increase cell death.

- **Brusatol**

Brusatol can be found in an evergreen shrub in Northern Australia and South-east Asia.
It has the ability to modify the levels of Nrf2 protein whilst keeping the Keap1 protein constant.
It can increase sensitivity to chemotherapeutic agents e.g. paclitaxel, carboplatin and 5-flourouracil.
Further studies need to fully understand its anti-cancer mechanism.

- **Chrysin.**

This can be found in honey, fungi (mushroom), fruits, vegetables and even flowers (blue passion)
It can prevent inflammation by decreasing the expression of nuclear factor kappa B (NF-kB), tumor necrosis factor α (TNF-α), and interleukin 1β (IL-1β).
It can increase cell death to prevent the cancer spreading (metastasis) and forming new blood vessels for nutrients (angiogenesis)
It can inhibit Nrf2 genetic and protein expression and its target genes by evading ERK and PI3K-Akt signalling pathways.

- **Trigonelline (TRG)**

TRG is commonly found in coffee and fenugreek seeds.
It can prevent Nrf2 expression of genes that encode the proteosome.
It decreased resistance by preventing ferroptosis. This is a form of a cell death that was discovered in recent years by increasing iron and degradation of lipids oxidatively forming lipid peroxides.
In combination with chemotherapy such as etoposide, it can increase the strength (potency) to kill cancer cells that have high Nrf2 activity and decrease tumour size.

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