Casual Friday Presents

NRF1 – NRF2, Functional Applications

A BIOGENETIX CLINICAL PRESENTATION

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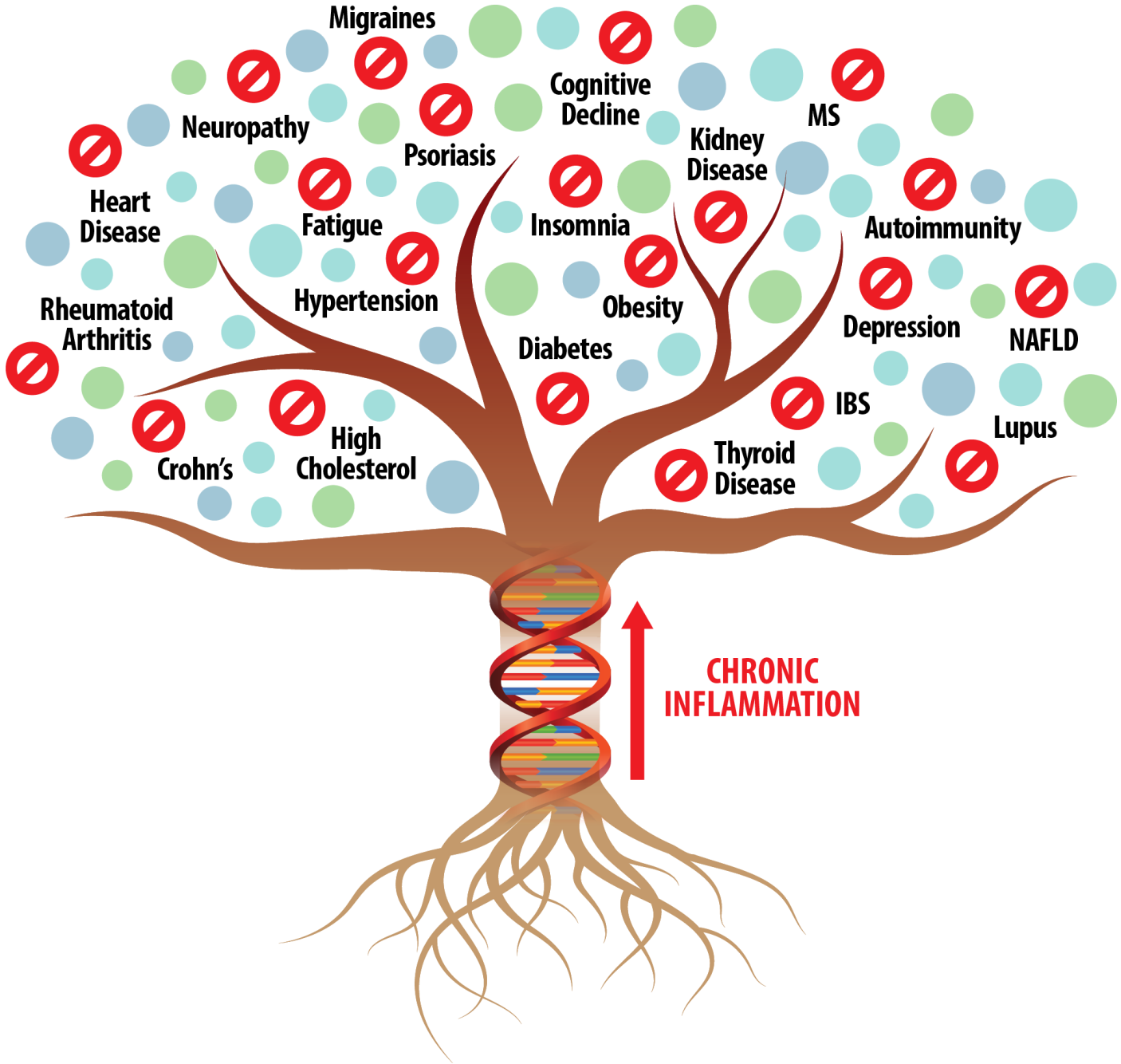
Migraines
Neuropathy
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MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Rheumatoid Arthritis
Hypertension
Obesity
Depression
NAFLD
Diabetes
IBS
Crohn's
High Cholesterol
Lupus
Thyroid Disease
CHRONIC INFLAMMATION

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Glucose Support Bundle

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Dictionary

Definitions from Oxford Languages · Learn more

transcription factor

noun **BIOCHEMISTRY**

plural noun: **transcription factors**

a type of protein that regulates the synthesis of RNA from DNA during transcription by binding to specific DNA sequences.

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J Clin Biochem Nutr. 2023 Nov 22;74(2):91–96. doi: 10.3164/jcbn.23-106

Unique and overlapping roles of NRF2 and NRF1 in transcriptional regulation

Hiroki Sekine [1,*], Hozumi Motohashi [1,2]

Nuclear factor erythroid 2-related factor 2 (NFE2L2/NRF2) is a transcription factor that activates genes involved in the oxidative stress response, such as *Nqo1*, *Gclm*, and *Gclc*, to protect cellular components from damage caused by reactive oxygen species (ROS).[1] Recent reports have also shown that NRF2 regulates cellular metabolism by activating genes such as the pentose phosphate pathway.[2–4] Under normal conditions, NRF2 is targeted for degradation by the Kelch-like ECH-associated protein 1 (KEAP1) E3 ligase-dependent proteasome pathway.[5,6] However, when exposed to oxidative stress, the activity of KEAP1 E3 ligase is suppressed, resulting in NRF2 stabilization, nuclear translocation, heterodimerization with small Maf (sMaf) proteins, and binding to the antioxidant response element (ARE) DNA sequences of target genes.[1,7] Some cancers possess loss-of-function mutation of *KEAP1*, leading to constitutive activation of NRF2.[8–13] The target gene activation by NRF2 is context dependent, especially in NRF2-activated cancer cells, NRF2 activates the gene expression of NOTCH3, a gene required for promotion of tumor-initiating activity.[14]

NRF1 and NRF2

NRF1 and NRF2 are part of the same family of transcription factors.

Main job: help cells adapt to stress and maintain homeostasis by turning genes on or off.

They both bind to AREs (Antioxidant Response Elements) in DNA—but they respond to different kinds of stress and have different control mechanisms.

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NRF2

NRF2: the stress response

The master regulator of antioxidant defense systems.

When activated, it increases expression of genes involved in:
- Antioxidants
- Detoxification enzymes
- Redox balance
- Anti-inflammatory responses

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NRF2 Regulation

•NRF2 is kept in check by counter measures. The fire crew is not needed all day everyday – needs to have an off switch.

Under stress (ROS, toxins, electrophiles):
•NRF2 escapes degradation by the countermeasures.
•NRF2 moves into the nucleus
•NRF2 binds AREs (antioxidant response elements) → protective genes turn on.

This makes NRF2:
•Fast
•Easily activated
•Transient

“Emergency Response”

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NRF2 Applications

Clinically…

- Protective in:
  - Neurodegeneration
  - Cardiovascular disease
  - Aging
- Problematic when overactive in:
  - Cancer (tumors hijack NRF2 to resist chemo & oxidative stress)

NRF2 can be a double-edged sword.

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Proteasomes

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NRF1

NRF1: the cellular maintenance

Like a “Building manager”

Action:
NRF1 is actively maintaining cellular homeostasis:

- Proteasome production
- Protein quality control
- Mitochondrial function
- Lipid and cholesterol metabolism
- ER stress responses

One of its most famous roles:

Proteasome recovery pathway

When proteasomes are inhibited, NRF1 turns on genes to make new proteasomes.

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NRF1 Regulation

NRF1:
•Is synthesized into the endoplasmic reticulum (ER) membrane (its office)
•Is normally inactive and stuck there.
•Must be:
- Translocated
- Deglycosylated (bound carbohydrates have to be removed)
- Cleaves off to become active

The multiple steps makes NRF1:
•Tightly controlled
•Slower
•Constitutive rather than inducible

The building manager “gets around to it” while the fire crew can be immediate.

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NRF1 Applications

- Function is essential (NRF1 knockout mice = lethal)

- Key in:
  - Neurodevelopment
  - Metabolic regulation
  - Proteostasis (balanced, functional, properly folded)

- Future applications:
  - Aging
  - Neurodegenerative disease
  - Cancer metabolism

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NRF1 vs NRF2

Feature	NRF1	NRF2
Gene	NFE2L1	NFE2L2
Role	Homeostasis & maintenance	Stress response
Speed	Slow, constitutive	Fast, inducible
Key pathway	Proteasome recovery	Antioxidant defense
Regulation	ER processing & cleavage	Mediated degradation
Essential?	Yes (developmental)	No (protective)

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Synergistic Activity

Not redundant - complementary:

•NRF2 handles acute stress

•NRF1 maintains long-term cellular capacity

•Both bind ARE (antioxidant response element):
- Activate different gene sets
- Respond to different signals

*fire crew vs building maintenance.

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Remember mTOR from last week:

mTOR is the cell's "growth mode" switch:
•increases protein synthesis
•increases lipid synthesis
•increases ribosome production
•suppresses autophagy

When mTOR is upregulated, cell growth is flipped on.
Anabolic activity creates:
•oxidative stress
•misfolded proteins
•proteasome burden
•mitochondrial strain

This is where the NRF1/NRF2 activation comes into play.

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NRF2/mTOR

NRF2 <-> mTOR connection:

mTOR activity increases ROS -> activates NRF2
When mTOR drives mitochondrial metabolism and anabolic growth, ROS goes up.

ROS/electrophiles modify NRF2 regulator, freeing NRF2 → antioxidant genes turn on.

NRF2 regulates that growth mode by keeping cell somewhat clean.

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NRF2/mTOR

NRF2 supports the metabolic program that mTOR wants

NRF2 doesn’t just drive antioxidants — it can also direct resources toward anabolic end points:

- Glutathione recycling
- Fatty Acid synthesis

NRF2 increases effectiveness in the anabolic program that mTOR is trying to run. (Body building, obesity, etc).

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NRF1/mTOR

NRF1 <-> mTOR connection (proteostasis + proteasome supply)

mTOR increases protein synthesis → requires proteasome capacity
mTORC1 ramps translation (transcription → translation).
More translation = more proteins = more mistakes (cancer?).

Mass anabolic activity requires “quality control”

NRF1 turns on quality control.
→proteasome control (recycling, quality control measures).

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Summary

mTOR -> growth accelerator
NRF2 -> oxidative stress shield
NRF1 -> proteostasis / proteasome supply chain

mTor -> build program
NRF2 -> Fire and rescue program
NRF1 -> building maintenance

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Hgb A1c with eAG Estimation

Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲ **Hemoglobin A1c** [01]	**10.7**	**High**		%	4.8-5.6
Estim. Avg Glu (eAG)	260			mg/dL	

Thyroxine (T4) Free, Direct

Test					e Interval
T4,Fr					-1.77

C-Pepti

Test					e Interval
C-Pep					-4.4

Vitamin

Test					e Interval
Vitam					100.0

Medicine and an Endocrine Society practice guideline as a
level of serum 25-OH vitamin D less than 20 ng/mL (1,2).
The Endocrine Society went on to further define vitamin D

Diabetes creates chronic oxidative + metabolic stress.

NRF pathways either fail, get suppressed, or maladaptively activated.

-> mTOR running wild -> fatty acid synthesis -> fire crew can't handle (NRF2) -> maintenance guy has left the building (NRF1).

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NRF2 & Metabolic Disease

NRF2 can be suppressed in chronic hyperglycemia

As metabolic syndrome sets in, adaptation and activation begins to decline.

- impaired NRF2 nuclear translocation
- reduced NRF2 transcription (gene activation)
- NRF2 regulator in overdrive

Antioxidant response becomes blunted. ROS piles up,
Tissue gets destroyed.

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NRF1 & Metabolic Disease

Diabetes increases proteotoxic stress, catabolic muscle for fuel activity, and protein creation mistakes (cancer rates, etc.)

High glucose drives:
•glycation of proteins (HbA1c)
•misfolding
•ER stress – NRF1 stuck in the office.
•damaged mitochondria proteins

This increases demand for:
•proteasome activity
•protein quality control

If NRF1 is impaired → protein quality control fails.

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Glucose Support Bundle

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Aging (Albany NY). 2018 Jan 11;10(1):83–99. doi: 10.18632/aging.101361

Resveratrol, an Nrf2 activator, ameliorates aging-related progressive renal injury

Eun Nim Kim [1], Ji Hee Lim [1], Min Young Kim [1], Tae Hyun Ban [1,2], In-Ae Jang [1], Hye Eun Yoon [1,3], Cheol Whee Park [1,2], Yoon Sik Chang [1,4], Bum Soon Choi [1,2]✉

Abstract

Background. Two important issues in the aging kidney are mitochondrial dysfunction and oxidative stress. An Nrf2 activator, resveratrol, is known to have various effects. Resveratrol may prevent inflammation and oxidative stress by activating Nrf2 and SIRT1 signaling. We examined whether resveratrol could potentially ameliorate the cellular condition, such as renal injury due to cellular oxidative stress and mitochondrial dysfunction caused by aging.

Methods. Male 18-month-old C57BL/6 mice were used. Resveratrol (40 mg/kg) was administered to aged mice for 6 months. We compared histological changes, oxidative stress, and aging-related protein expression in the kidney between the resveratrol-treated group (RSV) and the control group (cont). We performed experiments using small-interfering RNAs (siRNAs) for Nrf2 and SIRT1 in cultured HK2 cells.

Results. Resveratrol improved renal function, proteinuria, histological changes and inflammation in aging mice. Also, expression of Nrf2-HO-1-NOQ-1 signaling and SIRT1-

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Antioxidants (Basel). 2020 Dec 4;9(12):1228. doi: 10.3390/antiox9121228

Anti-Viral Potential and Modulation of Nrf2 by Curcumin: Pharmacological Implications

Mahdi ... di [1,6,*]

Auth

PMCID

Abstract

Nuclear factor erythroid 2-related factor 2 (Nrf2) is an essential transcription factor that maintains the cell's redox balance state and reduces inflammation in different adverse stresses. Under the oxidative stress, Nrf2 is separated from Kelch-like ECH-associated protein 1 (Keap1), which is a key sensor of oxidative stress, translocated to the nucleus, interacts with the antioxidant response element (ARE) in the target gene, and then activates the transcriptional pathway to ameliorate the cellular redox condition. Curcumin is a yellow polyphenolic curcuminoid from *Curcuma longa* (turmeric) that has revealed a broad spectrum of bioactivities, including antioxidant, anti-inflammatory, anti-tumor, and anti-viral activities. Curcumin significantly increases the nuclear expression levels and promotes the biological effects of Nrf2 via the interaction with Cys151 in Keap1, which makes it a marvelous therapeutic candidate against a broad range of oxidative stress-related diseases, including type 2 diabetes (T2D), neurodegenerative diseases (NDs), cardiovascular diseases (CVDs), cancers, viral infections, and more recently SARS-CoV-2. Currently, the multifactorial property of the diseases and lack of adequate medical treatment, especially in viral diseases, result in developing new strategies to finding potential drugs. Curcumin potentially opens up new views as possible Nrf2 activator. However, its low bioavailability that is due to low solubility and low stability in the physiological conditions is a significant challenge in the

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