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Induction of cellular stress responses by phytochemicals for nutritional applications toward anti-aging interventions

Background

Human lifespan has increased significantly in developed and developing countries, raising considerably the percentage of elderly people. Aging is an important risk factor for the development of age-related diseases and is associated with decreased cellular antioxidant defenses and impaired stress responses, reducing the ability of cells to cope with stress. . As xenobiotics, we hypothesize that antioxidant phytochemicals , by imposing mild stress on human cells, may afford anti-aging properties through induction of stress responses and cellular antioxidant defenses.

Our group, under the scope of the undergoing **NaturAge project**, is currently investigating this hypothesis, namely the ability of some plant extracts and isolated phytochemicals to induce antioxidant defenses through Nrf2/ARE signaling. That, by making use of biochemical and molecular tools, will be associated with possible anti-aging effects using normal human skin fibroblasts undergoing aging *in vitro*.

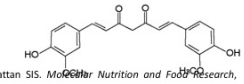
Recently, we have shown the ability of the polyphenol curcumin to induce cellular antioxidant defenses through induction of a stress response in normal human skin fibroblasts, affording protection from a further oxidant challenge with *tert*-BOOH [1].

Aim of the presentation

→ Present the objectives of the project NaturAge (https://sites.google.com/site/naturageproject/).

→ Present results concerning the curcumin-induced hormetic stimulation of cellular stress responses in normal diploid human skin fibroblasts (ASF-2 cells), and their association with potential anti-aging effects [1].

Curcumin structure:



[1] Lima CF, Pereira-Wilson C, Rattan SIS. *Molecular Nutrition and Food Research*, 2010, in press. (DOI: 10.1002/mnfr.201000221)

Project NaturAge — Anti-aging properties of natural compounds

→ Selected plant extracts / phytochemicals

→ Induction of hormetic effects (ability to condition cells to a further oxidant challenge)

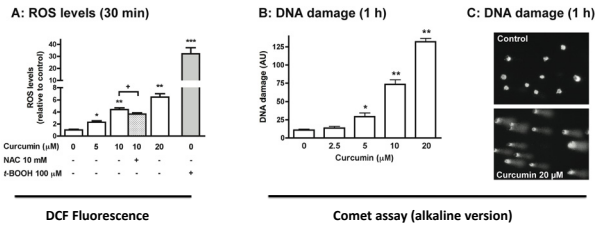
→ Induction of antioxidant defenses by Nrf-2/ARE signaling

Biological model: normal diploid human skin fibroblasts

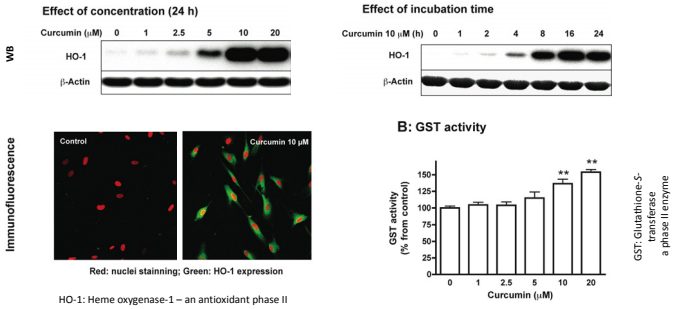
→ Anti-aging effects in stress-induced premature senescence

→ Anti-aging effects of selected phytochemicals in human skin fibroblasts undergoing replicative senescence *in vitro*

1. Curcumin induces oxidative stress

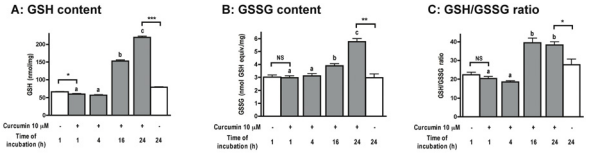


2. Curcumin induces antioxidant/phase II enzymes

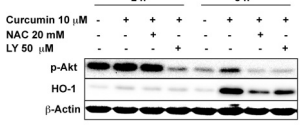


HO-1: Heme oxygenase-1 – an antioxidant phase II enzyme

3. Curcumin affects GSH-redox state

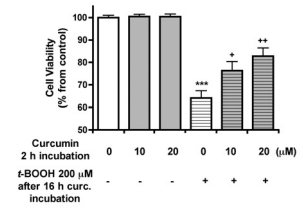


4. Effects of curcumin are redox and PI3K/Akt dependent

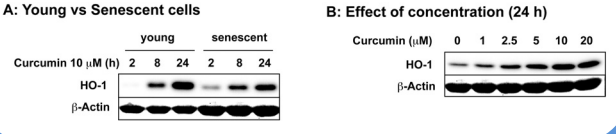


NAC: N-acetyl cystein – increases cellular GSH redox state
LY: LY 294002 – inhibitor of PI3K

5. Hormetic effects



6. Curcumin-induced HO-1 is impaired in senescent cells



Conclusions

- Curcumin induces HO-1 and other antioxidant defenses in normal human skin fibroblasts through redox and PI3K/Akt-dependent pathways. HO-1 induction in senescent cells was considerably impaired.
- Curcumin-induced stress response led to protective hormetic effects via a further oxidant challenge.
- Our observations support the view that curcumin-induced mild stress and antioxidant defenses can be applied in the prevention of oxidative stress-associated diseases, and as a possible useful approach towards anti-aging intervention.

Acknowledgements:

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