Clinical Summary

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Malavolta M, Bracci M, Santarelli L, et al. Inducers of Senescence, Toxic Compounds, and Senolytics: The Multiple Faces of Nrf2-Activating Phytochemicals in Cancer Adjuvant Therapy. Mediators Inflamm 2018;4159013.

Certain Senolytic Phytonutrients May Also Trigger the Antioxidant Response

The concept of cellular rejuvenation centers upon encouraging immune-mediated autophagy of aged or dysfunctional 'senescent' cells. For maintaining performance of healthy cells, the ability to trigger a robust antioxidant and detoxification response is equally important. This review examines current research on how fifteen phytonutrients that possess both of these qualities may be potentially useful for targeting therapies aimed at transformed senescent cells.

Senescent cells are aged or damaged cells with significantly decreased functionality and resistance to normal programmed cell death. Their existence is thought to represent a metabolic compromise: until cell death occurs, in the form of apoptosis (programmed death) or autophagy (immune-mediated cell clearance), senescence decreases the likelihood of these proinflammatory cells transforming into cancer cells. While this protective strategy is generally effective, senescent cells are often far from quiescent, and may even create microenvironments that promote certain forms of cancer.

The Nrf2 antioxidant response pathway is able to upregulate the coordinated activities of over 200 genes related to detoxification and antioxidant protection as part of the cellular reaction to injury, inflammation, and oxidative stress. Key enzymes involved include glutathione transferases and peroxidases, hemeoxygenases, and superoxide dismutase. What's the connection? This research team proposes that the Nrf2 pathway may, in cells with irreparable damage, like cancer cells, help trigger senescence or cell death as a means of mitigating damage and protecting normal cells.

According to the authors, “several natural compounds that activate [the] Nrf2 pathway, which is involved in complex cytoprotective responses, have been paradoxically shown to induce cell death or senescence in cancer.” The fifteen phytonutrients profiled in this review article for their dual impacts on cell senescence and the Nrf2 response include:

- The polyphenols quercetin, fisetin, epigallocatechin gallate (EGCG), resveratrol, genistein, curcumin, silybin (from milk thistle seed), and phloretin (found in apple leaves)
- The organosulfur compounds sulforaphane (a human metabolite of cruciferous vegetable phytonutrients), phenylethyl isothiocyanate (PEITC) (found in cruciferous vegetables), and allicin (found in garlic)
- Tocotrienols
- The alkaloids piperlongumine (found in black pepper) and berberine
- The diterpene triptolide, a somewhat toxic component of the TCM herb thunder god vine

These researchers hypothesize that the Nrf2 and senescence pathways may be part of a broader network that regulates cell function and tissue microenvironments:

“It is becoming evident that some effects of [the] Nrf2-Keap1 pathway may be mediated through crosstalk with additional pathways affecting aspects of cell fate that provide a multitiered, integrated response to chemical stresses which, in turn, could eventually culminate in a senescent response.”

Review Summary

Highlights from this research review include the following:

- Quercetin is a well-known activator of the Nrf2 signaling system. In past research, quercetin has shown the ability to induce senescence in certain populations of cancer cells yet also, somewhat paradoxically, to act as a senolytic in non-transformed senescent cells. Research suggests that, in certain cell types, quercetin may be able to bypass transformed cells’ resistance to programmed cell death.

- While the senescence-associated secretory phenotype (SASP) may aggravate tissue inflammation and accelerate biological aging processes, it also plays a key role in immunosurveillance and in promoting immune-mediated clearance of senescent cells.

- Genistein, an isoflavone found in soy and other beans, is a Nrf2 activator that may delay senescence in vascular smooth muscle cells. In cancer research, it has also been seen to modulate the expression of tumor suppression genes and to aid the induction of senescence in transformed cells.

- The research team notes, that, because individual phytonutrients with senolytic activities tend to act on a narrow range of cell types, combinations of phytonutrients with complementary targets or combinations of phytonutrients with other senolytic agents may prove more effective in targeting aged, damaged, or transformed cells.

- Fisetin, curcumin, tocotrienols, resveratrol, berberine, EGCG, phloretin, and piperlongumine have each shown preclinical evidence of selectively inducing clearance of senescent cells and inducing senescence, as a tissue-protective mechanism, in transformed cells. All have also been seen to influence signaling within the Nrf2 antioxidant response.

- The researchers also describe an array of biomarkers that may be used to identify senescent cells, and they emphasize that different biomarkers may be necessary for identifying such cells originating in different tissues.

- The authors are currently unaware of evidence of senolytic effects of PEITC or sulforaphane, though they are relatively strong Nrf2 response initiators and may induce senescence in transformed cells. Allicin has not been investigated for senolytic activity, though it also activates Nrf2 and can induce senescence in damaged cells.

Senolytic research is relatively new, and further studies may uncover new findings for these and other phytonutrients.

NUTRITION CONCLUSION

Phytonutrients have unique and varying influences on cells of different types and in different states of function or dysfunction. In addition, high tissue concentrations of these phytonutrients may produce effects quite distinct from those at lower tissue levels. This review documents 15 phytonutrients that have, individually, shown a spectrum of cell- and tissue-regulating activities, ranging from protecting normal cells to encouraging senescence or cell death in dysfunctional cells.