

Expression Profile of Apoptosis-related Genes in Breast Cancer Cell Lines after Benzylisothiocyanate Application

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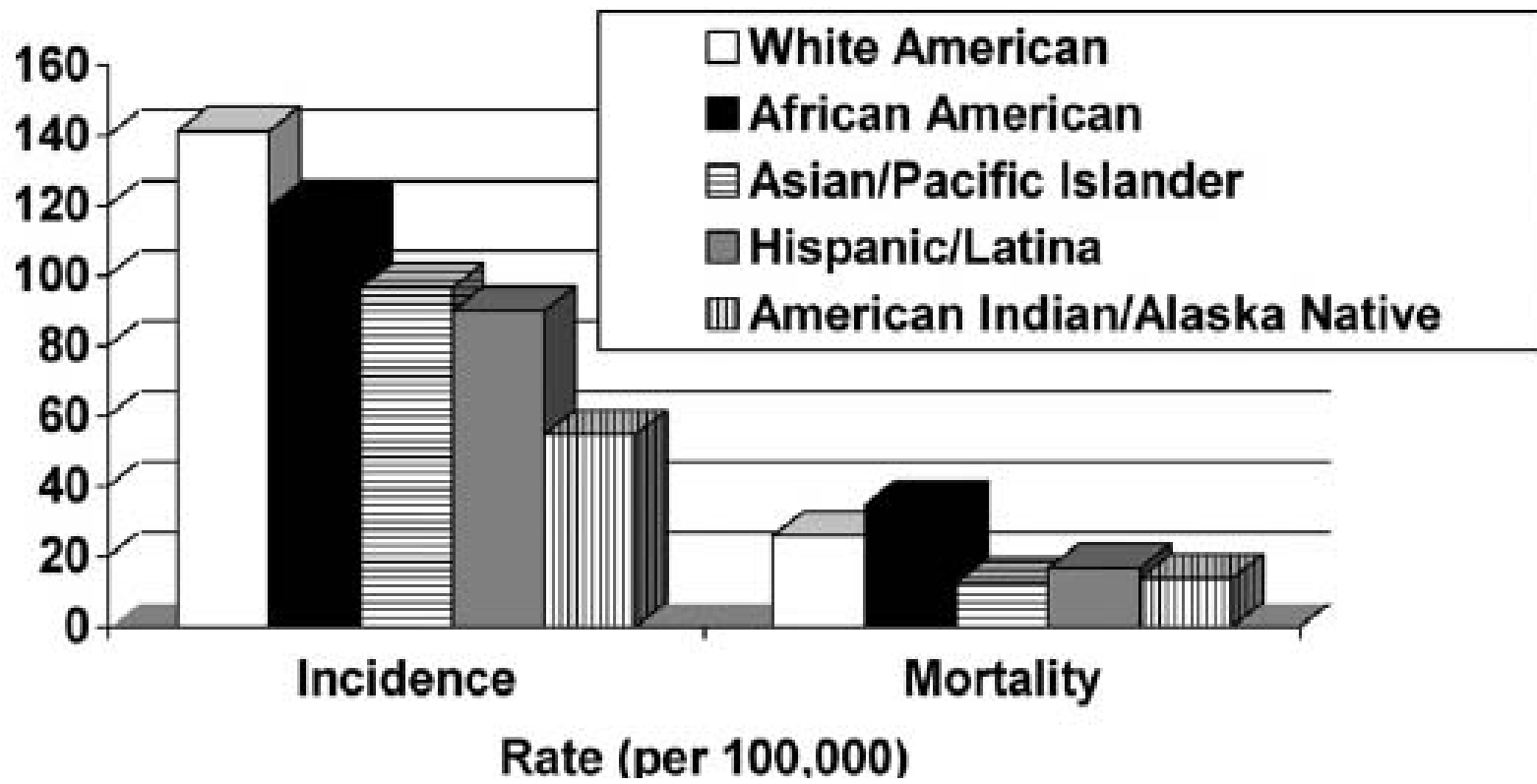
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Breast Cancer

Breast Cancer

- Currently the leading cause of cancer incidence among women worldwide [1]
- 55% of cases occurring in more industrialized countries and 45% in less industrialized countries.
- Rates are highest in USA and lowest in the countries of eastern Asia (91 and 18 per 100000 woman-years, respectively) [2]



Ries and coworkers. [4]

Ethnicity-related variations

African American Vs Caucasian

- Incidence 119 versus 141 per 100,000, mortality rates are 35 versus 26 per 100,000, respectively
- The median age at diagnosis 57 years compared with 62 . Approximately one-third of patients are younger than 50 years compared with only one-fifth [5]
- Male breast cancer is another area of disparities fewer than 1% , incidence rates approximately twice as high for African American men compared with Caucasian and European men.

Disparity in African American women

- Increased prevalence of estrogen receptor negative breast cancers more likely to have alterations in p53 protein.
- Abnormal expression of a variety of proteins involved with cell cycle regulation (cyclins E and D1, and p16)
- Inflammatory and locally advanced breast cancer were higher for African American compared with White American women (3.1 versus 2.2 per 100,000 for inflammatory disease; and 3.8 versus 2.1 for locally advanced cancer).



IS FOOD IS GOOD OR BAD?

Diet / Cancer

It has been estimated that up to **70%** of all cancer is attributed to diet [5]

Dietary hypotheses:

↑ fat consumption breast & colorectal cancers

↑ alcohol intake respiratory, gastrointestinal
breast, and liver cancers;

↓ fiber intake colorectal cancer.

Diet / Cancer

Identification of plant-based dietary agents that may serve as natural inhibitors of carcinogenesis.

- High consumption of vegetables and fruit is protective against cancer of a variety of anatomical sites.
- Intake of 400-600 g/day of fruits and vegetables is associated with reduced risk of several cancers [6]
- Consumption of 2 ounces of watercress (PEITC), at each meal for three days increased the urinary excretion of metabolites of the tobacco specific nitrosamine NNK in smokers [7]

Isothiocyanates (ITCs)

Isothiocyanates (ITCs) are a group of naturally occurring compounds that occur as thioglucoside conjugates, termed glucosinolates.

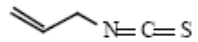
Cruciferous vegetables such as watercress, Brussels sprouts, broccoli, cabbage, kai choi, kale, horseradish, radish, turnip...etc

ITCs inhibit the development of tumors in many of the experimental models investigated, and are being investigated as possible chemopreventive agents for specific human cancers [8]

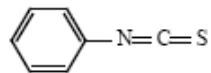
Isothiocyanates (ITCs)

- Several recent epidemiological studies have suggested that humans who consumed higher levels of ITCs might be less likely to develop lung and colon cancer [9]
- Potent cancer chemopreventive agents in animals [10]

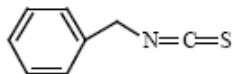
Structure



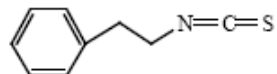
AITC



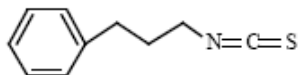
PITC



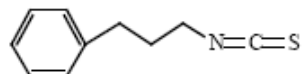
BITC



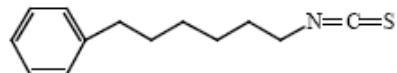
PEITC



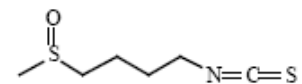
PPITC



PBITC



PHITC



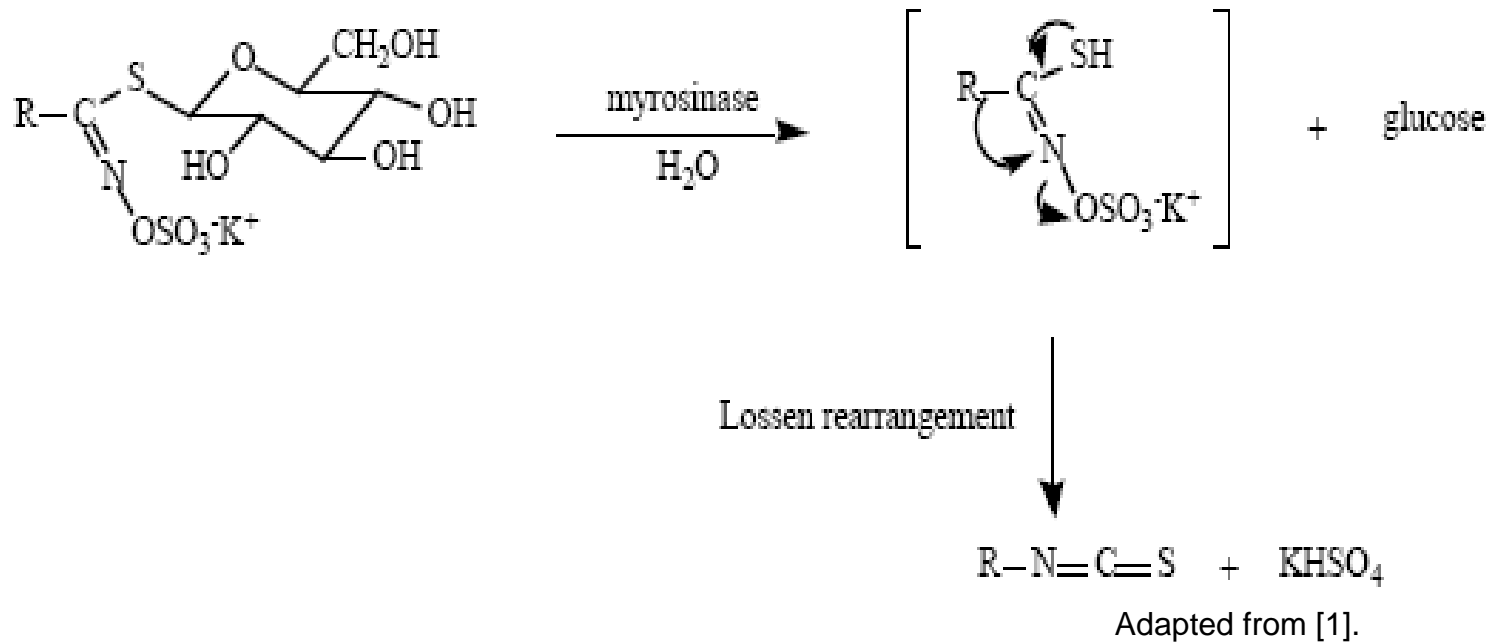
SFO

Structures of major ITCs;

BITC

- Low concentrations has antimicrobial properties
- Marketed in Germany to treat infections of the respiratory tract and urinary tract (capsule of Tromacapâ)
- 14.4 mg BITC (~0.1 mmol), Urinary excretion reached maximum levels after 2-6 h, and excretion was essentially complete by 10-12 h.
- 54% of the administered dose was excreted as BITC-NAC in the urine, but no other major metabolites were identified.

Conversion of glucosinolates to isothiocyanates, catalyzed by myrosinase



When damaged or chewed, ITCs are released by the hydrolytic action of the enzyme myrosinase; the reactions involve initial cleavage of the thioglucoside linkages spontaneously forms sulphate and ITCs by a Lossen rearrangement,

Mechanism

ITCs possess multiple anticarcinogenic mechanisms, including

- inhibition of carcinogen-activating enzymes

- induction of carcinogen-detoxifying enzymes

- increase of apoptosis

- arrest of cell cycle progression

- several other mechanisms that are not yet fully described.

These mechanisms depends on multi-faceted context

Inhibition of Cell Proliferation Mechanisms

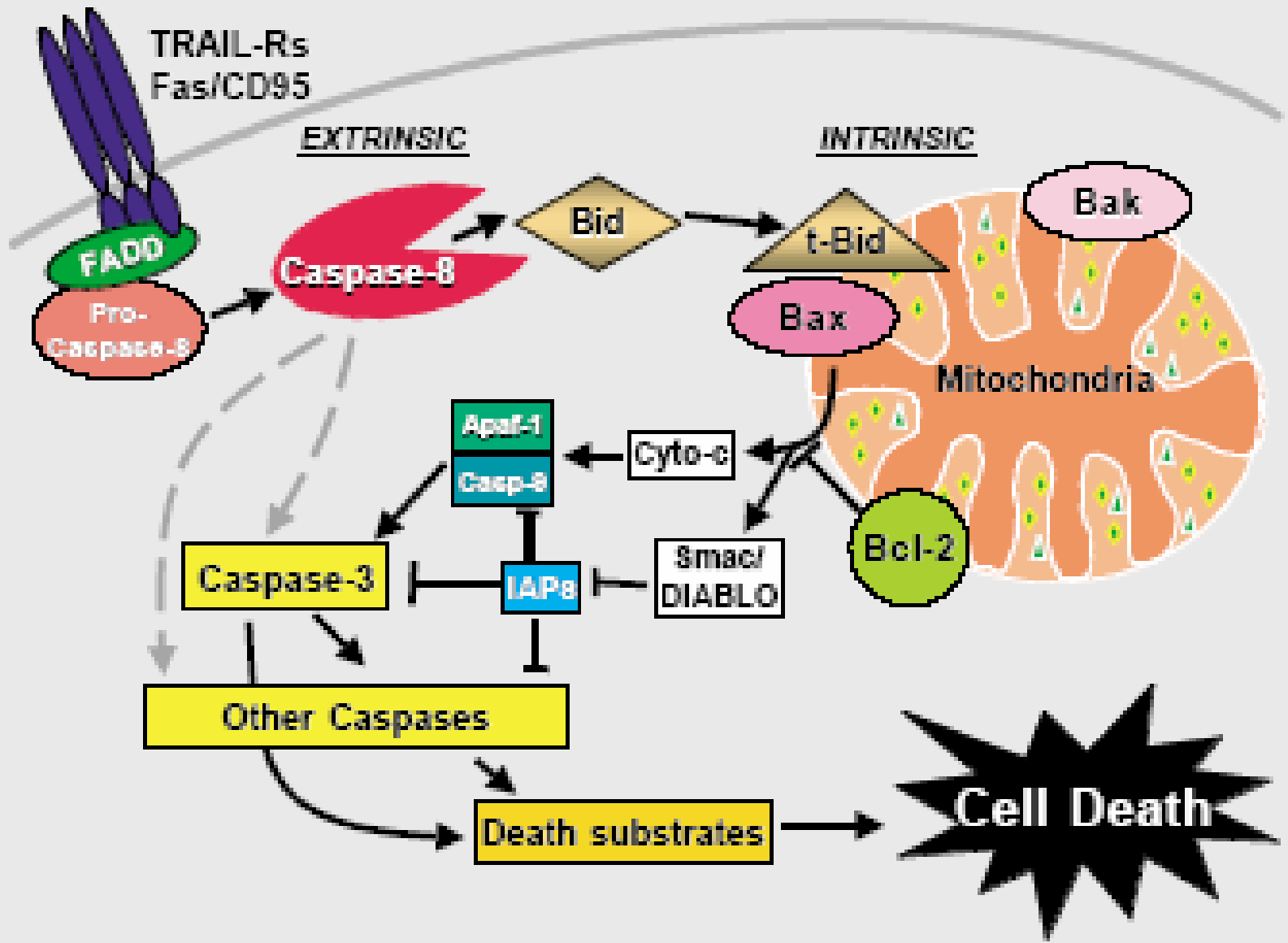
	References
<p>Modulating the activities of phase I and phase II drug metabolism enzymes Direct inhibition or down-regulation (or both) of the cytochrome P-450 enzymes</p>	[7,8]
<p>Bak and Bax proteins involvement of mitochondrial death pathway (caspase-9-dependent apoptosis and alteration of mitochondrial transmembrane potential , involved in the activation of a caspase-3 (-like) protease</p>	[9,10]
<p>Activation of the G2/M DNA damage checkpoint.</p>	[11]
<p>BITC Induction of GST(reactive oxygen intermediates)</p>	[12,13]
<p>Mitogen-activated protein kinases (MAPKs) involvement Phosphorylated Bcl-2 as a key molecule linking the p38 MAPK-dependent cell cycle arrest with the JNK activation by BITC</p> <p>Activation of JNK, MAP kinase, and p 38</p>	[14,15]
<p>Arresting cells in the same phases (S and G2/M) and targeting cell cycle regulator (Cdc25C),</p>	[16]
<p>Oxidative damage has been suggested as playing an important role in carcinogenic processes induced by AITC</p>	[17]

Objectives

OBJECTIVES

- to evaluate the antiproliferative effects of BITC and determine the profile of apoptotic-related genes

Dysregulation of apoptosis has been implicated in carcinogenesis, tumor progression, resistance of tumor cells to chemotherapy, and tumor recurrence.



Why ?????

- Antiproliferative effects
- Differential response in different cell lines
- Pathway-focused interpretation Vs drug design

Tamoxifen

Chemoprevention to reduce breast cancer incidence is one potential

Tamoxifen might be expected effective for African American women,

- relatively fewer adverse effects experienced by premenopausal women (morbidity from venous thromboembolism)
- the increased risk for early-onset breast cancer among African American women.

On the other hand,

- Prevent estrogen receptor-positive breast cancer.

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