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The Epigenetic Impact of Cruciferous Vegetables on Cancer Prevention

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Abstract

The answer to chemoprevention has perhaps been available to the general public since the dawn of time. The epigenetic diet is of extreme interest, for research suggests that cruciferous vegetables are not only an important source of nutrients, but perhaps a key to eliminating cancer as life threatening disease. Cruciferous vegetables such as kale, cabbage, Brussels sprouts, and broccoli sprouts contain chemical components, such as sulforaphane (SFN) and indole-3-carbinol (I3C), which have been revealed to be regulators of microRNAs (miRNAs) and inhibitors of histone deacetylases (HDACs) and DNA methyltransferases (DNMTs). The mis-regulation and overexpression of these genes are responsible for the uncontrolled cellular proliferation and viability of various types of cancer cells. The field of epigenetics and its incorporation into modern medicinal investigation is an exponentially growing field of interest and it is becoming increasingly apparent that the incorporation of an epigenetic diet may in fact be the key to chemoprevention.

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Compliance with Ethics Guidelines

Conflict of Interest

Kendra J. Royston and Trygve O. Tollefsbol declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

sulforaphane; indoles; glucosinolates; cruciferous; vegetables; cancer; prevention; chemo-preventive diet; epigenetics; food; broccoli; cabbage; isothiocyanates; indole-3-carbinol; medicine; heredity; HDAC; DNMT; miRNA; nutrients; apoptosis

Introduction

The field of epigenetics has rapidly expanded since the 1940's, especially with respect to cruciferous vegetables and chemoprevention. The answer to chemoprevention has perhaps been available to the masses in the form of healthy eating throughout the course of mankind's existence. This fast growing field of study— in which investigators are quickly approaching broader comprehension of many diseases that occur through epigenetic modifications—has grown in importance over the years. Epigenetics, or the study of hereditable changes (passed from cell to cell or generation to generation) that are not related to the changes in underlying DNA sequences [1], is regulated via many processes but perhaps most notably DNA methylation, modifications of the histones and non-coding microRNA. DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) play important roles in cellular proliferation and viability [2–4]. MicroRNAs (miRNAs) are important in the inhibition of translation and the degradation of mRNA [5]. miRNAs negatively regulate many genes, and their malfunction has been linked to various pathways of cancer [6]. One issue that arises with uncontrolled proliferation is the ability of cancer cells to use these epigenetic traits in the continued growth and spread of diseased cells. The incorporation of miRNA regulators and DNMT /HDAC inhibitors as a means to promote apoptosis and prevent uncontrolled cellular proliferation through dietary consumption has proven to be a promising field of study to improve current cancer remediation [2, 7–9]. The ingestion of indoles and isothiocyanates show tremendous results on improving both hormone [10–12] and non-hormone based chemotherapies, which is another reason the epigenetic diet, or the control of epigenetic modifiers through the consumption of dietary phytochemicals, is of extreme interest. Many studies suggest that cruciferous vegetables are not only an important source of nutrients, but important in the elimination of cancer as a life threatening disease [7, 13–15].

The idea that the consumption of an epigenetic diet can have life altering effects is remarkable and there are ongoing efforts to unravel the mysteries regarding the impact of glucosinolates, isothiocyanates and indoles, which have been reported to lead to apoptosis and cell cycle arrest in carcinogenic cells [13, 16–18]. Cruciferous vegetables (CV) such as kale, cabbage, Brussels sprouts, and broccoli sprouts contain chemical components including sulforaphane (SFN) and indole-3-carbinol (I3C) which have been revealed to be potent inhibitors of HDACs and DNMTs [2–4, 9, 19]. The field of epigenetics and its incorporation into modern medicinal regimens appears to have considerable potential in health maintenance in that the incorporation of an epigenetic diet may in fact be the key to the prevention of cancer and many other diseases regulated via epigenetic modifications to the histones. Additionally, some studies have shown SFN and I3C to have an effect on estrogen receptor (ER) in breast cancer cells [10, 20]. These specific studies suggest that

future research may lead to breakthroughs in understanding better means to treat breast cancer and enhance hormone based therapies through the incorporation of broccoli and other cruciferous vegetables into the human diet.

Cruciferous Vegetables (CV)

Brassicaceae, or cruciferous vegetables, have chemical components that exhibit anti-inflammatory effects [21]. These foods also drive the detoxification of certain carcinogenic enzymes and are toxic to many types of cancer cells [22]. The consumption of a typical serving of vegetables such as cabbage, broccoli, Brussels sprouts and many others of cruciferin nature (Table 1), may significantly decrease and lessen the incidence of carcinogenic fatality [23]. In fact evidence shows that individuals who consume a diet rich in CV have lower risks of developing cancer [24]. As seen in Table 2, cruciferous vegetables contain chemical components referred to as glucosinolates which give rise to indoles, isothiocyanates, thiocyanates and cyano-epithioalkanes via mastication as a result of the release of the enzyme myrosinase [25]. Thiocyanates are compounds found in great abundance in foods such as cassava and yams and are evidenced to be inversely associated with sickle cell anemia and hypertension, diseases prevalent in the African American community [26, 27]. In fact, it has been reported that individuals who consume diets rich in yams and cassava are less likely to suffer from sickle cell anemia due to the high availability of thiocyanates and the anti-sickling effects of these foods [28]. Cyano-epithioalkanes are components that can be found in rapeseeds in which canola oil is derived [29]. Canola is used as common cooking oil and is beneficial in lowering cholesterol levels [30]. Of the glucosinolates listed in Table 2, indoles and isothiocyanates reveal promising results with respect to cancer prevention. These glucosinolates are important for they are precursors to compounds such as sulforaphane and indole-3-carbinol.

Isothiocyanates: Sulforaphane

As aforementioned, isothiocyanates are derived from glucosinolates and their exposure to myrosinase (Figure 1). Phenethyl isothiocyanate (PEITC) and sulforaphane (SFN) are two dietary isothiocyanates studied in abundance. PEITC modulates miRNA expression and protects the lungs from environmental smoke induced miRNA alterations [31]. This is important because miRNA mutations are one mechanism by which cancer can develop. The isothiocyanate SFN is found in abundance in cruciferous vegetables, more specifically, broccoli sprouts are the most prevalent and common source for this compound [3, 8, 9, 32]. SFN became the subject of considerable interest as a result of the development, by Prochaska and associates in the late 1980’s, of a cell-culture system that detected the induction of anti-carcinogenic phase 2 enzymes. Upon analyzing a vast array of extracts from fruits and vegetables, Prochaska discovered that the broccoli extract had a significant amount of impact on phase 2 enzyme induction [33, 34]. According to Zhang and Tang, they were successful in isolating the liquid component that was responsible for more than 80% of inducer activity; thus began the incorporation of SFN as an anti-carcinogen in the vast array of chemoprevention investigations. SFN has several benefits and may be an effective therapy for the reduction of tumor size as well as for combating multiple pathways of cancer.

Various studies reveal SFN to be an effective inhibitor of HDACs and an inducer of apoptosis through multiple pathways in different cancer types as well as a repressor of human telomerase reverse transcriptase (*hTERT*) gene and its protein product in breast cancer cells [35]. As an HDAC inhibitor, SFN destabilizes androgen receptor, the main signaling pathway regulated by the HDAC6 enzyme, in prostate cancer cells [36]. It is important to note that the use of the SFN HDAC inhibitor for chemoprevention renders very little effect on non-transformed cells [16]. The introduction of SFN causes the activation of caspase-3, 8 and polymerase as a result of the incorporation of the Fas ligand in the breast cancer cell line MDA-MB 231; however, in the breast cancer cell lines MDA-MB-468, MCF-7, and T47D, it is the activation of caspase-3, caspase-9, polymerase cleavage, decreased expression of Bcl-2 and the release of cytochrome-C into the cytosol that are responsible for the initiation of apoptosis [37]. Recent findings, in addition to HDAC inhibition by SFN, have indicated that SFN is an inhibitor of DNMT expression [35, 38]. Therefore, the epigenetic impact likely extends beyond changes in the chromatin of key tumor-related genes and also affects DNA methylation. DNMTs, which are prominent in most cancers, enhance and increase the methylation of DNA. Evidence from our laboratory suggests that SFN serves as a down-regulator of DNMT and is involved in the demethylation of the *hTERT* control region in the process of anti-carcinogenesis [35, 41–43]. SFN also suppresses polycomb group protein (PcG) levels in skin cancer cells which are instrumental in the methylation of histones and suppression of gene expression [39]. This isothiocyanate has also been shown to regulate miRNAs which have major roles in the regulation of genes that manipulate chemoresistance. In fact, miRNA knockdown results in not only increased apoptosis of cancer cells and sensitivity to certain cancer therapeutics, but also the restoration of ERα in ERα-negative cell lines which has implications of improving current chemotherapies and making them more effective through the activation of estrogen hormone receptors [6, 40]. Furthermore, SFN is effective in combination with other chemopreventive compounds such as epigallocatechin-gallate [41], a green tea polyphenol which functions as an enhancement of SFN, as well as in combination with other chemotherapeutic agents making those therapies more effective [42–44]. Other sources indicate that the incorporation of SFN into the human diet may in fact help to prevent and lessen the incidence of the acquisition of breast, prostate, colon and many other cancers [2, 9, 18].

Indoles: Indole-3-carbinol

There is more than just one mechanism by which CVs negatively impact cancer progression. Indoles, another derivative of glucosinolates, are found in abundance in CVs, and indole-3-carbinol (I3C) is showing promising evidence as a cancer preventive therapeutic. I3C has been reported to be an inducer of estradiol 2-hydroxylation which influences estrogen activity, and may be one reason why it has shown positive results as a cancer therapy [45]. Further, I3C may serve as a natural antioxidant and as such is likely to intervene in cancer progression [46]. Estrogen is instrumental in the increase of tumor size in breast cancer patients, and I3C is extremely significant in this regard for it serves as a negative regulator of estrogen [10, 12]. A separate study also reveals I3C to be an inhibitor of mammary gland tumorigenesis which may be due to the increase of 2-hydroxyestrone and the decrease of

16α-hydroxyestrone [47]. This is remarkable for multiple studies reveal other byproducts of cruciferous vegetables, such as SFN, to have similar effects [48]. I3C also facilitates protection from cellular damage caused by free radicals [46], and it is instrumental in defending against hormonal imbalances rendering it ideal as a component of prostate and breast cancer prevention in certain cases [11, 12, 49–51].

p21 and p27 are associated with cell cycle progression and Bax/BCI2 is associated with apoptosis. I3C has several effects on the expression of many genes via nuclear regulation of transcription factors which include the up-regulation of p21, p27, Bax/BCI2, CYP1A, BRCA, GADD153 and the down-regulation of the food carcinogen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) [11,12, 48–50]. PhIP is a heterocyclic amine resultant from the preparation of meats at high temperatures [48,49]. This has significance because BRCA and GADD153 are associated with carcinogen bio-activation and PhIP-DNA is associated with DNA repair [49, 50]. Additionally, the down-regulation of miRNA-21, a miRNA that is typically overexpressed in chemo-resistant pancreatic cancer cells, is induced by I3C. This down-regulation is important in the increased sensitivity and cytotoxicity of pancreatic cancer cells [52].

Conclusion

Many studies have contributed to the incorporation of dietary agents as forms of cancer remediation. Cruciferous vegetables are enriched with several chemical components that have tremendous negative effects on multiple pathways of cancer cells due to their anti-proliferative and anti-tumorigenic properties. The consumption of these vegetables is beneficial in the sense that they are precursors to glucosinolates which give rise to isothiocyanates such as sulforaphane and indoles such as indole-3-carbinol. Most cancers are characterized by the overexpression of HDAC and DNMT and the mis-expression of miRNAs. Both I3C and SFN are inhibitors and regulators of these processes and the incorporation of these compounds causes cancerous cell lines to take on a healthier, and more normalized appearance. In addition, significant decreases in uncontrolled cell growth as well as increases in programed cell death are noticed with the incorporation of SFN and I3C. Many studies reveal that cruciferous vegetables are key instruments in advancing progress toward the prevention of cancer. Future studies will undoubtedly be directed toward further deciding the epigenetic events impacted by the bioactive components of cruciferous vegetables and their significance with respect to not only cancer prevention, but also many other biological processes.

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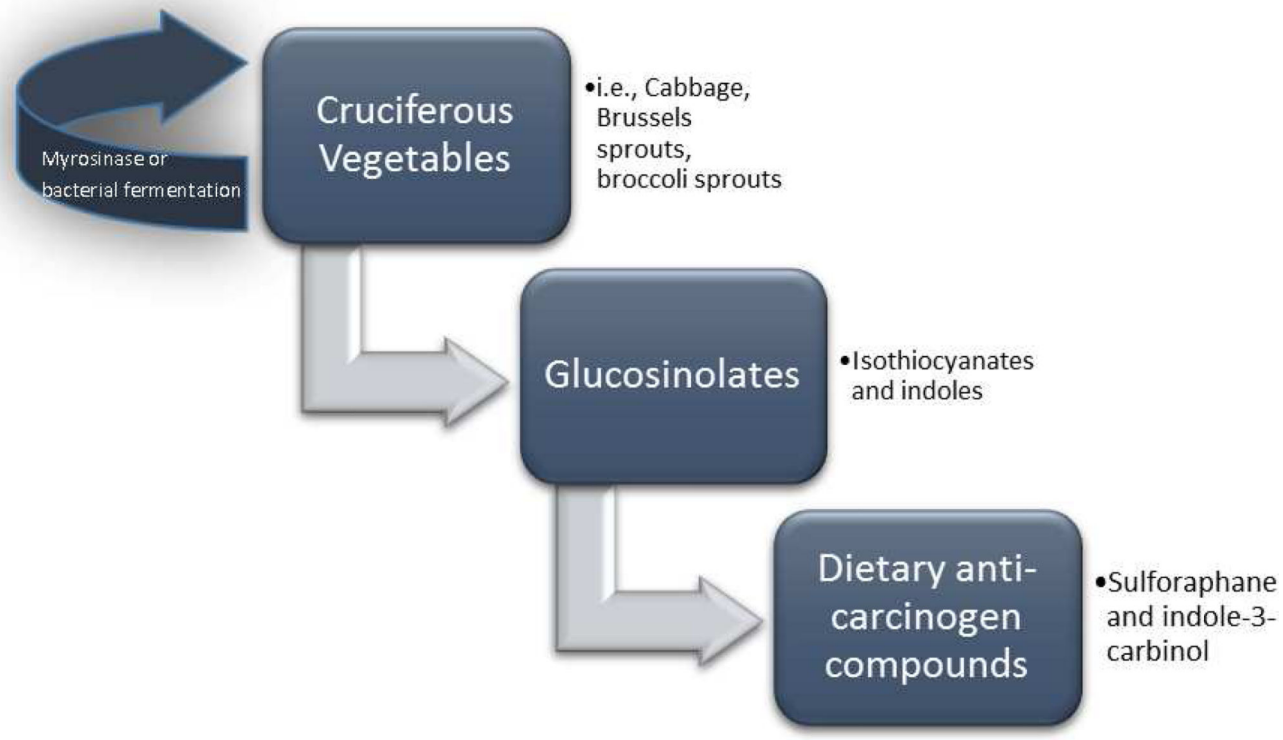

Figure 1. Steps to Anti-Carcinogen Compounds

This flow chart is a simple depiction of how compounds such as SFN and I3C are formed. Once the myrosinase enzyme is released via mastication or bacterial fermentation of cruciferous vegetables, glucosinolates are formed which give rise to isothiocyanates, indoles and other compounds.

Table 1

Concentrations of glucosinolates present in a typical serving of CV

Common CV	Approx. Amount	Glucosinolates	References
Brussels Sprouts	50 g	123 mg	[53]
Broccoli	50 g	30.5 mg	[53]
Cabbage	50 g	54.5 mg	[53]
Cauliflower	50 g	31 mg	[53]

The amounts of glucosinolates in milligrams that are present in a typical serving of a few common cruciferous vegetable are summarized.

Table 2

Glucosinolates and their subcategories

Glucosinolates	Sub-Categories	References
Isothiocyanates	Sulforaphane, Erucin, Phenethyl isothiocyanate	[54]
Indoles	Indole-3-carbinol	[55]
Nitriles	Propionitrile, Succinonitrile, Crotonitrile, Cyanopyrazine	[56]
Thiocyanates	Cavernothiocyanate, 2-Thiocyanatoneopupu-keanane, 4-Thiocyanato-9-cadinene	[57]

Isothiocyanates, indoles, nitriles and thiocyanates give rise to a varied array of compounds. This table lists examples of the compounds in which glucosinolates are the precursors.