Significance of indole-3-carbinol and its metabolite in human cancers

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Abstract: Epidemiological studies have demonstrated that a significant difference exists in the incidence of cancer among different ethnic groups. This difference is known to be partly attributed to dietary factors. Indole-3-carbinol (I3C) and its in vivo dimeric product 3,3’-diindolylmethane (DIM) are produced from naturally occurring glucosinolates in the family Cruciferae. They have received much attention as dietary components that have an inhibitory effect on cancer. I3C and DIM up-regulate the expression of phase I and phase II enzymes, suggesting an increased role in the detoxification and inhibition of carcinogens. They also inhibit the growth of cancer cells through the modulation of genes that are related to the control of cell proliferation, cell cycle, apoptosis, signal transduction, oncogenesis, transcription regulation and protein phosphorylation. Moreover, I3C and DIM inactivate NF-κB, Akt and MAPK signalling pathways, all of which are believed to be potential targets in cancer prevention and therapy. Collectively, several studies have provided evidence for pre-clinical and clinical activities of I3C and DIM against some cancers. Hence, significant advances have been made to date that show I3C and DIM as promising agents for cancer chemoprevention and/or treatment. This review summarises the well accepted inhibitory effects of I3C and DIM on cancer cells and provides a comprehensive view on their molecular mechanism(s) of cancer chemoprevention.

Keywords: I3C, DIM, cancer, prevention, treatment

Introduction

Epidemiological studies have demonstrated that a significant difference exists in the incidence of cancer among different ethnic groups. This difference is known to be partly attributed to dietary factors. Studies from in vitro and in vivo experiments have shown that dietary factors regulate the processes of carcinogenesis, including the initiation, promotion and progression of human cancers (Meyskens 1992; Yang et al 2001). It has been reported that certain components of plant foods, such as fiber, isoflavone and hydrolysis products of glucosinolates, may be protective against cancers (Adlercreutz et al 1995; Steinmetz and Potter 1996; Verhoeven et al 1997). Indole-3-carbinol (I3C) is produced from naturally occurring glucosinolates, contained in a wide variety of plants including members of the family Cruciferae and, in particular, members of the genus Brassica (Broadbent TA and Broadbent HS 1998). I3C is biologically active, and is easily converted in vivo to its dimeric product 3,3’-diindolylmethane (DIM), which is also biologically active. Over one hundred glucosinolates have been identified, predominantly in vegetables of the family Cruciferae (Verhoeven et al 1997; Johnson 2002). In this family, vegetables of the genus Brassica contribute most to our intake of glucosinolates, and include all kinds of cabbages, broccoli, cauliflower and Brussels sprouts.

All glucosinolates share a common basic skeleton containing a glucose group, a side chain and a sulphonated oxime moiety, but differ in side chain R (Figure 1). Glucosinolate hydrolysis products make a significant contribution to the health benefit of brassicaceous vegetables (Tawfiq et al 1995; Johnson 2002). The enzyme myrosinase, which is found in plant cells and also in certain intestinal microflora, catalyses the hydrolysis of glucosinolates (Verkerk et al 1997; Johnson 2002). The glucosinolate hydrolysis products include equimolar amounts of aglucon, glucose and sulphate. The aglucones are unstable and undergo further reactions. The nature of aglucones depends primarily on the side chain of the glucosinolate (Tawfiq et al 1995; Verhoeven et al 1997). Glucosinolates with an indole side chain form indoles. The
most prevalent glucosinolate with an indole side chain is glucobrassicin, which is predominant in brassicaceous vegetables. When hydrolysis occurs, glucobrassicin forms an unstable isothiocyanate, which degrades to I3C (Verhoeven et al 1997; Broadbent TA and Broadbent HS 1998). I3C is the immediate precursor of DIM. Under the acidic conditions of the stomach, I3C undergoes extensive and rapid self-condensation reactions to form several derivatives (Dashwood et al 1994; Verhoeven et al 1997). DIM is the major derivative and condensation product of I3C (Figure 1), and its formation from I3C has been believed to be a likely prerequisite for I3C-induced anticarcinogenesis (Dashwood et al 1994).

It has been reported that I3C and DIM possess anticarcinogenic effects in experimental animals and inhibit the growth of human cancer cells (He et al 1997; Oganessian et al 1997; Cover et al 1998; Kadtare et al 1998; Jin et al 1999; Chen DZ et al 2001; Murillo and Mehta 2001; Hong, Firestone et al 2002; Hong, Kim et al 2002). I3C has also been found to sensitise multidrug resistance (MDR) tumours to chemotherapeutic drugs without eliciting direct toxicity to the host (Christensen and LeBlanc 1996). Moreover, I3C may inhibit breast cancer invasion and migration (Meng, Goldberg et al 2000; Meng, Qi et al 2000). Because of these pleiotropic effects, the interest in I3C and DIM as cancer chemopreventive agents has increased significantly in the past years. Although dietary, epidemiological and experimental studies have shown the benefits of I3C and DIM in the prevention and inhibition of cancer, the molecular mechanism(s) by which I3C and DIM exert their tumour-suppressive effects on cancers have not been fully elucidated. This review summarises the well accepted inhibitory effects of I3C and DIM on cancer cells, and provides a comprehensive view on the molecular mechanism(s) of cancer chemopreventive and therapeutic effects of I3C and DIM.

**Inhibition of oncogenesis**

Oncogenesis is a multistep process, and there is a great opportunity for intervention to stop, revert or delay the oncogenic process. One anti-oncogenic action is the modulation of carcinogen metabolism, including inhibition of procarcinogen activation, induction of detoxification and blocking of reactive metabolites (Verhoeven et al 1997; van Iersel et al 1999). The molecules involved in this modulation are phase I and phase II biotransformation enzymes. I3C has been shown to inhibit chemically induced tumourigenesis of the liver, mammary gland, colon and other tissues, and suppress spontaneous carcinogenesis in mammary gland and endometrium (Bradlow et al 1991; Kojima et al 1994; Verhoeven et al 1997). It has been reported that treatment of rat with I3C increases CYP1A1, 1A2, 2B and 3A activity in rat liver (Stresser et al 1994; Manson et al 1998). I3C also up-regulates the level and activity of glutathione S-transferases (GST) (Bradfield and Bjeldanes 1984; Manson et al 1998). Therefore, the anti-oncogenic activity of I3C administered before or concurrently with a carcinogen is thought to be mediated through alternations in the levels and activities of phase I (eg p450 or CYP) and phase II (eg GST) isozymes in the liver and/or extrahepatic tissues, resulting in their increased capacity for detoxification of carcinogens.

The authors utilised cDNA microarray technique to determine the alternation of gene expression profiles of PC3 prostate cancer cells exposed to I3C and DIM. From microarray analysis, both I3C and DIM up-regulated the expression of phase I and II enzymes in PC3 prostate cancer cells (Li et al 2003). The most important phase I enzymes are cytochrome p450 enzymes, which oxidise carcinogens and make them more hydrophilic and susceptible to detoxification. Phase II metabolism comprises detoxification and conjugation reactions, making phase I metabolites more polar and readily excretable. I3C and DIM up-regulated