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Sulforaphane and prostate cancer interception

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Whereas much attention is focused on distinguishing newly diagnosed prostate cancers that will progress to become aggressive forms of the disease from those that will remain indolent, it is also appropriate to explore therapeutic and lifestyle interventions to reduce the risk of progression. Diets rich in broccoli have been associated with a reduction in risk of progression, which has been attributed to the compound sulforaphane. Although the mode of action of sulforaphane has been extensively studied in cell and animal models and a multiple of mechanisms that could underpin its protective effects have been proposed, recent evidence from human intervention studies suggests that sulforaphane is involved in a complex interplay between redox status and metabolism to result in a tissue environment that does not favour prostate cancer progression.

Introduction

The incidence of prostate cancer has risen substantially over the past few decades. This is likely to be caused by an ageing population and a greater degree of diagnosis, largely owing to an increase in testing for prostate-specific antigen (PSA) in plasma and the introduction of routine screening programmes, with considerable implication for healthcare costs [1,2]. The dilemma that physicians and patients face is that only a minority of these newly diagnosed prostate cancers will become aggressive in nature with serious consequences for health but, currently, it is not possible to identify the 'pussy cats' from the 'tigers' [3]. Clinical and therapeutic interventions for all diagnosed prostate cancers are neither feasible nor advisable owing to the potential adverse nature of the treatments. One option that has been widely advocated and adopted is 'watchful waiting' or 'active surveillance', in which men with a diagnosis of low-grade cancer have regular PSA testing and annual prostate biopsies, with further therapeutic or clinical intervention only taking place upon evidence of cancer progression [4]. Lifestyle interventions, such as diet and exercise, might however be effective in reducing the probability of prostate cancer progression and could be readily integrated with an active surveillance or watchful waiting programme [5].

Diets that are rich in cruciferous vegetables such as broccoli have been associated with a reduction in progression from localised to more aggressive forms of prostate cancer [6], a phenomenon referred to as 'cancer interception' [7]. These vegetables uniquely contain a group of sulfur-containing glycosides known as glucosinolates that are hydrolysed upon consumption, either by the endogenous plant myrosinase or, if myrosinase has been denatured by cooking, by putative thioglucosidases within the gut microbiota to isothiocyanates and indoles [8]. These glucosinolate hydrolysis products have been shown in animal models to prevent or delay cancer development, and are thought to underpin the health-promoting properties of cruciferous vegetables [8]. The most studied of the glucosinolate hydrolytic products is sulforaphane (1-isothiocyanato-4-methylsulfinylbutane, SF), derived from glucoraphanin (4-methylsulfinylbutyl glucosinolate) (Fig. 1) which specifically accumulates in broccoli florets [9]. Following consumption of broccoli, sulforaphane is metabolised via the mercapturic acid pathway and excreted in urine predominantly as a conjugate with *N*-acetyl cysteine. In plasma, it has been found that approximately 50% of sulforaphane is found unconjugated with other thiols [10]. If a standard portion of broccoli is consumed in which the plant myrosinase enzyme is active, plasma levels of sulforaphane and its thiol metabolites peak at about 2 μM after one hour [10]; whereas if plant myrosinase has been denatured through cooking the peak sulforaphane concentration occurs after three to four hours and is less than 100 nM [11]. High-glucoraphanin broccoli has been developed through the introgression of a Myb28 allele from a wild brassica species that delivers 3–4-times

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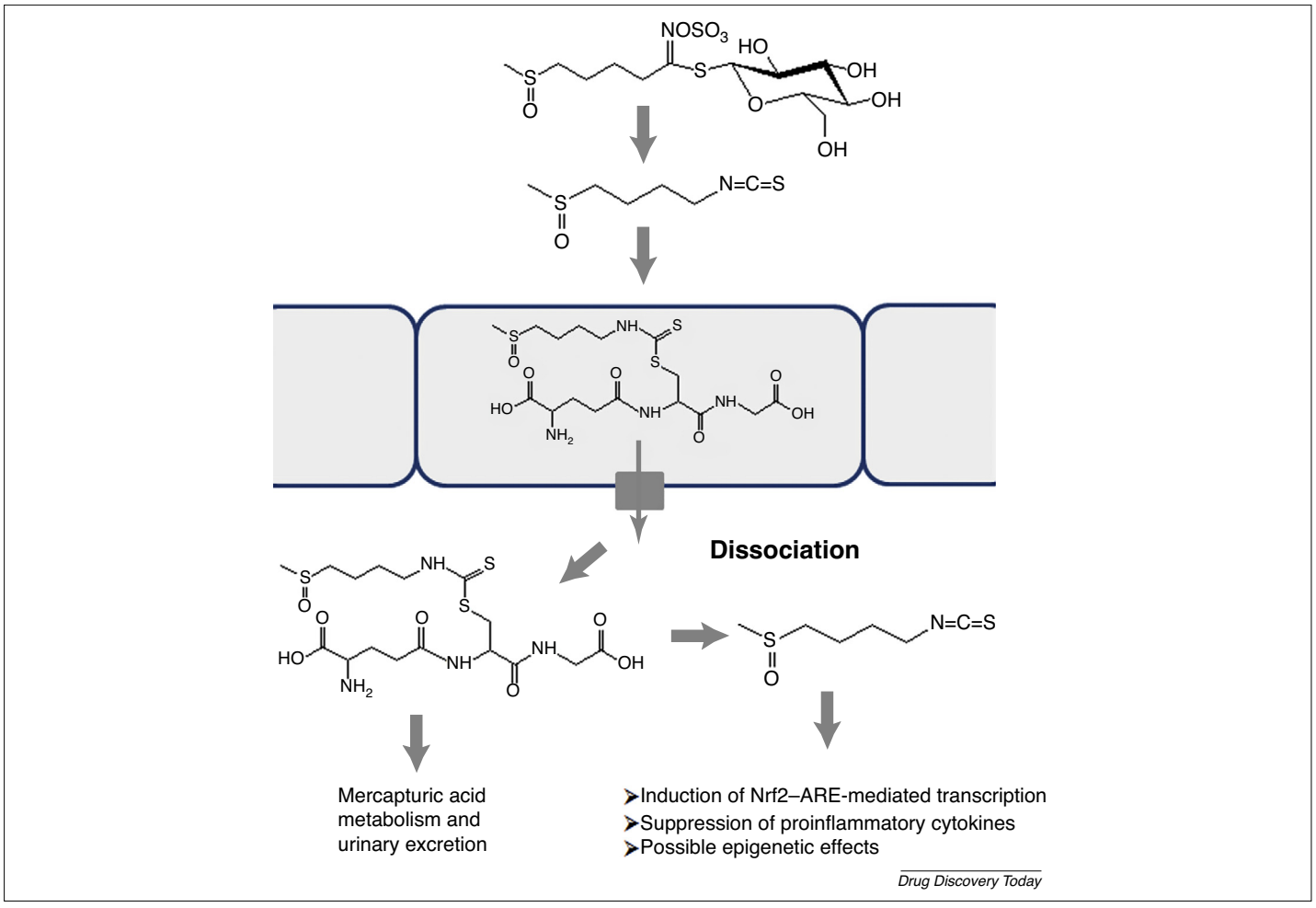

FIGURE 1

The hydrolysis of glucoraphanin that accumulates in broccoli to generate sulforaphane, and its subsequent metabolism and biological activity. Abbreviation: ARE, antioxidant response element.

more sulforaphane than standard broccoli [10,12]. Sprouted broccoli seeds have also been widely used as a means to deliver sulforaphane [13,14].

Consistent with epidemiological studies that have correlated diets rich in broccoli with a reduction in the risk of aggressive prostate cancer, sulforaphane has been shown to prevent or delay tumour development in a variety of animal models of prostate cancer, through a multitude of mechanisms [9,15–18]. However, the majority of these studies has exposed cells and animal models to levels of sulforaphane far greater than that which human tissues would be exposed to following broccoli consumption. In this review, we discuss two modes of action that we consider most likely to underpin the chemopreventive effects of sulforaphane obtained from diets rich in cruciferous vegetables, namely modification of redox status and its effects on cell signalling pathways and the suppression of proinflammatory cytokines.

The Warburg effect, prostate metabolism and the 'anabolic phenotype'

In contrast to normal differentiated cells that primarily generate ATP through oxidative phosphorylation, most cancer cells rely on aerobic glycolysis to generate their energy needs, a phenomenon known as the Warburg effect [19]. Energetic considerations suggest that this is not driven by a need to generate more ATP but by a need to provide the metabolic building blocks to make new cell membranes and associated structures, nucleotides and proteins to underpin cellular proliferation [19]. Thus, enhanced glycolysis is associated with an enhanced pentose phosphate cycle to generate NADPH required for lipid and steroid synthesis and nucleotides for DNA synthesis. Citrate is shunted out of the tricarboxylic acid (TCA) cycle, compensated for by enhanced glutamine and other amino acid anaplerosis [20]. This 'anabolic phenotype' is likely to be maintained through enhanced AKT/phosphoinositide-3-kinase (PI3K) activity that drives metabolic processes required for cellular proliferation [20]. Although mutation and inactivation of the tumour suppressor phosphatase and tensin homologue (PTEN) is a frequent occurrence within prostate tumours, PTEN can also be reversibly inactivated owing to the well characterised oxidative formation of a disulfide bridge between Cys-71 and Cys-124 in the active site of the enzyme following an increase in the oxidative status of the cells and tissues [21] (Fig. 2). Thus, lifestyle factors that increase oxidative stress such as diets rich in branch-chain fatty acids and a sedentary lifestyle combined with ageing can enhance AKT/PI3K signalling and drive the anabolic phenotype that contributes to cell proliferation. Important other proteins that could contribute to this anabolic phenotype are also redox sensitive, of

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