ANDROGEN RECEPTOR MODULATION AND BLADDER CANCER PREVENTION – A SHORT REVIEW

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Abstract

The prevalence of bladder cancer (BCa) is 4 times higher in men as compared to women, and gender differences have been the focus of attention for few years. Androgen receptor (AR) may be a putative explanation for gender differences. It may also be related to unfavourable BCa progression and development because of the increased androgen sensitivity of urothelium to carcinogens. Moreover, cigarette smoking and occupational exposure to carcinogens have been reported to play contributory roles with the highest attributable risk of BCa. In this review, the authors attempt to summarize the seminal research works that synthesized current understanding of the central role of AR in the negative regulation of carcinogen detoxification activity in BCa. In particular, the authors discuss the regulatory effects of 3,3'-diindolylmethane on AR gene transcription through microRNA as its suggested effect on the prevention of BCa. Moreover, to show the still existing problem of occupational exposure and BCa incidence, the authors review recent studies in this area. Based on the rapidly accumulating scientific evidence, it seems pragmatic that androgen/AR-mediated interference in the detoxification mechanism may be inhibited by phytochemicals. Therefore, collectively, nutrition has a key role as gene–nutrient interactions are important contributors to BCa prevention, also through epigenetic modifications. Here, the authors have derived suggestions for future research. Med Pr. 2022;73(2):151–62

Key words: AR, detoxification, DIM, epigenetic regulation, occupational exposure, UGT

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INTRODUCTION

The World Health Organization estimates that in Europe premature mortality before the age of 70 was caused by cancer [1]. According to the world trends, the authors observe a rapid increase in the number of seniors in Europe [2]. The growing number of people over the age of 65 increases the incidence of cases of old-age cancers such as bladder cancer (BCa). Therefore, BCa will be more and more frequently reported in males and females, especially in Europe. The Global Cancer Statistics in 2020 showed that in terms of new cases in the world BCa ranks 12th with the number of 573 278, which means 3% of all sites [3]. The World Health Organization/Europe predicts that the number of new cases of BCa from 2020 to 2040, in both sexes and age groups between 0 to >85 will increase by 36.7%, from 221 298 to 302 479 [4]. The gender disparity is important to note, as early studies have shown that BCa is 4 times more common in men than in women and that this proportion remains the same all over the world [5].

Apart from the influence of age and gender on the risk of BCa development, the remaining risk factors such as cigarette smoking and occupational exposures should not be forgotten. An increased risk of BCa is associated with workplace chemical carcinogens and widespread exposure to tobacco smoke in the environment. It is regarded that up to 50% and 20% of BCa sites is the result of tobacco smoking and occupational or environmental toxins, respectively [5,6]. Depending on the profession occupational exposure and environmental exposure to airborne metals (mercury, lead,

and manganese), traffic air pollution, aromatic amines (4-aminobiphenyl, 2-naphtylamine and benzidine), asbestos – they are all suspected or linked to BCa risk [7].

Attempts to understand gender differences in BCa have been the focus of attention for few years [8,9]. Considering the importance of gender in this disease, it is believed that the incidence may be related to hormones, i.e., androgens and estrogens. Although the bladder is not regarded a sex organ that responds to androgen signals [10], studies to date have shown that differences between men and women in carcinogen sensitivity are observed, and that they may be related to sex hormone activity. The differences in carcinogen detoxification metabolism and impact of environmental exposure will vary according to gender [11]. Numerous studies indicate the potential role of androgens, estrogens and their corresponding receptors in BCa development and the disease course [6].

Androgens and androgen receptor (AR) in several investigations have been shown as key players in the BCa progression and development [12]. The basic molecular mechanisms through which androgens promote BCa development and affect the course of the disease include an increased androgenic sensitivity of urothelium to carcinogens, impaired degradation of carcinogens via androgen-dependent pathways or direct oncogenic effect of androgens [13]. Long-term cigarette smoking and occupational exposure have a potentially negative effect and influence BCa neoplastic processes also depending on gender [14,15].

The use of a high-quality diet and nutrition is highly effective in the prevention of cancer [16]. Due to bioactive phytochemical compounds of cruciferous vegetables, they can inhibit tumour initiation, promotion, metastasis and improve cancer cells' sensitivity to chemotherapy by epigenetic regulation of microRNA (miRNA, miR) expression [17,18]. One of them is indole-3-carbinol (I3C) and its bioactive product 3,3'-diindolylmethane (DIM).

The DIM triggers a pleiotropic effect on cancer cells by modifying many important genes for cell cycle control, cell proliferation, signal transduction and other cellular processes. In this sense, DIM is important for its strong inhibitory effects on the expression of AR and the activation of AR signaling [19,20]. Moreover, DIM causes suppression of cancer growth by increasing the efficiency for detoxification and suppression of carcinogens by AR gene transcription through epigenetic modulation [21].

In this review, the authors present important information about aspects of DIM via modulation of AR in BCa and provide a brief overview of the literature on the occupational BCa incidence. This paper may provide some suggestions for further research direction in novel epigenetics targets for the prevention of BCa.

METHODS

The objective of this paper is to evaluate the published evidence about the aspects of DIM via modulation of AR in BCa, and to summarize findings across the studies on occupational exposure and BCa incidence. The authors reviewed the published literature by searching for relevant publications in Google Scholar, MEDLINE (PubMed) and Web of Science databases using the following key phrases: "bladder cancer" and "DIM" and "AR" from 2011 to October 2021 or "bladder cancer" and "workers" and "case-control study" from 2020 to October 2021. Two investigators reviewed independently the titles and abstracts of all the studies identified from the literature search against the inclusion criteria to determine those eligible for inclusion and retrieval of full-text articles. Inclusion criteria included English language papers containing original data.

RESULTS

Cigarette smoking

Tobacco is the greatest known environmental risk factor for developing BCa. Cigarette smoking is a major risk factor for BCa in the general population [14,22]. Cigarette smoking causes a 2- to 4-fold increased risk of BCa [23]. The incidence of BCa among men is the highest in Europe and North America, these global trends reflect the prevalence of smoking. Especially long-term cigarette smoking has a potentially negative effect. The effects of smoking appear to be alleviated after smoking cessation >10 years [24]. Although cessation reduces the risk of BCa, even after 10 years of not smoking the risk of developing BCa is still almost twice higher than in never-smokers [25].

Toxins in cigarette smoke come from approx. 70 carcinogenic substances out of the total of 7000 chemicals [26,27]. The most studied carcinogens such as polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are metabolically activated. It is worth mentioning that also very popular smokeless tobacco products contain different concentrations of nicotine, toxic metals and carcinogens [28].

Additionally, smoking addiction is a factor that has a negative impact on eating habits. Studies show that smokers have a much less healthy lifestyle and have worse eating habits. Smokers often do not eat breakfast and do not eat between meals, which leads to their

being underweight. Being underweight is mainly due to the low caloric content of consumed dishes and the low content of nutrients. It can result in functional and physical impairment as well as a reduced quality of life [29]. Especially in smokers, lower daily intake of key nutrients, e.g., vitamin C, is observed.

Exposure to tobacco smoke may also occur during work. For example, many waiters are exposed to both passive tobacco smoke and active cigarette consumption. The research shows that smoking cigarettes often occurs simultaneously with other risk factors such as specific occupations. Therefore, for some professions smoking changes the risk of developing BCa. The impact of the occupation-specific prevalence of tobacco is of great importance in the exposure assessment. Occupation-specific smoking habits are difficult to assess individually [30].

Occupational exposure
Research on the relationship between occupational exposure to carcinogenic substances or their mixtures and the occurrence of cancer in workers is a topic of concern for occupational medicine in many countries. Getting to know the problem better has led to, *inter alia*, widespread use of preventive measures in the workplace, as well as closing or transforming industries. Owing to occupational regulations numerous sources of exposure have been reduced in majority of the countries. However, despite the closure of harmful factories, there are still industries that pose risk to workers. Occupational epidemiology studies confirming the influence of carcinogens on the risk of BCa and studies on long-term adverse effects are still an important field of research. The authors summarize the BCa studies that have evaluated the importance of occupational exposure to carcinogenic substances in the last year.

Table 1 summarizes findings across the studies on occupational exposure and BCa. A total of 22 studies in the field of occupational exposure and BCa incidence were published. Majority of the studies are cohort ones, but there are also case-control studies carried out all over the world. The research has focused primarily on assessing the risk of developing BCa [31–36], but also overall survival rates [37], overall incidence [38], mortality odds ratio [32,39,40] and lifetime prevalence [41,42]. Most of the studies have found an increased risk of developing BCa among exposed workers. In addition, the authors also observe effects of occupational exposure to carcinogens from the remote past.

Toxic ingredients that are most commonly used in the industry include, among others, aromatic amines such as 2-naphthylamine, 4-aminobiphenyl and benzidine, and 4,4'-methylenebis like 2-chloroaniline, which are present in many chemical products and which are used by dye and rubber industries [42]. Aromatic amines are also used in the manufacturing of products such as hair dyes, paints, fungicides, metals and plastics. In addition, these substances are present in cigarette smoke, motor vehicle exhaust or drinking water contaminants [34]. Research also confirms that exposure in the aluminum production industry causes BCa. Aluminum smelting is associated with a wide range of toxic exposure constituents including asbestos, beryllium, lead, polycyclic aromatic hydrocarbons (PAHs), silica and other chemical vapours [40]. Asbestos exposure is also significant for the health of workers. Studies show that occupational asbestos exposure is carcinogenic to humans. Workers involved in asbestos-cement sector production jobs, rolling stock, shipbuilding, glasswork, harbours, insulation and other industries are likely to have an elevated exposure to asbestos [32].

Substances such as ortho-toluidine, benzidine, and 2-naphthylamine have been classified by the International Agency for Research on Cancer (IARC) into Group 1 carcinogens, 2012–2020 [42]. In this group there are also chemicals or mixtures of chemicals such as diesel engine exhaust, PAHs, asbestos, trichloroethylene and benzene to which mechanics are exposed. Car mechanics are exposed to many other substances that have been identified as probable human carcinogens (Group 2A) like lead, styrene and tetrachloroethylene or possible human carcinogens (Group 2B) such as gasoline, carbon tetrachloride, and metallic fumes containing nickel and chromium. However, the products made from substances included in the above-mentioned groups are still used worldwide. In turn, trucking industry workers are regularly exposed to vehicle exhaust from diesel, other types of vehicles on the streets, traffic exhaust and so on. At the same time, it has been found that gasoline engine exhaust as possibly carcinogenic to humans belongs to Group 2B, while diesel engine exhaust is carcinogenic to humans and belongs to Group 1 [31,38]. Some of the agents listed here are also classified by IARC as those with sufficient or limited evidence of human BCa [43].

Cotton production also causes exposure to pesticides, while dyes leave residues such as sulfur on the product, which indirectly exposes workers to chemicals. Products from cotton fiber but also synthetic fiber influence the body because of carcinogenic substances used in the process of obtaining textile products [44]. However,

Table 1. Studies on the influence of occupational exposure to chemicals on bladder cancer (BCa) occurrence (from 2020 to October 2021)

Industry and worker type	Occupational exposure	Country and reference
Mechanics	diesel engine exhaust, polycyclic aromatic hydrocarbons, asbestos, trichloroethylene and benzene, lead, styrene, tetrachloroethylene	Brazil [100]
Different types of work	silica, asbestos	Canada [33]
Painters and rubber manufacturing industry	painting, trichloroethylene, asbestos, wood dust, diesel gasoline exhausts, formaldehyde, and painting or varnish	France [41]
Farmers, labourers (dye, chemical, fertilizer industry), housewives, businessmen	pesticides, insecticides, weedicides, herbicides	India [47]
Agriculturists	pesticides	Iran [46]
Military community	diverse carcinogens	Iran [101]
Factories using asbestos (asbestos cement, rolling stock, shipbuilding, glasswork, harbours, insulation and other industries)	asbestos	Italy [32]
Lumber, wood products, printing and allied industries, petroleum and coal products, fabricated metal products, electrical machinery, equipment and supplies, information and communication electronics	diverse carcinogens	Japan [36]
Professional and managerial, clerical, sales and service, agriculture, forestry, and fishery, transportation (including machine operation workers), construction and mining, manufacturing, (e.g., homemakers, students, unemployed, miscellaneous)	diverse carcinogens	Japan [37]
Factory manufacturing organic dye/pigment intermediates	aromatic amines: ortho-toluidine, aniline, para-toluidine, ortho-anisidine, 2,4-xylidine, ortho-chloroaniline	Japan [34]
Road transportation workers, motor vehicle engine exhaust, traffic exhaust, housework	detergents, cleaners, bleaches, oil fumes during frying, traffic air pollution	Korea [102]
Maritime workers – seafarers and fishermen	diesel exhaust, asbestos, polycyclic aromatic hydrocarbons, ultraviolet radiation	Nordic countries [38]
Textile industry	cotton dust, caustic soda, acetic acid, hydrogen peroxide, surfactants, formaldehyde, azo dyes, phthalates, perfluorinated compounds	Turkey [44]
Welding, making cement	lubricating/coolant oils, soldering/brazing, degreasing, fumes from quenching/forging or cooling	United Kingdom [103]
Firefighters	polycyclic aromatic hydrocarbons, polychlorinated biphenyls, formaldehyde, benzene, 1,3-butadiene, asbestos, diesel exhaust, circadian disruption from shift work	USA [39]
Aluminum smelting workers	airborne metal dusts, asbestos, polycyclic aromatic hydrocarbons, silica, chemical vapors	USA [40]
Boat builders	cumulative styrene	USA [104]
Benzidine manufacturing plant	benzidine, dichlorobenzidine	USA [35]
Chemical manufacturing plant	aromatic amine: ortho-toluidine	USA [42]
Automobile manufacturing workers	metalworking fluids	USA [105]
Heavy truck drivers, tractor-trailer drivers, bus drivers, engine mechanics, repairers, equipment operators	respirable elemental carbon	USA and Spain [31]

also during the cotton production process itself, workers at various stages of its production are exposed to chemical softeners, bleaches, synthetic wax, flame retardants and finally formaldehyde spray. Moreover, numerous cases of BCa are observed among workers working in the dying process. This is because of exposure to carcinogenic effective azo dyes and heavy metal-containing substances [45].

It is not only work in an industry that carries the risk of cancer. Considerable concern about cancer risk exists among agriculturists, farmers, firefighters, mechanics, aluminum smelting workers. Agriculturists and farmers are potentially exposed to a number of known and suspected carcinogens including pesticides, insecticides, weedicides and herbicides [46,47]. Firefighters constitute another professional group that is exposed to polychlorinated biphenyls, PAHs, asbestos, diesel exhaust, benzene, 1,3-butadiene, formaldehyde, and circadian disruption being a result of shift work [39].

**The importance of androgen receptor
in the carcinogen UGT detoxification system
in bladder cancer**
Androgen receptor is a steroid hormone receptor that is mainly activated by androgens: testosterone and dihydrotestosterone (DHT) [48]. Down-regulation of AR is observed in the case of various phytochemicals such I3C, DIM, sulforaphane, curcumin, oridonin, isoliquiritigenin and wogonin [49]. It is likely that the AR moves from the cytoplasm to the nucleus after binding androgens and controls various genes' transcription. AR can significantly impact urothelial signaling and negatively regulate the activity of detoxification enzymes like uridine-diphosphoglucuronosyltransferase (UGT).

The UGTs enzymes belong to the second phase of metabolism and they are very important for metabolizing carcinogenic compounds such as aromatic amines in detoxification processes. Sex-dependent differences in carcinogen degradation efficiency are related to the effect of AR [48]. Studies have shown male predominance in the presence of AR. Therefore, it has been suggested that the BCa is a sex hormone-dependent disease due to the greater susceptibility to carcinogens.

Ortho-toluidine, 4-aminobiphenyl, 2-naphtylamine and benzidine are aromatic amines occurring in the mainstream tobacco smoke and in the workplace, and they are currently listed in IARC Group 1 risk factors for BCa. Detoxification of these carcinogens primarily consist in their degradation via the hydroxylation, acetylation, and glucuronidation pathways. The primary metabolic pathway of the aromatic amine activates them into mutagenic and carcinogenic compounds. The UGTs catalyze the attachment of glucuronic acid to a lipophilic substrate containing a nucleophilic functional group. Studies have shown that reduction of UGT1 expression in endothelial cancer leads to accumulation of carcinogens in the bladder [50]. Expression of UGTs is reduced by AR signals in the urothelium, thereby promoting the development of BCa [51]. Thus, research indicates an important role of AR signals in the development of BCa. In both *in vitro* and *in vivo* tests, reducing AR expression inhibits the growth of cancer cells [52,53].

Androgen receptor plays an important role in promoting metastasis and progression of BCa [54,55]. It is also considered an indicator of BCa recurrence [56]. The AR interacts with major signaling pathways i.e., β-catenin and cyclin-d promoting the aggressive type of BCa [57–59]. In *in vitro* studies, knockout of the AR gene and lack of its expression increased apoptosis, reduced proliferation and migration of BCa cells. Silencing expression of AR through electroporation-assisted interference significantly inhibited AR-positive bladder tumour growth by reducing cell proliferation and increased apoptotic indices [60]. In BCa trials, an increase in co-regulators to form the AR transcription complex has been observed [61]. Studies in mice indicate that males exposed to carcinogens suffer from BCa more often than females. Besides, AR knockout has suppressed cell proliferation *in vitro* and xenograft tumour growth *in vivo* [52]. Also, Johnson et al. [62] have observed that castration limited BCa development and the use of DHT restored tumour growth. Studies on BCa cells confirm the effect of the used DHT on the increase in AR expression [10]. On the other hand, loss of AR expression may be associated with the invasive type of BCa [63]. Other authors discuss and explain that the decreased AR expression in higher-grade prostate cancer tumours may indicate a poorly differentiated cell type or transition to an androgen-independent state [62]. In conclusion, the potential for AR signaling mechanism in BCa is still not fully understood [64,65].

**Epigenetic modulation of androgen receptor
by dietary phytochemical – 3,3'-diindolylmethane**
Proper diet takes the second place after quitting smoking in terms of avoiding the cause of cancer in Western countries. Epidemiological studies suggest that people with an antioxidant diet rich in fruit and vegetables have a lower risk of developing chronic diseases [17,66]. The concept of using dietary ingredients to prevent cancer is nothing new, but the understanding of chemoprotective properties of dietary ingredients is still evolving. Epidemiological studies have shown that consumption of broccoli and other cruciferous vegetables such as cauliflower, kale and cabbage reduces the risk of developing different cancer types. Also, higher consumption of cruciferous vegetables by the diagnosed persons reduces the risk of the disease progression [67,68].

The idea of using dietary ingredients to prevent cancer is an important issue and therefore understanding of chemoprotective action is still being deepened. Phytochemicals have a positive effect on human health by regulating DNA methylation and chromatin modification in cancer. Modulation at a molecular level, i.e., miRNA expression, may change the gene expression profile of key oncogenes and tumour suppressor genes [69]. Plants contain many bioactive phytochemicals which can inhibit tumour initiation, promotion, metastasis and which can improve cancer cells' sensitivity to chemotherapy by epigenetic regulation of miRNA expression. Phytochemicals are an interesting and potential target in cancer therapy [69]. Multidirectional activity, low toxicity and phytochemicals' natural origin – these all characteristics make them good material supporting treatment processes.

Glucosinolates are the most characteristic phytochemical compounds of Brassica genus. These compounds are easily hydrolyzed to form the unstable isothiocyanate and degraded to I3C. The I3C is present at relatively high levels in brassica vegetables and has anticancer effect [70]. I3C is not stable at low pH, which spontaneously forms DIM in the acidic environment of the stomach. DIM is a dimer of I3C [71]. Animal and human studies indicate an anti-cancer effect of bioactive products like I3C and DIM [72–76].

The DIM has been shown to interact with several pathways, such as the androgen and estrogen receptor signaling pathway, the aryl hydrocarbon receptor pathway, the Nrf2 pathway and the NF-κB pathway. It potentially represents a multi-purpose drug [77–81]. Moreover, gene expression studies have shown that DIM regulates many important genes for cell cycle control, cell proliferation, signal transduction and other cellular processes, suggesting that DIM exerts a pleiotropic effect on cancer cells.

Inactivation of Akt and NF-κB by I3C helps in sensitizing cancer-resistant cancer cells, making I3C and DIM a potential new strategy for sensitizing cancer cells to chemotherapeutic agents [82]. Nowadays, DIM has become a popular dietary supplement because of the great therapeutic potential in many diseases. The DIM is also important in cancer therapy because it regulates and reduces AR expression [83]. It also shows much stronger inhibitory effects than I3C on the expression of AR and activation of AR signaling. Further studies in rats show that DIM affects not only AR but also testosterone levels [84]. The DIM affects the growth of biotransformation enzymes and increases efficiency for detoxification and inhibition of carcinogens by AR regulation [19,20,85,86]. Studies suggest a new role

for DIM in the epigenetic modulation of AR gene transcription [87].

3,3'-diindolylmethane regulatory effects on androgen receptor gene transcription through microRNA

Several clinical studies have examined DIM properties in various cancers such as prostate and breast cancer, thyroid disease, cervical dysplasia, etc. [20,88,89]. Perhaps the most interesting is that DIM affects the growth of biotransformation enzymes like UGT. Figure 1 shows the increased efficiency of detoxification and inhibition of carcinogens through regulating AR by DIM. Thus, it may support the detoxification process by growth of UGTs expression in the urothelium. Moreover, studies are suggesting that dietary DIM suppresses AR gene transcription through epigenetic modulation [21,90,91].

The MiRNA is one of the 3 main types of epigenetic regulation – along with DNA methylation and histone modification. They are a class of small, non-coding RNAs responsible for post-transcriptional regulation of gene expression. The MiRNAs modulate many different genes, including those that are involved in carcinogenesis [92]. They regulate cancer via the following mechanisms, i.e., proliferation, apoptosis, epithelial-mesenchymal transition, invasiveness, migration, metastasis, resistance to chemo- and radio-therapy, adaptation to hypoxia and angiogenesis [93].

Plant chemical compounds are thought to be important regulators of miRNA expression and are associated with the epigenetic regulation of genes responsible for cancer development. Research indicates that phytochemicals have an anti-cancer function by affecting various paths, including regulating miRNA expression. Much has been written on bioactive compounds isolated from edible plants, studied as oncogenic and suppressor miRNA expression modulators [16,94]. The findings indicate that DIM also modulates miRNA levels during carcinogenesis. Studies on cancer cells have shown that I3C and DIM compounds regulate miRNAs, e.g., it has been proven that these compounds increase expression of miR-34a suppressor [91]. Jin [95] has observed that DIM modulates miR-21 and cdc25A expression, which is important in cell cycle management. To sum up regulatory effects of DIM: it down-regulates the expression of miR-30e, miR-21 [96], miR-92a [97], and miR-34a, miR-124, miR-27b, which are known to be associated with the regulation of AR [98]. Furthermore, the epigenetic effect of DIM treatment on miR-34a and let-7 family expression has been observed in prostate cancer patients [91,99].
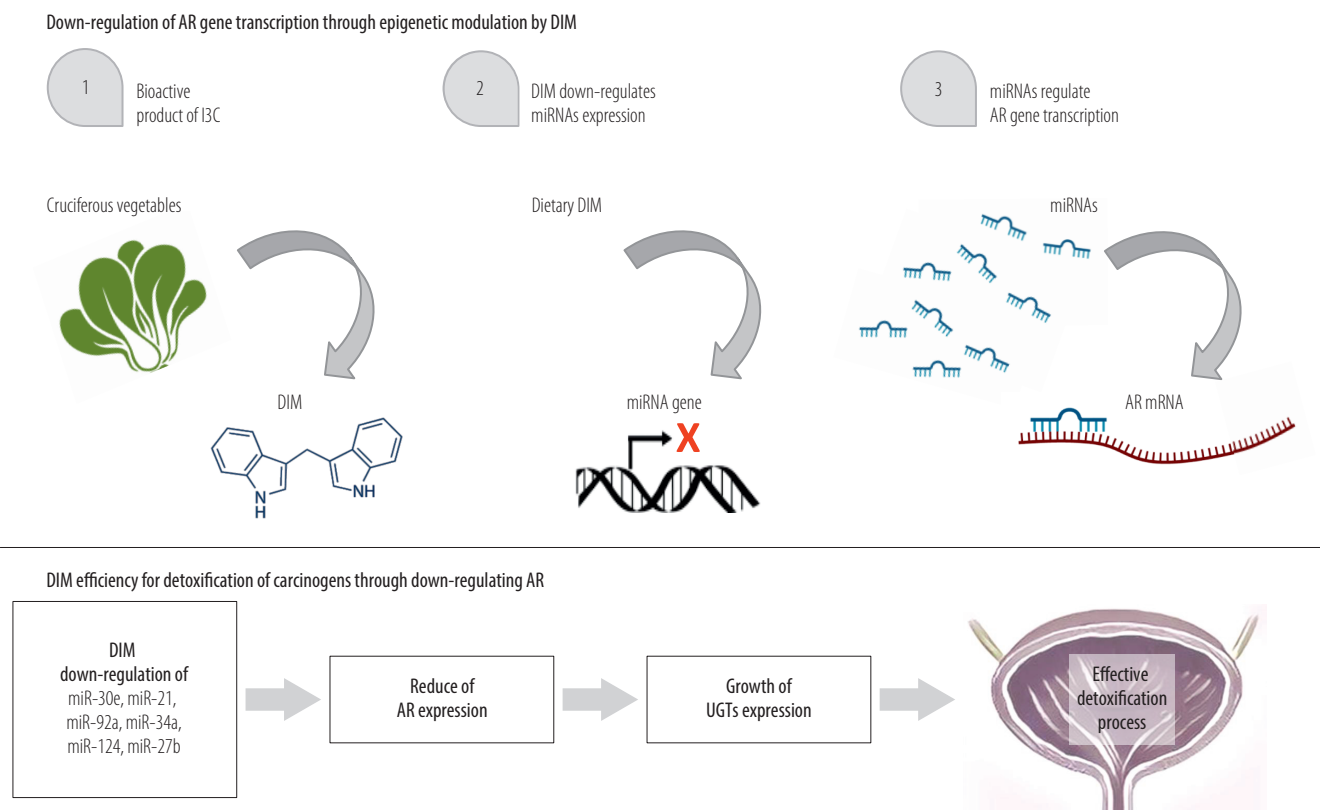
Down-regulation of AR gene transcription through epigenetic modulation by DIM

1   Bioactive product of I3C

2   DIM down-regulates miRNAs expression

3   miRNAs regulate AR gene transcription

Cruciferous vegetables

Dietary DIM

miRNAs

DIM

miRNA gene

AR mRNA

DIM efficiency for detoxification of carcinogens through down-regulating AR

DIM down-regulation of miR-30e, miR-21, miR-92a, miR-34a, miR-124, miR-27b → Reduce of AR expression → Growth of UGTs expression → Effective detoxification process

Figure 1. Dietary 3,3'-diindolylmethane (DIM) down-regulates androgen receptor (AR) through regulation of miRNAs

CONCLUSIONS

The current understanding of the mechanisms by which smoking induces BCa and the factors, such as industrial exposure, that determine interindividual susceptibility to smoking-induced BCa is remarkably limited. Moreover, smoking and occupational exposure to carcinogens are two most common risk factors for BCa. These are risk factors that can be excluded or limited in our lives, unlike other important risk factors such as age and sex. Reduction of occupational exposure would presumably reduce urothelial cancer risk, but as research shows in recent years, occupational exposure is still present.

Many studies have been conducted to use beneficial properties of a diet to counteract cancer formation and its further development. Prevention of BCa by a nutritional diet is important as certain dietary components may be of particular importance in supporting the inefficiency of detoxification processes of carcinogens. Supporting detoxification processes through alteration of epigenetic status by supplementation is important from the point of view of carcinogenesis. Gene–nutrient interactions are important contributors to cancer prevention. Nutrition can alter gene expression, as well as the susceptibility to disease, including cancer by epigenetic changes.

The use of dietary supplements influences the epigenetic status through DNA methylation and miRNA-dependent gene silencing. There are many known processes for forming tumours regulated by miRNA, e.g., proliferation, apoptosis and epithelial-mesenchymal transition. These alterations may be associated with the course and occurrence of BCa. It is known that AR expression is regulated by a diet. Moreover, adverse sensitization to carcinogens induced by androgen may be inhibited especially by phytochemicals present in plants.

In this review the authors seek to summarize the current state of knowledge about the effects of phytochemical DIM on epigenetic changes of the AR in terms of importance of dietary ingredients in the prevention of cancer. The DIM supplementation affects AR signaling pathways and reduces AR expression, thereby improving detoxification processes associated with aromatic amines' degradation through the glucuronidation pathway. Despite numerous reports indicating the effect of AR on cancer, the role of AR in BCa has not been fully understood yet and the regulatory role of the miRNA in BCa requires new research. Better understanding of the effects of DMI and AR on BCa growth may provide important information and directions for the future development of epigenetic targets for novel prevention of BCa.

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