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Review Article

Tobacco smoke and bladder cancer: the current research status and the future challenges

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Abstract: Bladder cancer is the ninth most common malignant tumors worldwide. Tobacco smoke is the primary risk factor for bladder cancer. The relationship and underlying mechanisms between tobacco smoke and the disease etiology are not, however, fully delineated. Understanding the role of tobacco smoke in the initiation and progression of bladder cancer is essential for clarifying the molecular mechanisms, improving future strategies for prevention, early detection, exploring novel diagnostic markers and effective therapeutics. Therefore, this review summarizes the relationship between tobacco smoke and bladder cancer. The direction of future research and the challenges on tobacco smoke-associated bladder cancer are also outlined.

Keywords: Bladder cancer, tobacco smoke, research progress, mechanisms

Introduction

Overview of bladder cancer

Bladder cancer (BC) is a worldwide public health problem. BC is the ninth most common tumor and one of the most common tumors in the genitourinary system, with about 429, 793 new cases and 165,084 deaths every year [1]. The incidence of BC varies widely in different countries. The highest incidence of BC usually occurs in Western countries including Europe, the United States and Australia and the lowest incidence rate is generally observed in Asian countries including China [2]. Most cases are diagnosed as advanced and these patients cannot undergo curative surgery [3]. Chemotherapy remains the main treatment, but the effect and prognosis are not particularly ideal. Although targeted therapies and immunotherapy have been introduced into clinical applications, these treatments are still limited, mainly due to drug resistance [3-6]. On the other hand, the incidence of BC is increasing year by year, probably due to high tobacco consumption, air pollution, unhealthy diet, chronic infection and other factors [7]. Therefore, it is urgent to understand the pathogenesis of BC for the better prevention, early intervention and identifying new therapeutic approaches.

Tobacco smoke and the relationship with BC

Tobacco smoke consumption is an important global public health problem [8]. It is reported that there were more than 1.2 billion smokers in the world [8]. It is estimated that tobacco smoke is associated with more than 6 million deaths every year, related to some diseases and different types of cancers [9]. Tobacco smoke is composed of more than 5,000 chemicals, many of which induce free radicals, possess toxic and carcinogenic activities [9-11].

Tobacco smoke is associated with many diseases and cancers [1, 10-14]. Studies have revealed that tobacco smoke is strongly associated with the initiation and progression of BC [15, 16]. Some researchers believe that tobacco smoke is the most important single risk factor for BC. It is estimated that approximately 23% of female BC and 50% of male BC are caused by tobacco smoke [13, 17]. Evidences suggested that the current smokers have about 4-fold higher risk of BC compared with non-smokers [13, 17]. Analysis of some case-control studies found that the risk of BC increased with duration and intensity of smoking [15, 18]. In addition, different types of cigarette smoke have different correlations with the incidence of BC. It has been reported that users of air-cured

cigarette have a higher risk of BC than flue-cured cigarette [19, 20].

Components related to BC in tobacco smoke

More than 70 carcinogens have been found in tobacco smoke, including aromatic amines (2-naphthylamine (2-NA), 4-aminobiphenyl (4-ABP)), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N*-nitroso compounds, polycyclic aromatic hydrocarbons (PAHs) and benzo(a) pyrene (BaP), etc [21]. In addition, peroxides and free radicals in tobacco smoke are associated with malignant transformation of cells and tumorigenesis. The occurrence of BC is highly correlated with aromatic amines, which cause cancer only after activation regulated by N-acetyltransferases 1 and 2 [22]. Studies have shown that acetylation of *N*-acetyl transferase 2 increases the risk of BC [22]. As a representative compound of aromatic amines, 4-ABP has been extensively studied to elucidate the association with the occurrence and development of BC [20]. Acrolein and PAHs are closely related to the occurrence of BC by inducing mutagenesis of DNA adducts, inhibiting DNA repair and enhancing the susceptibility of cells to mutagenesis [23, 24]. NNK has been identified as a potent carcinogen which induces DNA adducts, mutates and promotes tumor growth [21]. Recently, researchers have discovered that hyper methylation of xenobiotic enzymes was associated with BC progression [21]. Oxides and free radicals in tobacco smoke can attack macromolecules such as DNA and proteins, and activate important cellular signaling pathways involved in BC tumorigenesis.

Exposure to tobacco smoke or its constituents is known to trigger a cascade of events in the multistage process of carcinogenesis including BC [20]. Another important effect of tobacco smoke is to reduce the effectiveness of BC treatment [15, 25]. Enormous progress in understanding its mechanisms leading to BC has been made. Herein, we summarize the research status of tobacco smoke and BC.

Tobacco smoke induces aberrant methylation in BC

It is well known that alteration of methylation can silence tumor suppressor genes and activate oncogenes. The changes of DNA methylation are common and early events in the occurrence and development of BC [26]. Brait *et al.* found that methylation of urinary epithelial cells treated with tobacco smoke extract increased compared with controls [27]. In a recent study, the researchers also found that the BC-associated metabolome was enriched with methylated metabolites DNA adducts and PAHs, suggesting that methylation is a hallmark of BC in tobacco smokers [21]. Abnormal DNA methylation plays an important role in the occurrence and progression of BC induced by smoking, and thus DNA methylation can be a promising biomarker for diagnosis and prognosis.

Tobacco smoke induces DNA adducts and DNA damage in BC

Formation of repair-resistant DNA damage and DNA adducts in the key cancer-related genes is a common event in tobacco smoke-associated BC [20]. It is hypothesized that aromatic amines derived from tobacco smoke induce BC by inducing DNA adducts and DNA damage in the crucial cancer-related genes. Jin *et al.* found that tobacco smoke induces elevated levels of DNA adducts and DNA damage in the tissues of patients with BC and BC cell lines [21]. Ding *et al.* found that tobacco smoke constituents induced DNA adducts and DNA damage in both human bladder cells and mouse bladder tissues [28]. The data of Yoon *et al.* supported a possible etiologic role of 4-ABP in bladder carcinogenesis and provided insights into how DNA adducts induce mutation [29]. Tobacco smoke contains a large number of polycyclic aromatic hydrocarbons, aromatic amines and *N*-nitroso compounds, which lead to DNA adducts and DNA damage. Therefore, a clear understanding of the role of DNA adducts and DNA damage in tobacco smoke-induced bladder carcinogenesis will be beneficial to the prevention and treatment of BC.

Tobacco smoke induces EMT in BC

Epithelial-mesenchymal transition (EMT) is a reversible process that involves the changes from an epithelial to a mesenchymal cell phenotype. The accumulated evidence indicates that EMT is the crucial underlying mechanism for initiation, invasion and metastasis of various cancers including BC [1, 10, 12, 13, 30]. Gen and Sun *et al.* demonstrated that tobacco smoke promotes the progression of EMT and

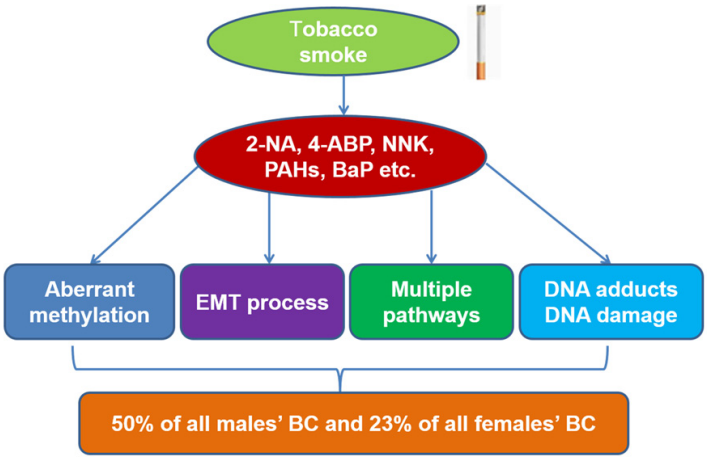

Figure 1. Working model showing the current status of tobacco smoke and bladder cancer.

the development of BC in SV-40 immortalized normal human urothelial cells and T24 cells [31, 32]. Liang and Yu *et al.* demonstrated that tobacco smoke induces EMT and promotes the development of bladder cancer in the mouse model [13, 17, 33]. In addition, Liang *et al.* found that long-term tobacco smoke can induce bladder EMT progression and stem cells characteristics to promote BC development *in vivo and in vitro* [1]. Tobacco smoke promotes the EMT process, which regulates early events in bladder carcinogenesis. However, the mechanism leading to EMT is not fully understood, which has hindered the development of effective targeted therapies and the chemoprevention of BC.

Tobacco smoke activates multiple pathways in the process of inducing BC

The initiation and development of BC involves multiple steps and the abnormal activation of multiple signaling pathways. Tobacco smoke is one of the leading risk factors for BC. Herein, we summarize these signaling pathways involved in tobacco smoke induced bladder carcinogenesis. Liang *et al.* demonstrated that chronic tobacco smoke exposure induces urocystic EMT and acquisition of cancer stem cells properties through Wnt/β-catenin pathway [1]. Liang and Geng *et al.* indicated that MAPKs pathway plays an important role in tobacco smoke-induced proliferation and EMT progression of BC cells or mice bladder tissues [17, 32, 34]. Deng *et al.* found that cigarette smoke extract induced the proliferation of normal human urothelial cells via the NF-κB pathway [35]. Brait *et al.* suggested that PI3K-AKT pathway is associated with tobacco smoke-induced urothelial cell carcinoma [27]. Chen *et al.* demonstrated that composition of tobacco smoke induces the oncogenic factor COX-2 and this induction is mediated by NADPH oxidase-derived ROS-dependent JNK/ERK pathway in a human bladder cancer cell line [36]. It is reported that tobacco smoke exposure enhances COX-2 activity and increase PGE2 release, which contributes to carcinogenesis and progression of BC [37]. The results of Chen *et al.* showed that nicotine simultaneously activates Stat3 and ERK1/2 pathways in T24 cells [38]. Tobacco smoke induced expression of the NF-κB-regulated gene products cyclooxygenase-2 and vascular endothelial growth factor in BC cell lines, which are involved in proliferation and angiogenesis, respectively [39]. Although enormous progress in understanding the mechanisms by which tobacco smoke causes BC has been made, the molecular pathogenesis remains largely unknown. Understanding the molecular mechanisms of tobacco smoke-induced BC will help target and accurately treat the disease.

Summary and the future challenges

BC is an important disease that threatens people's health, causing significant mortality and morbidity worldwide. Tobacco smoke is the primary risk factor for BC. In recent years, many efforts have been made to clarify the components of tobacco smoke which induce BC and the mechanisms involved (**Figure 1**). Although great progress has been made and we have learned a lot about tobacco smoke-induced BC (**Table 1**), there are still many problems that cannot be solved or are not fully understood. There are still many unknowns that we need to study and many challenges in the future research.

Future research is expected to fill the knowledge gap by identifying the genetic changes that occur during the initiation and progression of tobacco-induced BC, and provides a scientific basis for early diagnosis and treatment of

Table 1. Overview on the process of tobacco smoke induced BC

Components of tobacco smoke	Induced events	Type of sample	References
NNK	DNA adducts, mutates and promotes tumor growth	BC patient tissues and J82 cells	[21]
Acrolein and Side-stream smoke	Mutagenesis of DNA adducts, inhibiting DNA repair	Mouse bladder-mucosa and human urothelial cells	[23]
PAHs	Mutagenesis of DNA adducts, inhibiting DNA repair and aberrant methylation	Serum and urine specimens of patients with BC	[21, 23, 24]
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and BaP	DNA adducts and DNA damage	The tissues of patients with BC and J82 cells	[21]
4-ABP	DNA adducts and DNA damage	RT4 cells and mouse bladder tissues	[28, 29]
Tobacco smoke	The progression of EMT and reduce the effectiveness of BC treatment	Bladder tissue of mice and clinicopathological data	[13, 15, 17, 25, 33]
Tobacco smoke extract	The progression of EMT, proliferation and Aberrant methylation	SV-40 immortalized normal human urothelial cells, T24 cells and Urinary epithelial cells	[27, 31, 32, 34]
Tobacco smoke extract and tobacco smoke	Bladder EMT progression and stem cells characteristics	SV-40 immortalized normal human urothelial cells and bladder tissue of mice	[1]
Tobacco smoke extract and tobacco smoke	Activate multiple signaling pathways including MAPKs, NF-κB, Wnt/β-catenin, PI3K-AKT, etc	BC cell lines and bladder tissue of mice	[1, 17, 27, 32, 34-39]

BC. The availability of next-generation sequencing technologies will help overcome future research challenges regarding the mechanisms of tobacco smoke-induced BC. The development of DNA footprint technology based on next-generation sequencing will be able to target DNA adducts and DNA damage, helping to elucidate the occurrence of early events during tobacco smoke-induced BC. In addition, genome-wide detection of tumor-specific mutations in the BC genome is necessary to understand the molecular pathways that lead to malignant transformation of bladder urothelial cells. On this basis, active implementation of targeted therapy, precision therapy and immunotherapy will enable patients to have a better prognosis and a longer life cycle.

It is important to develop new technologies, but we also need to build excellent animal models of tobacco smoke-induced BC in the future research. Based on these animal models, we will be able to make better use of some new technologies to study the malignant transformation of bladder cells altered by tobacco smoke, the molecular mechanism of tobacco smoke-induced BC and the specific role of pathways involved in this process. Then, this will provide a better basis for targeted therapy and precise treatment.

Quitting smoking is part of many government cancer control programs or strategies. Do the benefits of quitting smoking also apply to BC patients? Unfortunately, little research has been done on this issue, and the results are somewhat inconsistent. Some studies suggested no association between smoking cessation and BC recurrence, progression and cancer-specific mortality [15, 40, 41]. Some researchers have found that quitting smoking early can reduce the risk of BC occurrence and recurrence [15, 41, 42]. But there is still a lack of solid evidence of reduced recurrence or cancer-specific mortality after smoking cessation. These evidence may be provided by randomized clinical trials in which newly diagnosed smokers of BC have or have not been assisted by smoking cessation. However, there is no prospective study to assess the effectiveness of smoking cessation at diagnosis, nor is there an optimal smoking cessation program for BC patients. We need to determine the relationship between smoking cessation and BC recurrence, progression and death as soon as possible. Meanwhile, the relationship between the number of cigarettes and the occurrence, recurrence, progression and death of BC should be clarified.

Disclosure of conflict of interest

None.

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