Genomics of Smoking Exposure and Cessation: Lessons for Cancer Prevention and Treatment

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Tobacco use is the greatest preventable cause of cancer in the United States, accounting for almost one third of all cancer-related deaths and 90% of deaths from lung cancer. Despite widespread knowledge of these risks, tobacco use prevalence rates are 20% in the United States and up to 30% to 50% in the developing world (1, 2). Nicotine, the addictive chemical in tobacco, produces a biological dependence (3), and therefore, even with the most efficacious medications available, only one in four smokers is able to maintain long-term abstinence (4). Persistent tobacco use is common even following a diagnosis of tobacco-related cancer and is associated with poorer outcomes of radiation therapy and chemotherapy and with increased risk of second primary malignancies (5). Although smoking cessation is optimal, it may not be realistic for all patients. Therefore, it is essential to gain a better understanding of the cellular and molecular mechanisms through which tobacco exposure contributes to cancer pathogenesis and outcomes, and to develop targeted prevention and therapeutic approaches.

Toward this end, a study reported by Gumus et al. (6) in this issue of the journal characterized gene expression profiles in the oral mucosa of smokers and nonsmokers and validated their findings by examining the *in vitro* effects of tobacco smoke condensate on gene expression in an oral leukoplakia cell line. Another related study also reported in this issue of the journal was conducted by Zhang et al. (7), who compared gene expression in cells obtained from bronchial brushes from never, current, and former smokers. Smoking effects on global gene expression were common across these studies. Certain genes (*CYP1A1* and *CYP1B1*) that were up-regulated in buccal oral specimens of smokers were part of a larger group (*CYP1A1*, *CYP1B1*, *ALDH3A1*, *NQO1*, and *AKR1C1*) up-regulated following *in vitro* exposure to tobacco smoke condensate (6) and in the airway cells of smokers (7). Zhang and colleagues provide further *in vivo* evidence that many of these genes are down-regulated in persons who reported quitting smoking at least 1 year before the assessment (*CYP1B1*, *AKR1C1*, *AKR1C2*, *AKR1B10*, and *ALDH3A1*). Many of these same genes were previously shown to be overexpressed in oral cancer cells exposed to tobacco smoke condensate (8), in bronchial epithelial cells of smokers, and in patients' non–small cell lung carcinoma cells (9, 10). The effects are also consistent with the effects of smoking on the airway transcriptome (11, 12). Taken together, these findings identify important tobacco smoke exposure response genes. The studies of Gumus et al. and Zhang et al. in this issue of the journal provide an elegant illustration of the value of cross-model (preclinical and clinical) validation in translational cancer prevention research.

Significance for Cancer Etiology

These findings are highly significant for our understanding of cancer etiology. Many of the altered enzymes play pivotal roles in the metabolism/activation of polycyclic aromatic hydrocarbons (PAH; refs. 13–16), which are tobacco carcinogens. Their up-regulation likely results in increased metabolism of PAH to biologically reactive intermediates that can lesion DNA. Importantly, *CYP1A1* and *CYP1B1* are induced when PAH bind to the aryl hydrocarbon receptor, which turns on gene transcription via the xenobiotic response element (refs. 13, 17, 18; Fig. 1A). CYP1A1/CYP1B1 are ultimately responsible for the monoxygenation of PAH to yield diol-epoxides, which form covalent bulky adducts with DNA that lead to mutation (19, 20). Paradoxically, studies with *CYP1A1* and *CYP1B1* knockout mice show that these enzymes protect against benzo[*a*]pyrene (B[*a*]P) toxicity because in their absence, diol-epoxide DNA adduct levels are even higher (21–23). This outcome is evident in human bronchoalveolar (H358) cells where cells induced to express CYP1B1 produced less *anti*-B[*a*]P-diol epoxide-N^2-dGuo adducts than uninduced cells (24). This suggests that in the absence of *CYP1A1/CYP1B1*, lower clearance of B[*a*]P leads to the formation of more diol-epoxide DNA adducts and that *CYP1A1/CYP1B1* induction is protective.

PAH *trans*-dihydrodiols formed en route to diol-epoxides are also oxidized by AKR1C1 or AKR1C2 to yield electrophilic and redox active PAH *o*-quinones (16, 25, 26). B[*a*]P-7,8-dione, because it is redox active, enters into futile redox cycles to amplify the formation of reactive oxygen species that results in oxidatively damaged DNA (e.g., 8-oxo-dGuo, a highly mutagenic lesion; refs. 27, 28). The AKR-generated B[*a*]P-7,8-dione is a ligand for the aryl hydrocarbon receptor and will induce *CYP1A1* and *CYP1B1* still further (29, 30). Moreover, the B[*a*]P-7,8-dione and the reactive oxygen species it generates induce *AKR1C1-AKR1C3* genes via their antioxidant response elements (31, 32). Nrf2 the transcription factor that binds to the antioxidant response element also induces the aryl hydrocarbon receptor (*AhR*) gene (33). Thus, tobacco exposure leads to the induction of the *CYP1A1 /CYP1B1* and *AKR* genes to stimulate B[*a*]P metabolism. On balance, this could result in less diol-epoxide DNA adducts and the formation of more

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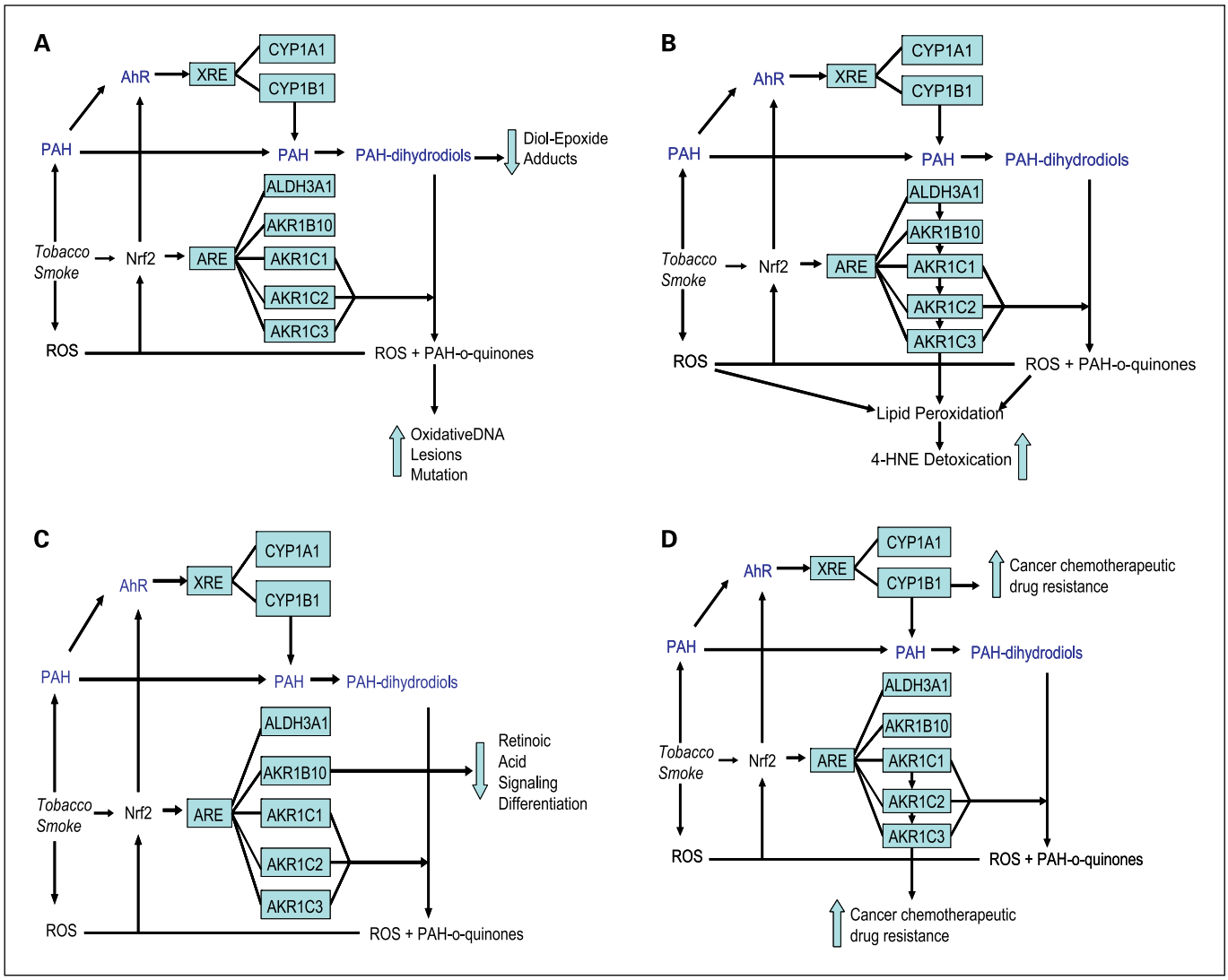

Fig. 1. Significance of tobacco exposure response genes. *A*, up-regulation of *CYP1A1/CYP1B1* and *AKR* genes leads to a decrease in diol-epoxide DNA adducts and an increase in oxidative DNA damage. *B*, up-regulation of *CYP1A1/CYP1B1* and *AKR* genes leads to an increase in reactive oxygen species and lipid peroxidation, which is counteracted by induction of *ALDH3A1* and the *AKR* gene battery. *C*, up-regulation of *AKR1B10* via the antioxidant response element leads to a loss of retinoic acid signaling. *D*, up-regulation of *CYP1A1/1B1* and *AKR* genes leads to an increase in cancer chemotherapeutic drug resistance. *AhR*, aryl hydrocarbon receptor; *ARE*, antioxidant response element; *4-HNE*, 4-hydroxy-2-nonenal; *ROS*, reactive oxygen species; *XRE*, xenobiotic response element.

B[*a*]P-7,8-dione and reactive oxygen species that will lead to mutagenic oxidative DNA damage.

Another gene that showed altered expression was *ALDH3A1*. When coupled with the overexpression of *AKR1C1*, *AKR1C2*, *AKR1B10*, and *NQO1* genes, another outcome of chronic tobacco exposure is to mount a counter-response to oxidative stress (Fig. 1B). Tobacco smoke leads to oxidative stress due to the presence of benzoquinone and heavy metals and the production of redox-active PAH *o*-quinones, which is AKR mediated (see above). Each of these up-regulated genes contains an antioxidant response element in their gene promoters (32, 34, 35). A consequence of oxidative stress is the formation of lipid peroxides that can break down to form reactive bifunctional electrophiles (e.g., 4-hydroxy-2-nonenal and 4-oxo-2-nonenal; refs. 36, 37). Induction of these genes provides a route to the detoxification of these reactive lipid aldehydes.

One remaining gene that deserves comment is the altered expression of *AKR1B10* (small intestine like aldose reductase; Fig. 1C). Whereas this gene can protect against the toxic effects of lipid aldehydes, it has another function (38–40). It is the most catalytically efficient of all the known all-*trans*-retinal reductases (40). Elimination of retinal as retinol prevents the conversion of retinal to retinoic acid. Retinoic acid is a ligand for retinoid acid receptor and retinoid X receptor, and activation of these nuclear receptors leads to cell differentiation (41). If retinoid acid receptor and retinoid X receptor are deprived of their ligand, this could lead to a pro-proliferative response. In fact, retinoid acid receptor and retinoid X receptor are often lost in lung cancer cell lines, suggesting that there is a coordinated loss of retinoic acid signaling (42).

Significance for Cancer Prevention and Treatment

Identification of tobacco exposure response genes has important implications for chemoprevention and chemotherapy of tobacco-related cancers in smokers. At first glance, inhibition of the *CYP1A1/CYP1B1* genes might be anticipated to be

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beneficial because it could reduce the level of diol-epoxides. However, the phenotype of *CYP1A1/CYP1B1* knockout mice indicates that this will increase PAH toxicity, and this should be avoided (21–23). Clearly, the overexpression of AKRs in smokers is a double-edged sword. On the one hand, this could lead to increased bioactivation of PAH and DNA mutation, and on the other hand, they are part of a counter-response to oxidative stress and lipid peroxidation. *AKR* genes are regulated by an antioxidant response element, and chemopreventive strategies that target this mechanism of gene induction (e.g., *R*-sulforaphane) should be considered with caution because it is uncertain that they will be harmful or beneficial in the context of lung cancer (43). Strategies aimed at the inhibition of AKRs may be more effective because although this will attenuate the detoxification of 4-hydroxy-2-nonenal, this may be compensated for by redundancy in the detoxifying enzymes (e.g., *ALDH3A1* and glutathione *S*-transferases) that compete for 4-hydroxy-2-nonenal. Approved drugs that are potent inhibitors of the AKRs are the nonsteroidal anti-inflammatory drugs (44).

If oxidative stress is a driving component of the lung carcinogenic process, antioxidant strategies may also be desirable. Two high profile clinical trials addressed the use of antioxidant vitamins: The Alpha-Tocopherol Beta-Carotene Prevention Study (45) and the Carotene and Retinol Efficacy Trial (46). Both studies revealed that lung cancer risk was significantly increased in heavy smokers receiving β-carotene (47). The altered expression of *AKR1B10*, reported to be coupled with the high overexpression of *AKR1B10* seen in non–small cell lung carcinoma by Fukumoto et al. (9), suggests why chemopreventive studies that target retinoid X receptor and retinoid acid receptor are likely to fail. AKR1B10 will rapidly eliminate retinal as retinol and prevent formation of retinoic acid. By contrast, in the Alpha-Tocopherol Beta-Carotene study, high serum α-tocopherol was associated with lower lung cancer incidence, although the effect was stronger in smokers with less cumulative tobacco exposure (48).

Overexpression of *CYP1B1* and *AKRs* may also contribute to cancer chemotherapeutic drug resistance, and therefore chronic smokers with lung cancer may have lower response rates on these therapies (Fig. 1D). *CYP1B1* is implicated in the metabolic clearance of docetaxel, gefitinib, and erlotinib (49, 50). In addition, AKR1C1 is overexpressed in HT29 colon cancer cells that are resistant to the glutathione *S*-transferase inhibitor ethacrynic acid (51). *AKR1C1* and *AKR1C2* genes are overexpressed in non–small cell lung carcinoma in patients with poor response to anti-pyrimidine therapy (52), and *AKR1C1* and *AKR1C2* are overexpressed in ovarian cancer cell lines resistant to cisplatin (53, 54). In the latter case, cisplatin resistance could be accomplished by transfection of AKR1C1. Because cisplatin is widely used for non–small cell lung carcinoma, this raises the prospect that its efficacy could be improved by the coadministration of nonsteroidal anti-inflammatory drugs, which are known inhibitors of AKR isozymes.

To increase our understanding of the molecular mechanisms through which tobacco smoke exposure influences the efficacy of cancer prevention and therapeutic agents, a more rigorous exposure measurement, beyond the traditional smoking pack-years assessment, is needed (5). This should include ongoing assessment of tobacco exposure following diagnosis, biochemical verification of self-reported use using biomarkers (e.g., cotinine, 3′-*trans*-hydroxycotinine, and 3-hydroxy-B[*a*]P), and use of pharmacotherapy to reduce tobacco exposure.

Conclusion

These emerging data raise exciting prospects for translation of genomics research on smoking exposure to practice. As shown by Beane et al. (55) in this issue, the integration of integrated clinical and genomic profiling information can provide a powerful risk assessment "clinicogenomic" tool that could be translated to the clinical setting. Genomic profiling strategies may also facilitate prevention of tobacco-related cancer by facilitating smoking cessation. For example, feedback to smokers about gene expression profiling of oral or airway cells may serve as a motivational intervention for smoking cessation (56). In addition, new data also support the potential application of profiling of inherited genomic variation to predict the risk of smoking relapse and to optimize smoking cessation therapy (57). Finally, the studies published in this issue identify genomic alterations associated with smoking exposure, and the mechanisms through which these genes alter therapeutic response will hopefully identify agents that can be used by smokers for cancer prevention and treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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