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Review

Pharmacological Modulation of Lung Carcinogenesis in Smokers: Preclinical and Clinical Evidence

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Many drugs in common use possess pleiotropic properties that make them capable of interfering with carcinogenesis mechanisms. We discuss here the ability of pharmacological agents to mitigate the pulmonary carcinogenicity of mainstream cigarette smoke. The evaluated agents include anti-inflammatory drugs (budesonide, celecoxib, aspirin, naproxen, licofelone), antidiabetic drugs (metformin, pioglitazone), antineoplastic agents (lapatinib, bexarotene, vorinostat), and other drugs and supplements (phenethyl isothiocyanate, myo-inositol, *N*-acetylcysteine, ascorbic acid, berry extracts). These drugs have been evaluated in mouse models mimicking interventions either in current smokers or in ex-smokers, or in prenatal chemoprevention. They display a broad spectrum of activities by attenuating either smoke-induced preneoplastic lesions or benign tumors and/or malignant tumors. Together with epidemiological data, these findings provide useful information to predict the potential effects of pharmacological agents in smokers.

Carcinogenicity of Cigarette Smoke in Humans and Animal Models

Tobacco smoke, and in particular cigarette smoke (CS), is a dominant risk factor in the epidemiology of human cancer and of several other chronic degenerative diseases worldwide. Mainstream CS (MCS) is generated at 1200–1600°C and is inhaled as an undiluted complex mixture by active smokers, whereas environmental CS (ECS), or second-hand smoke, is a mixture of that portion of MCS that is exhaled by active smokers and of sidestream CS (SCS) generated at 900°C at the tip of a lit cigarette and is inhaled by involuntary (or passive) smokers. Both MCS and ECS are categorized as Group 1 carcinogens by the International Agency for Research on Cancer (IARC) [1]. In particular, exposure to MCS is associated with cancers affecting several anatomical sites. Owing to obvious first-pass effects, the main target is the respiratory system, including the nasal cavity and paranasal sinuses, nasopharynx, oropharynx and hypopharynx, larynx, and above all the lung. In addition, MCS causes cancers in the urinary tract (kidney pelvis, ureter, and bladder), digestive system (oral cavity, esophagus, stomach, colon-rectum, liver, and pancreas), reproductive tract (ovary and uterine cervix), and hematopoietic system (myeloid leukemia) [1]. Furthermore, smoking is associated with a variety of chronic degenerative diseases, such as chronic obstructive pulmonary diseases (COPD), cardiovascular diseases, and cerebrovascular diseases, as well as reproductive effects. Overall, CS-related diseases result in a 10 year loss of life-expectancy and are responsible for 443 000

Trends

Many drugs possess pleiotropic properties that, potentially, would be expected to interfere with carcinogenesis mechanisms.

Assessment of protective effects in humans is exceedingly challenging, and there are difficulties in reproducing smoke carcinogenicity in experimental animals.

A murine model can be used to evaluate pharmacological agents by simulating interventions either in current smokers or in ex-smokers, or even mimicking transplacental chemoprevention.

Reviewed agents include anti-inflammatory drugs, antidiabetic drugs, antineoplastic agents, and other drugs and supplements.

These drugs display a broad spectrum of activities by attenuating smoke-induced preneoplastic lesions or benign tumors (adenomas), and/or malignant tumors in mouse lungs.

Both experimental and epidemiological data contribute to predict the possible effects of pharmacological agents in smokers.

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deaths in the USA and 650 000 deaths in the EU [2]. The large majority of the smokers live nowadays in low- and middle-income countries, and this in the future is expected to produce large disparities in cancer-related mortality rates between the developed and less-developed countries of the world [3].

The overwhelming epidemiological evidence supporting the major role of CS in human cancer epidemiology is mechanistically strengthened by the fact that both MCS and ECS are positive in virtually all *in vitro* and *in vivo* short-term genotoxicity tests in which they have been tested. For instance, we demonstrated evident alterations of a variety of intermediate biomarkers in the lung and other organs of either MCS-exposed or ECS-exposed rodents, such as chromosome aberrations, bulky adducts to either nuclear DNA or mitochondrial DNA, hemoglobin adducts, oxidative DNA damage, miRNA, transcriptome and proteome alterations, and apoptosis and proliferation of bronchial epithelial cells [4,5]. Combustion of tobacco leaves generates more than 8000 identified chemical compounds, including molecules that virtually belong to any chemical family, 73 of which have been evaluated by IARC to be carcinogenic in humans and/or experimental animals [6]. The prototypes of carcinogenic CS compounds are polycyclic aromatic hydrocarbons such as benzo(*a*)pyrene [B(*a*)P], tobacco-specific nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*'-nitrosonornicotine (NNN), and reactive oxygen species (ROS) and in general free radicals [6].

It is very difficult to reproduce the carcinogenicity of CS in animal models, which limits the studies on CS and evaluation of protective effects. This drawback depends on the general difficulty of testing complex mixtures rather than individual compounds in experimental settings, as well as on various problems inherent to exposure by inhalation of rodents, such as the different anatomy of the upper respiratory tract and the fact that rodents are obligate nose-only breathers. As a consequence, most carcinogenicity studies in a variety of animal species showed that inhaled CS is either negative or only weakly positive [7–10]. Our attempts to use transgenic mice, such as *p53* mutant mice [11], failed to enhance the carcinogenic response.

Physiologically, nucleotide and transcriptional alterations occur in the mouse lung at birth [12]. This finding prompted us to start exposure of mice soon after birth, when the respiratory tract is particularly stressed, for a period corresponding to weaning, adolescence, and young adulthood in mice. In humans, that period would cover the postnatal period, followed by puberty, adolescence, and adulthood. Under these conditions, MCS becomes a potent carcinogen [13], especially when compared to exposure during adulthood [14].

Prevention of Smoking-Related Cancers

The most obvious strategy to prevent smoking-related cancers and other diseases is to minimize exposures to both MCS and ECS. Avoiding exposure to MCS can be achieved either by refraining from smoking (never-smokers) or by quitting smoking (ex-smokers), whereas diseases associated with exposure to ECS can be prevented by suitable regulations that prohibit smoking in public areas and indoor environments. Epidemiological studies have demonstrated, on a large scale, that a decrease in the consumption of cigarettes is successful in attenuating the epidemic of lung cancer either in selected groups of population or in the whole male population of several countries [15].

As a complementary strategy, it is possible to interfere with the mechanisms of the carcinogenesis process, at any stage [16], and to render the host organism more resistant during the long latency time (generally 2–3 decades) elapsing between the first exposure to CS and the clinical onset of CS-related cancers. This strategy, referred to as cancer chemoprevention, uses dietary