Chemoprevention of cigarette smoke-induced tumors and molecular alterations

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Cigarette smoke (CS) plays a dominant role in the epidemiology of lung cancer, cancer at other sites, and a variety of chronic degenerative diseases. Avoidance of exposure to CS is the imperative goal. However, chemoprevention provides a complementary strategy, which is addressed to current smokers who are addicted and unable to quit smoking and especially to ex-smokers and passively exposed subjects. We have developed an animal model that is suitable to detect the induction of lung tumours and other histopathological alterations induced by mainstream CS (MCS). This model, which involves the whole-body exposure of Swiss H mice to MCS during the first 4 months of life, followed by 3–4 months in filtered air, was validated by evaluating a number of dietary and pharmacological agents. The agents were administered orally under conditions mimicking interventions either in current smokers or ex-smokers or even reproducing a transplacental chemoprevention. They included berry extracts, phenethyl isothiocyanate (PEITC), ascorbic acid, N-acetylcysteine (NAC), myo-inositol, metformin, pioglitazone, bexarotene, vorinostat (SAHA), lapatinib, budesonide, and NSAIDs inhibiting COX-1, COX-2 and/or 5-LOH, such as aspirin, naproxen, celecoxib and licofelone. In addition, we evaluated a number of agents for the ability to affect molecular biomarkers in the same mouse model or in rats exposed either to MCS or to environmental CS (ECS). The investigated end-points included adducts either to nDNA or mtDNA, oxidative DNA damage, cytogenetical damage, apoptosis, proliferation, alterations of oncogenes and tumour suppressor genes, multigene expression, microRNA and proteome profiles. Combinations of chemopreventive agents, such as NAC and oltipraz, PEITC and indole-3-carbinol, bexarotene and pioglitazone, were also investigated. The results obtained provide evidence that experimental studies evaluating lung tumours and/or molecular alterations may be useful to predict both safety and efficacy of putative lung cancer chemopreventive agents and to explore their mechanisms of action.