Tobacco smoke, carcinogens, and p53 mutations in lung cancers

Cigarette smoking and lung cancer

Cigarette smoking kills over 1,000,000 people each year in the world by causing lung cancer as well as many other cancers. Tobacco smoke contains over 3500 different chemicals, and 60 of them have been classified as “carcinogenic to humans” by the International Agency for Research on Cancer (Lyon, France). Many pieces of evidence demonstrate the role of tobacco smoke in causing lung cancers. Lung cancers were rather rare one century ago, when cigarette smoking was not yet a widespread habit. The rapid increase in lung cancers in the second part of the 20th century has mirrored the increase of smoking in both men and women. A lifelong study of smoking and non-smoking doctors in Britain has shown that those who smoke die, on average, 8 to 10 years younger than those who do not smoke, and that lung cancer is one of the main reason for the difference. However, this study also showed that quitting smoking works: doctors who ceased smoking even after 30 of 40 years of daily cigarette consumption, have seen a clear reduction in their risk of having lung cancer.

The evidence that cigarette smoke causes cancer is also based on laboratory work. Thus, over the past 50 years, the works of many chemists and biologists have uncovered the harmful effects of many tobacco components. A well proven effect is mutagenesis, that is, the capacity to induce permanent changes into DNA called mutations. DNA is the molecule that contains the genetic code and works as the software that controls how the cells of our body develop and work. Cancer arises when mutations accumulate within DNA, causing bugs in the software that induce some cells in our body to behave as outlaws, growing in an uncontrolled manner and laying mines in vital organs.
“Fingerprints” of tobacco carcinogens in the p53 gene

One of the central pieces of DNA that is often damaged in cancer cells is the $p53$ gene. This gene works as a cellular policemen that halts the abnormal proliferation of cancer cells. Thus, if $p53$ is damaged, the cell can go wild, escape control and proceed down the road that leads to malignant cancer. In contrast, as long as $p53$ works well, cells are relatively protected against becoming cancerous. This is why damaging $p53$ by mutation is a frequent event in many cancers, including lung cancers. To keep track of all the mutations in $p53$, the International Agency for Research on Cancer (IARC) has developed an international database of all $p53$ mutations ever described in the scientific or medical literature. This database is freely available on the web (http://www-p53.iarc.fr/) and is used by scientists all over the world for studies on the causes of cancer.

As soon as 1994, Curtis Harris at NCI and Monica Hollstein at IARC, had pointed out that there were special $p53$ mutations in lung cancers. They found that many mutations were of a particular kind called “G to T transversion”. This mutation consists into the replacement of one of the building block of DNA, guanine, by another (the thymine), at precise positions into the molecule. This induces a change in the meaning of the genetic code. This type of mutation is found in almost all types of cancer but is much frequent in lung cancers than in cancers not caused by tobacco.

In 1996, Gerd Pfeifer and his collaborators at the City of Hope Cancer Center, Duarte, California, sought to determine how tobacco carcinogens could damage $p53$ and destroy its function. They used normal bronchial cells in culture and exposed them to one of the most damaging chemicals found in tobacco smoke, benzo(a)pyrene. Then, they zoomed on the piece of DNA that contains $p53$ and they mapped with great precision the positions where benzo(a)pyrene could bind and cause permanent damage. They immediately recognized that these positions were exactly the same Guanines as those that were often damaged by G to T transversions in lung cancers of smokers. Later in 2000, they showed that some other chemicals of the same family as benzo(a)pyrene could also induce the same form of damage in $p53$. 
In 1998, Pierre Hainaut and his collaborators at IARC analyzed the mutations in lung cancers that were at the time in the IARC p53 database. They found that the positions of damage by benzo(a)pyrene spotted by Pfeifer and his team were frequently the sites of mutations in lung cancers of smokers but rarely in lung cancers of non-smokers. That observation tied up the loop and gave very strong proof that tobacco smoke was indeed a mutagen for cells of the human lung.

*Responses of the Tobacco Industry*

These findings were a cause of concern for the Tobacco Industry. At that time, the Industry had already understood that fighting against the idea that cigarette causes cancer was a lost battle. However, the industry was worried about the fact that Pfeifer’s and Hainaut’s findings could be used to make the point that smoke was the cause of lung cancer in individual patients. Until then, the industry has only acknowledged that there was a greater chance of getting lung cancer if you were a smoker. However, they reckoned that it was not possible to prove it at the individual level since, for one smoker patient with lung cancer, you could find another patient who is non-smoker but has the same cancer. However, the whole argument has been blown up by the identification of distinct mutations in the lung cancers of smokers and of non-smokers. Thus, they set up a concerted plan to tamper with this evidence.

The story of how the tobacco industry managed this operation is exposed in a paper by Stan Glantz and his collaborators, published in the issue of 14 January 2005 of The Lancet.

*Suggested readings*

*On cancer in general, including tobacco and cancer:*

On evaluation of tobacco smoke as carcinogen:
IARC monograph on the evaluation of carcinogenic risk to humans: tobacco smoke and involuntary smoking. Volume 83, IARC, Lyon, 2004

On p53 and p53 mutations in general

On the genetics of lung cancers

On p53 mutations in lung cancers
Concordance between the position of p53 mutations in lung cancer (top) and the position of where products of benzo(a)pyrene bind into the DNA of bronchial cells (bottom)