Can epigenetic changes cause COPD? Canaries in the coal mines

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The relentless rise of COPD prevalence worldwide is a major cause of concern for affected patients and their physicians who have to diagnose and treat this difficult disease (1). COPD is believed to be caused by toxic inhalation (2), but the biological mechanism of COPD development is poorly understood, and different mechanisms may be involved with different clinical presentations of what we call COPD. Genetic analysis of COPD patients' genomes indicates that the development of COPD is associated with many different genes (3). What biological regulatory mechanism could explain this process of causing COPD?

Recent studies (4,5) have identified more than 10,000 long intergenic noncoding RNAs (lincRNAs) that are coded for in human DNA but whose existence and function had been unknown. Although they do not code for proteins, these lincRNA molecules have been implicated in the epigenetic regulation of tissue-specific forms of gene expression. They represent a huge reservoir of regulatory elements whose modulation by environmental chemicals and signals is only beginning to be understood. They are the most likely candidates for the mediation of epigenetic changes that might be caused by environmental factors.

A recent study in the EPIC-Turin Investigations (6) demonstrates new findings that are relevant to this discovery. It indicates that tobacco smoke can cause substantial changes in the epigenetic regulation of gene expression in human cells. Smokers had characteristic epigenetic changes in 20 different regions of their genomes compared to non-smokers. Further, in a comparison of smokers with former and non-smokers, patients who developed cancers of the colon or breast had an "epigenetic footprint" at various loci among smokers that was not observed among controls who did not smoke. This is the first study that indicates a link between epigenetic modifications of genes and the risk of developing cancer. Tobacco smoke, a key predisposing cause of COPD, also predisposes to malignant changes.

The idea that epigenetic changes can be caused by toxic inhalations such as tobacco smoke and lead to malignancy suggests the possibility that COPD may also be the result of epigenetic changes caused by toxic inhalations. These new results, indicating that multiple genes activities can be affected by tobacco smoke and that a COPD co-morbidity, malignancy, is also associated with these epigenetic changes raise the possibility that such epigenetic changes could be the mechanism for activating multiple COPD-promoting genes in causing COPD. The fact that malignancy is also associated with these epigenetic changes strengthens the suspicion. Future research should try to identify epigenetic changes associated with the development of COPD and the genes that are involved. Identifying these genes and their protein products could allow researchers to attempt to find pharmaceutical agents that would modify their activity in an effort to block their COPD-inducing activity.

An even more important research agenda would be to identify the environmental factors that can cause the epigenetic changes associated with COPD and malignancy so that preventative efforts could be taken to limit exposure to them. Hopefully, epigenetic studies will help in this research effort and will ultimately allow physicians to prevent new and modify existing cases of COPD.

Meanwhile, it is important for physicians to redouble their efforts in tobacco cessation for all their patients and to inquire about and investigate possible toxic inhalations in their patients' lives.

Perhaps COPD patients play the same role as the canaries that miners have for many decades brought with them into the mines because the birds' sensitivity to toxic inhalations alerted the miners to the presence of danger and allowed them to protect themselves (7). The increase in COPD prevalence and the increasing number of cases not associated with tobacco smoking world-wide should warn us that we must suspect and identify other possible COPD-causing factors. COPD patients have borne the brunt of these toxic exposures and we should make every effort to improve the course of their disease and provide treatments that benefit them and improve their lives.

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