Epigenetics and health

Grandma's curse

Some of the effects of smoking may be passed from grandmother to grandchild

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ONE of biology's hottest topics is epigenetics. The term itself covers a multitude of sins. Strictly speaking, it refers to the regulation of gene expression by the chemical modification of DNA, or of the histone proteins in which DNA is usually wrapped. This modification is either the addition of methyl groups (a carbon atom and three hydrogens) to the DNA or of acetyl groups (two carbons, three hydrogens and an oxygen) to the histones. Methylation switches genes off. Acetylation switches them on. Since, in a multicellular organism, different cells need different genes to be active, such regulation is vital.

Think of your grandchildren!

What has got a lot of people excited, though, is the idea that epigenetic switches might be transmitted down the generations. Some see this as contrary to Darwinism, since it would permit characteristics acquired during an organism's lifetime to be passed on to its offspring, as suggested by a rival theory of evolution put forward by Jean-Baptiste Lamarck. This is an exaggeration. The DNA sequence itself is not being permanently altered. Even those epigenetic changes that are inherited seem to be subsequently reversible. But the idea that acquired characteristics can be inherited at all is still an important and novel one, and a worrying example of the phenomenon has been published this week in *BioMed Central Medicine*.

The study in question, by Virender Rehan of the Los Angeles Biomedical Research Institute, and his colleagues, was of the intergenerational effects of nicotine. It was done in rats, but a rat's physiology is sufficiently similar to a human's to suspect the same thing may be true in *Homo sapiens*. In a nutshell, Dr Rehan showed that if pregnant rats are exposed to nicotine, not only will their offspring develop the asthma induced by this drug, so will the offspring of those offspring.

Dr Rehan and his team injected their rats with nicotine when they were six days pregnant. (Rat pregnancies last 22 days.) They then allowed them to give birth and raised the pups to the age of three weeks, before some were examined. The rest were allowed to mature and breed, and their own offspring were similarly examined. There was, however, no further administration of nicotine.

The pups of the treated mothers had asthmatic lungs. The organs' airways were constricted, and molecular analysis showed abnormally high levels of fibronectin and collagen

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—which would stiffen the lung tissue—and also high levels of receptor molecules for nicotine. That was expected, since the developing embryos were exposed to the nicotine when their mothers were treated. However, when the team did similar tests on the grand-offspring of the treated mothers, they got similar results. Those grand-offspring had not been exposed to nicotine.

The cause of the grand-offsprings' asthma, Dr Rehan believes, is epigenetic modification. Nicotine is not only affecting lung cells, but also affecting sex cells in ways that cause the lungs which ultimately develop from those cells to express their genes in the same abnormal ways.

Exactly what those epigenetic changes are is hard to track down. The team have started looking, but could find no clear pattern except that one form of nicotine-induced acetylation, that of H3 histones (histones come in five varieties), could be blocked by a molecule called RGZ. This molecule is also known to protect lungs against the asthma-causing effects of nicotine. That suggests it is the acetylation of H3 histones rather than the methylation of DNA itself that is creating the effect.

Which crucial genes these histones surround remains obscure. Nor have the team yet found out whether the epigenetic effect they have discovered reaches further than grand-offspring. If it does, though, it suggests that epigenetics really might act like the biblical curse: that the sins of the fathers (or, in this case, the mothers) will be visited on the sons, even unto the third and fourth generations.

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