Medical Xpress

Mother's environment before conception may affect her child's life long risk of disease

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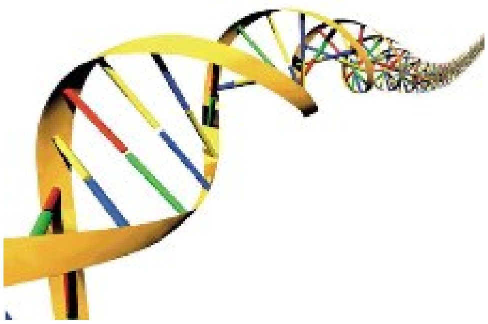

Scientists have shown for the first time that a mother's environment around the time of conception could permanently change the function of a gene influencing immunity and cancer risk in her child.

Diet is likely to play a role in this process, according to the study published in *Genome Biology*.

This is the latest discovery by an international collaboration led by researchers at the Medical Research Council (MRC) Unit, based in The Gambia, West Africa, and the MRC International Nutrition Group at the London School of Hygiene & Tropical Medicine together with a team at Baylor College of Medicine in Houston, Texas.

Previous studies by the scientists showed that a child's DNA can be affected by their mother's diet before pregnancy* but they have now hit upon a gene called VTRNA2-1 as being particularly sensitive to these changes. VTRNA2-1 is a tumour suppressor gene which also affects how the body responds to viral infections.

It is well established that small differences in the DNA that makes up our genes can affect our risk of having a range of diseases. While a child's genes are inherited directly from their parents, how these genes are expressed is controlled through 'epigenetic' modifications to the DNA. The most commonly studied epigenetic modifications are chemical marks (methylation) placed on the DNA of genes that can prevent the message from being read; like sleepers laid across a railway track. Importantly, these marks can be influenced by an individual's environment.

By searching for genes that have very similar patterns of methylation in all tissues we can infer that the marks are laid down in the first few days of life - before the embryo starts to divide into the specialist tissues that make up the developing baby. These so called 'metastable epialleles' thus provide a convenient device for studying the influence of the embryo's very early environment on its epigenome. Because methylation requires a defined set of nutrients, a mother's nutrition before and during pregnancy can affect the 'setting' of these tags, with potentially permanent consequences for her child's gene function.

The Gambian data comes from a unique "experiment of nature" where the population's dependence on own grown foods and a markedly seasonal climate impose large differences in diet and other environmental factors between rainy ('hungry') and dry ('harvest') seasons. The researchers enrolled 120 pregnant women who conceived at the peak of either the rainy or dry season and measured the concentrations of nutrients in their blood. They later analysed blood and hair follicle samples from their 2-8 month old infants.

Lead author, bioinformatician Dr Matt Silver, of the MRC International Nutrition Group at the London School of Hygiene & Tropical Medicine, said: "By studying babies conceived to mothers eating very different diets in the dry and rainy seasons in rural Gambia we could exploit a natural experiment. Our results show that the methylation marks that regulate how VTRNA2-1 is expressed are influenced by the season in which babies are conceived. Maternal nutrition is the most likely driver."

The London/Gambian and Houston teams took two complementary and independent approaches to discover new metastable epialleles in the human genome. Remarkably, both zeroed in on the same top hit: the VTRNA2-1 gene.

Associate Professor Rob Waterland of Baylor, who led the US arm of the study, said: "There are around 20,000 genes in the human genome. So, for our two groups, taking different approaches, to identify this same gene as the top epiallele was like both of us digging into different sides of a gigantic haystack and finding the exact same needle."

Prior evidence concerning the VTRNA2-1 gene suggests that the observed epigenetic changes could affect an individual's ability to fight viral infections (such as influenza) but reciprocally alter its tumour suppressor activity and possibly offer protection against certain cancers (so far shown for acute myeloid leukaemia, lung and oesophageal cancers).

Study author Professor Andrew Prentice, who leads the Nutrition Theme of the MRC Unit, The Gambia, and the MRC International Nutrition Group at the London School of Hygiene & Tropical Medicine, said: "We think this is the first concrete evidence that a mother's diet before pregnancy can affect the disease risk of her child by rewriting a tiny portion of its epigenome.

"Because this gene plays a key role in controlling response to viral infections and offering protection against certain cancers, the potential implications are enormous.

"Our next step is to follow Gambian children to test exactly how epigenetic differences in the VTRNA2-1 gene affect gene expression and life-long health. This could help shed light on longstanding questions such as why mortality rates due to infection are higher in Gambians born in the rainy season."

More information: Matt Silver, Noah J. Kessler, Branwen J. Hennig, Paula Dominguez-Salas, Eleonora Laritsky, Maria S. Baker, Cristian Coarfa, Hector Hernandez-Vargas, Jovita M. Castelino, Michael N. Routledge, Yun Yun Gong, Zdenko Herceg, Yong Sun Lee, Kwanbok Lee, Sophie E. Moore, Anthony J. Fulford, Andrew Prentice, Robert Waterland, Independent genomewide screens identify the tumor suppressor VTRNA2-1 as a human epiallele responsive to periconceptional environment, *Genome Biology*. DOI: 10.1186/s13059-015-0660-y

* Paula Dominguez-Salas, Sophie E. Moore, Maria S. Baker, Andrew W. Bergen, Sharon E. Cox, Roger A. Dyer, Anthony J. Fulford, Yongtao Guan, Eleonora Laritsky, Matt Silver, Gary E. Swan, Steven H. Zeisel, Sheila M. Innis, Robert A. Waterland, Andrew M. Prentice & Branwen J. Hennig. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. *Nature Communications*. DOI: 10.1038/ncomms4746

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