Research Brief 365: Mechanism Linking Preconception Arsenic Exposure and Diabetes in Offspring Revealed

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You are listening to the Superfund Research Program's Research Brief podcast. This month's brief is titled, "Mechanism Linking Preconception Arsenic Exposure and Diabetes in Offspring Revealed," and will highlight researchers' efforts to better understand how exposure to arsenic before conception can trigger changes that are passed down to the next generation – including key changes in paternal sperm DNA that were reflected in offspring, particularly among males. These changes may explain how preconception exposure to arsenic leads to disease in offspring, including diabetes.

Exposure to inorganic arsenic before conception can trigger changes in gene activity that are passed down to offspring and increase their risk of developing diabetes, according to a study in mice funded by an NIEHS individual research grant and by the NIEHS Superfund Research Program, or SRP. These changes, known as epigenetic changes, alter how genes work without changing the genes themselves. In this study, the researchers looked at a type of change called CpG methylation. CpG refers to regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide.

University of North Carolina at Chapel Hill SRP Center Director, Dr. Rebecca Fry, shared that previous studies conducted by the center and co-led by Dr. Mirek Stýblo, linked preconception arsenic exposure with differences in gene expression and diabetes in offspring. The researchers wanted to dig deeper and explore if heritable changes in CpG methylation could be a mechanism by which these birth outcomes occur.

The team exposed adult male and female mice to inorganic arsenic in drinking water for ten weeks prior to mating. They then examined DNA methylation patterns across the entire genome — an organism's complete set of DNA — in both paternal sperm and in the livers of their adult offspring.

The researchers explored differences in CpG methylation and levels of expression among genes that are known to be associated with diabetes as well as in imprinted genes. Normally, offspring inherit two copies of each gene — one from each parent — and both can be expressed. But, in imprinted genes, only one copy — either the maternal or paternal — is expressed while the other one is turned off.

Dr. Fry noted that imprinted genes are particularly susceptible to environmental factors because only one copy of the gene is functional. Imprinted gene expression is tightly regulated by CpG

methylation, so if arsenic exposure alters methylation in these genes, one would expect important consequences for expression.

Results showed that male mice exposed to arsenic before conception had altered CpG methylation in their sperm. Most affected genes had less methylation than usual – called hypomethylation – and more than half of these changes were associated with increased gene expression. These findings were similar in the livers of male and female offspring, though the largest percentage of differentially expressed genes with altered methylation occurred in males.

In many cases, the same genes that showed changes in paternal sperm were also affected in the offspring, and in exactly the same CpG sites. These changes occurred in several imprinted genes as well as in genes known to be involved in diabetes. For example, in male offspring, an important imprinted gene called *Kcnq1* was hypomethylated and had increased expression. This gene is important in regulating insulin secretion. Impaired insulin secretion, along with resistance to insulin, is a key marker of diabetes. Similarly, these animals had differentially methylated and expressed *Pola1*, a gene known to be associated with diabetes.

The researchers underscored that these findings show that exposure to inorganic arsenic before conception can alter DNA methylation in a way that can be passed down across generations. The more pronounced changes in male offspring and the specific genes involved help explain sex-specific differences in arsenic-induced diabetes observed in previous studies.

The team is continuing to examine the role of epigenetic inheritance related to diabetes in two consecutive generations of offspring.

According to the researchers, there is strong evidence linking arsenic exposure and diabetes in humans, and previous studies performed by the group have identified preconception as a critical window of susceptibility. The researchers also highlighted that this is the first study to show that heritable epigenetic changes from preconception arsenic exposure are a key underlying mechanism.

If you'd like to learn more about this research, visit the Superfund Research Program website at www.niehs.nih.gov/srp. From there, click on the Research Brief title under the banner, and refer to the additional information listed under the research brief. If you have any questions or comments about this month's podcast, send an email to srpinfo@niehs.nih.gov.

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