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Study reveals how changes in gene expression could lead to infertility

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(PhysOrg.com) -- Researchers used a yeast model to map epigenetic processes-- those that influence gene expression -- in cells as they undergo sperm formation. Understanding the process can help explain how it goes awry in cases of human male infertility. They found several sites on proteins that may be important epigenetic regulators of sperm and egg formation: Novel chemical changes key to gamete formation could be potential biomarkers of human male infertility.

Male infertility is a common medical problem, affecting millions of men in the United States annually. Its causes include an inability to make productive sperm. Now, using yeast as a model organism, researchers at the University of Pennsylvania School of Medicine are beginning to identify the molecular signals that could in part underlie that problem.

Shelley Berger PhD, the Daniel S. Och University Professor, and director of the Epigenetics Program at Penn, with postdoctoral fellow Jérôme Govin, PhD, and colleague Saadi Khochbin of INSERM in France, screened yeast to find mutants that were unable to form spores - a process that is analogous to sperm formation in mammals. Their goal was to map epigenetic processes-- those that influence gene expression - in cells as they undergo sperm formation. By piecing together the mechanics of the process, ultimately, they can understand how that process can go awry. They found several sites on proteins that may be important epigenetic regulators of sperm and egg formation: Novel chemical changes key to gamete formation could be potential biomarkers of human male infertility. They published their findings this

month in *Genes and Development*.

Epigenetics, the factors influencing an organism's genetics that are not encoded in the DNA itself, are more subtle than genetic mutations, which typically affect the function of proteins a cell produces by following the recipe coded in the DNA. Epigenetic factors instead alter the readout of that code, ramping their expression up or down as if with a dimmer switch.

A process under strong epigenetic control is sperm and egg formation.

Sperm and eggs (gametes) contain only a single chromosome of each type -- they contain 23 chromosomes instead of the 46 found in most human body cells, which have two copies of each (one copy inherited from each parent). The process of gamete formation involves a specialized form of cell division called meiosis, which is tightly regulated by molecular processes within the cell. The question is, what are the epigenetic players involved in that process?

To begin to answer that question Berger, Govin, and their colleagues developed a way to systematically mutate portions of two proteins, histone H3 and histone H4, looking for defects in spore formation.

DNA in a cell is not like a free-floating tangle of yarn; it is tightly wrapped around protein spindles. Those spindles are built of histone proteins, and chemical changes to these spool proteins can either loosen or tighten their interaction with DNA, affecting, among other things, gene expression. Berger and her team used their mutants - more than 100 were tested -- to identify novel histone modifications key to gamete formation.

According to Berger and Govin's analysis, sites on both histone H3 and H4 turned out be important. One critical modification site the team

picked up is threonine-11 on histone H3 (H3T11), the phosphorylation of which is required to complete meiosis. The researchers also found a trio of lysines on histone H4, whose acetylation enables efficient compaction of chromosomal DNA into mature spores. The team demonstrated that these modifications also occur during mouse sperm formation and identified some candidates for the proteins that both "read" and "write" those modifications, as well.

Berger said the study is noteworthy on several levels. First, it establishes a screening method to identify epigenetic changes during sperm or egg formation, a process Govin is already applying to other histone proteins. Second, it proves that yeast spore formation closely models the mechanisms of mammalian sperm formation, a key advance given the complexity of mammalian genetics and the technical hurdles inherent in running a genetic screen in mice. Finally, assuming these epigenetic marks are also present and serve similar functions in humans, the study identifies potential biomarkers of human male infertility.

"It is almost certain that some fertility problems relate to epigenetics," Govin said.

Given the conservation of the process of sperm formation across evolutionary time, said Berger, it is likely that the histone modifications identified in this study represent just the tip of the proverbial iceberg.

"We are going to find brand new chromatin regulatory mechanisms that will be conserved all the way from yeast to mouse," Berger predicted.

Provided by University of Pennsylvania School of Medicine

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