Discovery of segregating infertility alleles in humans

Priti Singh, Ph.D.

Cornell University, Department of Biomedical Sciences, Ithaca, NY, USA, 14853

Infertility affects about 15% of child-bearing aged couples in the world today. Up to one-fourth of these cases are diagnosed as idiopathic and thought to have a genetic basis, but the underlying causes remain largely unknown. Over the last several years, we have worked on an association- and linkage-free approach to identify segregating infertility alleles. With the use of CRISPR/Cas9 genome editing, we have modeled multiple putatively deleterious, nonsynonymous SNPs in mouse orthologs of fertility genes and identified some interesting infertility alleles. I will discuss our approach that we practice here to identify segregating infertility alleles and present some data on an interesting allele, thus discovered, in the gene cyclin dependent kinase 2 (*Cdk2*). *Cdk2-Y15S* allele mimicking SNP rs3087335, which alters an inhibitory WEE1 protein kinase phosphorylation site, caused infertility and revealed a novel function in regulating spermatogonial stem cell maintenance. Our results suggest that phosphorylation of this site has dual roles in germ cells maintenance: **1)** in the first wave of spermatogenesis, to restrain proliferation of meiocytes, and **2)** maintaining a steady-state of spermatogenesis balancing proliferation and differentiation of spermatogonial stem cells (SSCs). I will report on how this gain-of-function point mutation results in failure of SSCs to propagate and initiate waves of spermatogenesis in a P21 dependent manner.