ARRDC5 Regulation of Histone-to-Protamine Exchange During Spermiogenesis

LeeLa D. Robinson[1], Melissa J. Oatley[1], and Jon M. Oatley[1]

1. School of Molecular Biosciences, College of Veterinary Medicine, Washington State University, Pullman, USA

Spermiogenesis is the final phase of spermatogenesis when haploid round spermatids undergo a transformation to yield specialized elongated cells that are released from the seminiferous epithelium as spermatozoa. During this process, the paternal genome is condensed into toroid structures via an exchange of histones with protamines. Disruption in the histone-to-protamine exchange leads to sperm head malformations and elevated DNA damage, both of which are prominent abnormalities associated with the most common clinical description of male infertility, oligoasthenoteratospermia (OAT). In previous studies, we discovered that the molecule arrestin domain containing 5 (*Arrdc5*) is an essential regulator of spermiogenesis. Knockout of *Arrdc5* in mice leads to genesis of sperm with severe head malformations and a significant increase in DNA damage compared to sperm from wild-type mice. Here, we explored whether the histone-to-protamine exchange is abnormal in the absence of ARRDC5. Sperm from *Arrdc5* knockout mice were found to stain more intensely with the preferential histone binding dye aniline blue compared to sperm from wild-type mice. In addition, outcomes of immunoblot analyses revealed significantly greater amounts of histone variants in the DNA of sperm from *Arrdc5* knockout mice compared to sperm from wild-type counterparts. Furthermore, protamine content was found to be reduced and the ratio of protamine 1 and 2 variants altered in sperm of *Arrdc5* knockout mice compared to sperm from wild-type mice. Taken together, these data indicate that ARRDC5 influences the histone-to-protamine exchange process during mammalian spermatogenesis and aid in explaining the OAT phenotype that is caused by inactivation of the encoding gene.