Testis-Specific Actin-Like 7 Family Members A and B (ACTL7A/B) Are Key Components of Cytoskeletal Regulation in Spermatid Development and Are Required for Male Fertility.

Pierre Ferrer[1,2]; Srijana Upadhyay[2]; James J. Cai[3]; Tracy M. Clement[1,2]

1. Interdisciplinary Faculty of Toxicology Program, Texas A&M University, School of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX USA

2. Department of Veterinary Physiology and Pharmacology, School of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX USA

3. Department of Veterinary Integrative Biosciences, School of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX USA

Spermiogenesis is a drastic cellular process required for male fertility where round haploid spermatids develop into functional sperm. This process requires the formation of many unique structures and organelles to both support this morphogenic development as well as to provide key sperm functions. These unique elements created during spermiogenesis include the acrosome (a specialized vesicular body essential for oocyte fertilization), the manchette (a tubulin cuff around the nucleus of spermatids required for intracellular transport and nuclear reshaping), and the flagellum (a predominantly cytoskeletal suprastructure responsible for the motility of sperm). Despite the well-established presence of cytoskeletal actin and actin related proteins (ARPs) in these structures, their specific function and involvement in spermatid development has remained enigmatic.

Recent findings have tied several different human polymorphisms of testis-specific ARPs, like members of the ACTL7 and ACTRT subfamilies, to infertility in men. Through the use of mouse KO models, our data has concurred with these observations. We specifically show that ACTL7A plays a crucial role in coordinating the formation of perinuclear theca-associated F-actins for proper acrosomal attachment. Similarly, we have shown ACTL7B to be required for sperm flagellar stability and structural integrity.

However, the mechanistic underpinnings of both ACTL7A and ACTL7B in spermatid cytoskeletal regulation and their importance of male fertility is still poorly understood. In this study, we seek to further hone our understanding of the mechanistic functions of these ARPs given their importance for fertility and the multifaceted nature of their respective KO phenotypes that remain unexplained. Herein, we further investigated the dynamic localization of these ARPs during the development of the germline, their molecular associations with other cytoskeletal components, and their direct impact on microtubule stability and PTM status, as well their effect on HDAC localization and nuclear transport. These findings have allowed us to better delineate the diverse impact these ARPs have across different cellular structures and refine already existing models for cytoskeletal dynamics in spermatids. Further study of the functions of proteins like ACTL7A and ACTL7B may lead us to better understand causes for male infertility as well as provide a new avenue towards non-hormonal contraceptive development.