Accelerated Mitochondrial Dynamics Promote Spermatogonial Differentiation

Zhaoran Zhang[1,2], Junru Miao[1,2], Hanben Wang[1,2], Wei Chen[1,2], and Yuan Wang[1,2]

Reproductive and Developmental Sciences Program[1],

Department of Animal Science[2], Michigan State University, East Lansing, USA.

ABSTRACT

Spermatogonial stem cells (SSCs) maintain a pool of undifferentiated spermatogonia and the subsequent production of progenitor spermatogonia that are poised for differentiation during spermatogenesis. At different stages of spermatogenesis, germ cell mitochondria differ remarkably in morphology, architecture, and functions. However, it remains elusive how mitochondria change these features to impact the SSC fate decision during spermatogonial development. Mitochondrial features are largely regulated by continuously go through fusion and fission cycles, the processes that are collectively called mitochondrial dynamics. In this study, we found that mitochondrial number, morphology, and DNA copies were not altered during spermatogonial differentiation. By contrast, increased opening of the mitochondrial permeability transition pore (mPTP) along with decreased mitochondrial membrane potential (MMP) was observed during this process. Importantly, we found that regulators of mitochondrial fusion (MFN1 & MFN2) and fission (DRP1) were both upregulated in differentiating spermatogonia. Accelerated mitochondrial dynamics in turn promoted spermatogonial differentiation. Using a *Drp1* conditional knockout mouse model, we demonstrated that *Drp1* deficiency in germ cells led to the stage-specific block of spermatogenesis at differentiating spermatogonia. In addition, our data suggested that MFN1 promoted differentiation through the regulation of metabolism, while DRP1 impacted spermatogonial differentiation *via* mPTP opening. Taken together, our findings support that stage-specific, precisely regulated mitochondrial dynamics are required for proper spermatogonial differentiation, thereby providing insights about how mitochondrial activities and functions are maintained so in order to support critical and unique events of germ cell development.