IVIRMA Innovation

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MFN1 IS REQUIRED FOR FOLLICLE DEVELOPMENT, OOCYTE MATURATION, AND FEMALE FERTILITY.

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Proportions of males within Groups over time (RMA and IVI samples combined 2011-2017)

	2002 - 2005	2006 - 2009	2010 - 2013	2014 - 2017
N	8,302	7,906	43,687	60,077
Group 1 (TMSC >15M)	84.7%	85.5%	81.0%	79.1%
Group 2 (TMSC 5-15M)	6.3%	6.0%	8.5%	9.4%
Group 3 (TMSC 0-5M)	8.9%	8.9%	10.5%	11.6%

FERTILITY & STERILITY_ e27

OBJECTIVE: Mitochondria are dynamic organelles that continually adapt their shapes through fusion and fission in response to changes in energy demand and supply. Mitofusin-1 (MFN1) regulates mitochondrial dynamics by promoting mitochondrial fusion. The aim of the current study was to determine the role of MFN1 in female reproductive competence using a mouse model with oocyte-specific deletion of Mfn1.

DESIGN: Experimental study.

MATERIALS AND METHODS: Mfn1flox/flox mice were crossbred with Zp3-Cre mice to produce mice with oocyte-specific Mfn1 deletion (Mfn1-/-). Fertility was assessed by mating 8-week-old Mfn1-/- and wild type (WT) female mice (n¼7 per group) with WT fertile males for 12 weeks. Serial ovarian sections were stained with hematoxylin and eosin. Ability to generate oocytes (germinal vesicle [GV] and metaphase II [MII]) and 2-cell embryos was assessed after injection with PMSG (5IU) or PMSG and hCG (5IU) and mating with WT males as indicated. Mitochondrial morphology and dynamics were assessed using electron microscopy.
ATP levels were determined by bioluminescent assay. Mitochondrial DNA (mtDNA) copy number was measured in individual oocyte by cloning of mitochondria specific gene (Cox3) as a standard, followed by quantitative real-time PCR (qPCR). Finally, RNA sequencing analysis was performed using pooled Mfn1-/- and WT preantral follicle oocytes (n¼3 mice per group).

RESULTS: Mfn1-/- female mice were infertile and did not produce any pups. Mfn1-/- mice ovaries had similar number of primordial, primary, and secondary follicles compared to WT, but no antral follicles with or without PMSG stimulation. Mfn1-/- mice generated a significantly lower number of GVoocyte (17_3.6 vs 40_3.0, p <0.01), no mature oocytes, and no 2-cell embryos (p <0.001). Electron microscopy revealed that Mfn1-/- oocyte mitochondria were larger (5.4_0.19 vs 4.54_0.19 mm2; p<0.01) with lower aspect ratio (length/width; 1.23_0.01 vs 1.83_0.08; p<0.001). Mfn1-/- oocytes had decreased ATP production (0.61_0.07 vs 1.45_0.17; p<0.001) and mtDNA copy number (13,398_870 vs 99,108_151; p<0.001), and decreased expression of follicular development factors (Gdf9 and Bmp15) (p <0.05). RNA-seq analysis revealed a total of 982 genes

that were differentially regulated in Mfn1-/- oocytes with a number of affected pathways including cell death (apoptosis) signaling and adhesion-junction signaling
($p<0.01$).

CONCLUSIONS: Targeted oocyte-specific deletion of Mfn1 results in impaired mitochondrial function and dynamics and female infertility, associated with defective follicle development, lack of oocyte maturation and embryo development. Future studies are required to determine how MFN1- dependent signaling pathways affect female reproductive potential