Paternal Aggresome Content is Associated with Increased Reactive Oxygen Species and Impaired Mitophagy during Preimplantation Development of Bovine Embryos.

Everardo Anta Galvan[1], Karl Kerns[2], M. Sofia Ortega[1].

[1]Department of Animal and Dairy Sciences, University of Wisconsin-Madison, Madison, WI, 53706
[2]Department of Animal Sciences, Iowa State University Ames, IA, 50011

Male fertility studies have focused primarily on sperm morphology and fertilization, however, there is little research following paternal effects on embryo development. This knowledge gap often leads to fertility issues being solely attributed to the female, neglecting the potential impact of the male on pregnancy outcomes. Previous data from our group showed that sires have divergent embryo production abilities. Low-producing sires had embryos with increased autophagy throughout development. Moreover, some low-producing sires also had high aggresome (AGG) content in the sperm head, which also increased embryo AGG throughout preimplantation development. Nonetheless, how misfolded protein accumulation affects the embryo remains unclear. Here we hypothesize that high concentrations of AGG introduced by the sperm, trigger oxidative stress, endoplasmic reticulum stress, and compromise embryo development. Also, we propose that the increase in autophagy reported earlier could be explained by the clearance of paternal mitochondria or mitophagy. To test these, four sires classified as high or low AGG were used to produce embryos in vitro. Embryos were collected at the zygote (n=141), 4-6 cell (n= 139), 8-16 cell (n=138), and blastocyst (n=118) stages across three replicates. Embryos were then evaluated for AGG, ROS, and mitophagy. As previously reported, AGG content was elevated in the high AGG sires' embryos for all developmental stages ($P < 0.001$). It could be that AGG coming from the sperm induces AGG in the embryo and this is sustained through development. This would agree with the difficulty of cells to degrade AGGs through the proteasome due to their increased size and accumulation. In addition, in all the developmental stages, ROS was increased ($P < 0.001$) in the embryos coming from high AGG sires. This could be a result of two scenarios: AGG content causes cell stress and produces ROS, or this is a response mechanism to eliminate the AGG through free radicals. In embryos from low AGG sires, mitophagy goes up by the 4-6 cell stage and decreases by the 8-16 cell stage. In contrast, in embryos from high AGG sires, mitophagy stays up throughout development ($P = 0.0006$). If mitophagy is effectively regulating mitochondria turnover, a decrease in later stages is expected. However, it is possible that in embryos from high AGG sires, mitochondrial clearance is impaired, and the embryo autophagy system prioritizes AGG degradation leading to sperm mitochondria accumulation up to the 8-16 cell stage. This study provides new insights into how high paternal AGG can set off a cascade of events leading to reduced embryo development. Further research is needed to understand AGG origin and composition, and potential treatments to reduce its effects on embryo development.
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