Embryotropic actions of follistatin: Mechanisms and translational relevance

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A growing body of evidence suggests oocyte developmental competence is a limiting factor in efficiency of assisted reproductive technologies and pregnancy success in livestock species and humans, but the inherent phenotypic characteristics of competent oocytes are not well understood. Oocytes gradually and sequentially acquire developmental competence (during the course of folliculogenesis) by synthesizing and accumulating transcripts and proteins critical for successful meiotic maturation, fertilization, and early embryogenesis. We have conducted fundamental studies using the bovine model to elucidate differences in oocyte transcriptome associated with poor oocyte competence and the functional and therapeutic relevance of such results. Of particular interest were studies that showed a positive association of follistatin mRNA abundance with oocyte competence in two distinct bovine models. Follistatin treatment of bovine embryos during initial stages of in vitro culture increases proportion of embryos cleaving early, proportion of embryos developing to the blastocyst stage and numbers of blastocyst trophectoderm cells. Comparative studies in the rhesus monkey model demonstrated stimulatory actions of exogenous follistatin on rates of blastocyst development and support potential clinical relevance of results in the bovine model. Complementary loss of function studies in early embryos established a functional role for follistatin in control of bovine blastocyst development and cell allocation. To increase understanding of intrinsic role of TGFβ superfamily in regulation of early embryogenesis and elucidate mechanism of action of follistatin in mediating its embryotropic effects, studies utilizing a combination of pharmacological and siRNA mediated inhibition of TGFβ superfamily signaling pathway components in the presence or absence of follistatin treatment are being conducted. Results to date suggest a functional requirement for the common SMAD (SMAD4) and SMAD2/3 signaling pathways in promoting bovine early embryonic development and indicate stimulatory effects of follistatin on blastocyst

development, but not early cleavage are blocked when SMAD signaling is inhibited. Elucidation of the mechanism of action of follistatin in mediating above described embryotropic actions is critical to further understanding of the functional significance of follistatin to regulation of bovine early embryogenesis and the translational relevance of results to improvements in assisted reproductive technologies. (Supported by NIH grant HD072972 to GWS and JK).