The evolving potential translational importance of cumulin (GDF9: BMP15) treatments for female fertility

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Growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP15) are oocyte-derived growth factors with critical roles in mammalian reproduction, regulating species-specific fertility, ovarian granulosa cell function, and oocyte quality. In recent years, GDF9:BMP15 heterodimers have come up as one of the most bio potent regulators of follicular functions. The existence of a putative BMP15-GDF9 heterodimer and interactions between GDF9 and BMP15 at genetic, biochemical and functional levels was first modeled in the sheep. Lately, engineered recombinant mouse and human GDF9 and BMP15 homodimers and GDF9:BMP15 heterodimers have been developed and studies show that mouse GDF9:BMP15 heterodimer is approximately ten to thirty-fold more biopotent than mouse GDF9 homodimer, while human GDF9:BMP15 heterodimer is thousand-fold more bioactive than human BMP15 homodimer. GDF9:BMP15 is reported to regulate cumulus expansion genes in mouse granulosa cells, while in porcine oocytes GDF9:BMP15 heterodimer is reported to be more effective than all other growth factors at notably improving oocyte quality as assessed by subsequent day 7 embryo development. Recent studies in mouse granulosa cells and human cumulus cells now show that GDF9:BMP15 is an important regulator of Anti-Müllerian hormone (AMH) during follicular development. Therefore, GDF9:BMP15 heterodimer is emerging as a critical regulator of follicular development with significant practical implications for reproductive medicine. This talk will discuss the signaling mechanism of GDF9:BMP15 heterodimer, its physiological implications in ovarian function and its potential as a therapeutic option.