Molecular basis of oocyte-specific BMPs in regulating folliculogenesis and ovulation rate

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Recent genetic studies have uncovered critical roles of the bone morphogenetic protein (BMP) system in regulating female fertility. Two oocyte-specific BMPs, BMP-15 and its most homologous protein, growth and differentiation factor-9 (GDF-9), are of particular interest because mutations in these genes in ewes cause infertility in the homozygotes yet increased fertility in the heterozygotes as compared with the wild-type. Nevertheless, molecular basis of these BMP factors in regulating ovarian function is poorly understood. Our laboratory has accumulated an extensive body of data on the biochemical characteristics and biological roles of these proteins in regulating ovarian function. Recently, we have demonstrated that recombinant human BMP-15 (rhBMP-15) and rhGDF-9 are phosphorylated; the first members of the TGF-β superfamily to be reported as phospho-proteins. Importantly, the phosphorylation is essential for their biological activities. Moreover, de-phosphorylated rhBMP-15 and rhGDF-9 exhibited antagonistic activity toward not only their phosphorylated counterparts but also toward each other, as well as rhBMP-7, suggesting that the phosphorylation state of rhBMP-15 and rhGDF-9 is a determinant of their agonistic and antagonistic activities and that the non-phosphorylated forms of these oocyte-secreted factors may act more broadly as functional antagonists for other members of the TGF-β superfamily. A critical role for BMP-15 has also been demonstrated in women by the fact that a mutation in the BMP-15 gene is associated with hypergonadotrophic ovarian failure. Moreover, missense mutations in the BMP-15 and GDF-9 genes have been identified with a high incidence in women with premature ovarian failure (POF) and mothers of dizygotic twins, supporting the infertility and fecundity phenotypes found in ewes with mutations in these genes. Interestingly, the mutation sites in most BMP-15 and GDF-9 mutations identified to date in these women are located in the proregion, not in the functional mature region. Thus, if the processing of these mutant proproteins occurred normally, the resulting mature proteins should be indistinguishable from the wild-type, and no functional defects in these mutants would be expected. Using two representative mutants of BMP-15 (BMP-15<sup>Pro</sup> and BMP-15<sup>Rec</sup>) and of GDF-9 (GDF-9<sup>Pro</sup> and GDF-9<sup>Rec</sup>) identified in women with POF and/or mothers of dizygotic twins, we have recently found that they have defects in posttranslational processing of the proproteins, which lead to a significant reduction in production of the mature proteins. A current overview of the molecular basis of these oocyte-specific BMP molecules in regulating folliculogenesis and ovulation rate will be described.