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Cumulin and FSH Cooperate to Regulate Inhibin B and Activin B Production by Human Granulosa-Lutein Cells *In Vitro*

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Endocrinology, Volume 160, Issue 4, April 2019, Pages 853–862, https://doi.org/10.1210/en.2018-01026

Published: 08 February 2019 **Article history** ▾

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Abstract

The oocyte-secreted factors bone morphogenetic protein 15 (BMP15) and growth differentiation factor 9 (GDF9) interact functionally, and it is hypothesized that this interaction may be mediated by formation of a GDF9:BMP15 heterodimer termed cumulin. GDF9 and BMP15 regulate folliculogenesis and ovulation rate and have been shown to regulate inhibin and activin, local regulators of folliculogenesis. The objective of this study was to determine whether cumulin regulates granulosa cell inhibin and activin production and whether this requires cooperation with FSH. Human granulosa-lutein (hGL) cells collected from patients undergoing *in vitro* fertilization were cultured with or without FSH with various forms of recombinant cumulin (native and cysteine mutants, with or without the prodomains), and cysteine mutant GDF9 or BMP15. Messenger RNA expression of the subunits of inhibins/activins (*INHA*, *INHBA*, *INHBB*) and secretion of inhibin A, inhibin B, and activin B were measured. Mature forms and proforms of cumulin stimulated comparable *INHBB* mRNA expression and secretion of inhibin B and activin B, whereas GDF9 or BMP15 exhibited no effect. Cumulin, but not GDF9 or BMP15, interacted synergistically with FSH to increase *INHBB* mRNA and inhibin B expression. FSH markedly stimulated *INHA*, which encodes the α subunit of inhibin

A/B, and suppressed activin B. Cumulin with or without FSH did not significantly alter inhibin A. Together these data demonstrate that cumulin, but not GDF9 or BMP15, exerts paracrine control of FSH-induced regulation of inhibin B and activin B. The prodomains of cumulin may have a minimal role in its actions on granulosa cells.

Issue Section: Reproductive Biology and Sex-Based Medicine

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Online ISSN 1945-7170
Print ISSN 0013-7227