Abstract

The functional role of the transcription factors NR5A1 and NR5A2 and their interaction with Clock gene and bone morphogenetic proteins (BMPs) were investigated in human granulosa KGN cells. Treatment with BMP-15 and GDF-9 suppressed forskolin (FSK)-induced steroidogenesis as shown by the mRNA expression levels of StAR and P450scc but not the mRNA expression level of P450arom. Of interest, treatment with BMP-15 and GDF-9 also suppressed FSK-induced NR5A2 mRNA expression. Treatment with BMP-15 suppressed NR5A2 mRNA and protein expression but increased Clock mRNA and protein expression levels by granulosa cells. The mRNA expression levels of NR5A1, but not those of NR5A2, were positively correlated with the levels of Clock mRNA, while the mRNA levels of Id-1, the target gene of BMP signaling, were positively correlated with those of NR5A1 but not with those of NR5A2. It was also demonstrated that the mRNA expression levels of NR5A1 were positively correlated with those of P450arom and 3βHSD, whereas the mRNA expression level of NR5A2 was correlated with those of StAR and P450scc. Furthermore, inhibition of Clock gene expression by siRNA attenuated the expression of NR5A1, and the mRNA

levels of Clock gene were significantly correlated with those of NR5A1. Collectively, the results suggested a novel mechanism by which Clock gene expression induced by BMP-15 is functionally linked to the expression of NR5A1, whereas NR5A2 expression is suppressed by BMP-15 in granulosa cells. The interaction between Clock NR5A1/NR5A2 and BMP-15 is likely to be involved in the fine-tuning of steroidogenesis by ovarian granulosa cells.