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The newly established bovine endometrial gland cell line (BEGC) forms gland acini in vitro and is only IFN γ -responsive after E2 and P4-pre-incubation

Jan-Dirk Haeger, Christian Loch, Christiane Pfarrer



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1 Key words: implantation, uterine glands, endometrial gland cell culture, progesterone,
2 estrogen, interferon tau

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4 **1. Introduction**

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6 Embryonic loss occurs within the first two weeks of gestation and is of
7 economic importance [1]. During bovine implantation significant alterations take place
8 in the endometrium concerning changes in endometrial structure [2] and gene
9 expression [3]. Key regulators of such alterations are estrogen (E_2), progesterone
10 (P_4) [4] and interferon tau ($IFN\tau$), which is the pregnancy-recognition signal in
11 ruminants [5, 6]. In bovine E_2 and P_4 exert cellular effects via the nuclear
12 progesterone PR [7] and estrogen receptors ESR1/2 [8]. In addition membrane-
13 associated steroid receptors are used by P_4 [9] and E_2 [10]. In humans the activation
14 of the receptors leads to the release of intracellular calcium and activation of
15 mitogen-activated protein kinases [11, 12]. The steroids promote implantation by
16 modifying bovine endometrial histiotroph [13] and downregulating tight-junction-
17 associated proteins in the ovine endometrium [14].

18 Bovine interferon tau ($IFN\tau$) is produced in mononuclear trophoblast (TR) cells
19 during ruminant blastocyst elongation [15] and acts via the receptor subunits
20 $IFNAR1/2$ [16]. It has also been associated with ovine blastocyst elongation [16] and
21 the induction of an anti-inflammatory response in uterine epithelial cells from GD 5-9
22 in cattle [17, 18]. In ruminants $IFN\tau$ mediates its effects via non-classical signaling
23 pathways involving mitogen-activated protein kinases (MAPK) and by classical
24 pathways encompassing activation of Janus-activated kinases (JAKs) and signal
25 transducer and activator of transcription 1 (STAT1) [19, 20]. During implantation E_2 ,
26 P_4 , and $IFN\tau$ act in a precisely orchestrated chronological sequence [21]. In previous
27 studies it has been shown that P_4 is permissive to the expression of ISGs which are

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