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Follicle stimulating hormone receptor protein is expressed in ovine uterus during the estrous cycle and utero-placenta during early pregnancy: An immunohistochemical study

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ABSTRACT

Follicle stimulating hormone (FSH) is a well characterized gonadotropin that controls primarily development and functions of ovarian follicles in mammalian species. FSH binds to a specific G protein-coupled receptor (FSHR) belonging to the glycoprotein hormone receptor family that plays an essential role in reproduction. Although the primary location of FSHR is in the gonads (mainly in ovarian follicles), FSHR protein and/or mRNA have also been detected in extragonadal female reproductive tissues including embryo, placenta, endometrium, cervix, ovarian cancer tissues, and/or endometriotic lesions in several species. To determine the pattern of FSHR expression in the uterus and placenta, uterine tissues were collected at the early, mid- and/or late luteal phases of the estrous cycle from non-treated or FSH-treated ewes, and utero-placental tissues were collected during early pregnancy followed by immunohistochemistry and image generation. FSHR was immunolocalized to several uterine and utero-placental compartments including luminal epithelium, endometrial glands and surrounding stroma, myometrium, and endothelium and vascular smooth muscle cells in endometrium, myometrium and mesometrium. Intensity of staining and distribution of FSHR in selected compartments differed and seems to depend on the stage of the estrous cycle or pregnancy, and FSH-treatment. These novel data demonstrate differential expression of FSHR protein indicating that FSH plays a specific role in regulation of uterine and utero-placenta functions in sheep.

1. Introduction

Follicle stimulating hormone (FSH) is a well characterized gonadotropin that controls primarily development and functions of ovarian follicles in mammalian species (Simoni et al., 1997; Vegetti and Alagna, 2006; Hunzicker-Dunn and Mayo, 2015). FSH binds to a specific G protein-coupled receptor belonging to the glycoprotein hormone receptor family that plays an essential role in reproduction (Simoni et al., 1997; Ulloa-Aguirre and Zarinan, 2016). Although the primary location of FSHR is in the gonads, FSHR protein and/or mRNA have also been detected in extragonadal female reproductive tissues including embryo, placenta, endometrium, cervix, ovarian cancer tissues, and/or endometriotic lesions in humans, cows and mice (Mizrachi and Shemesh, 1999; Shemesh, 2001; Shemesh et al., 2001; Leethongdee et al., 2010, 2014;Stilley et al., 2014; Papadimitriou et al., 2016; Ponikwicka-Tyszko et al., 2016; Robin et al., 2016; Wei et al., 2016). In addition, it has been demonstrated that endometrial and placental FSHR expression depends on the stage of the estrous cycle or pregnancy in humans (La Marca et al., 2005; Stilley et al., 2014).

Follicle stimulating hormone is widely used in the assisted reproductive technologies (ART) to induce multiple follicle development in humans and other species (Vegetti and Alagna, 2006; Grazul-Bilska et al., 2012). However, through direct or indirect mechanisms, FSH may also affect uterine functions. Existing limited data indicate that FSH affects several uterine functions including expression of steroid receptors, and other hormone and growth factor receptors in human endometrium (Tropea et al. 2004, Detti et al. 2011, 2013), and uterine secretory functions, morphology, vascular density, and expression of selected genes in ruminants (Forde et al. 2012;Mona e Pinto et al., 2014; Rasolomboahanginjatovo et al. 2014; Grazul-Bilska et al., 2017).

We hypothesized that FSHR are expressed in ovine uterine and utero-placental tissues, and FSHR expression is affected by reproductive status (e.g., non-pregnant, pregnant, stage of the estrous cycle or pregnancy) and/or FSH treatment of non-pregnant females. The objective of this study was to immunolocalize FSHR in the uterus at early-, mid- and/or late-luteal phases of the estrous cycle in non-treated or FSH-treated ewes, and in utero-placenta on days 14, 16, 20 and 30 of pregnancy.

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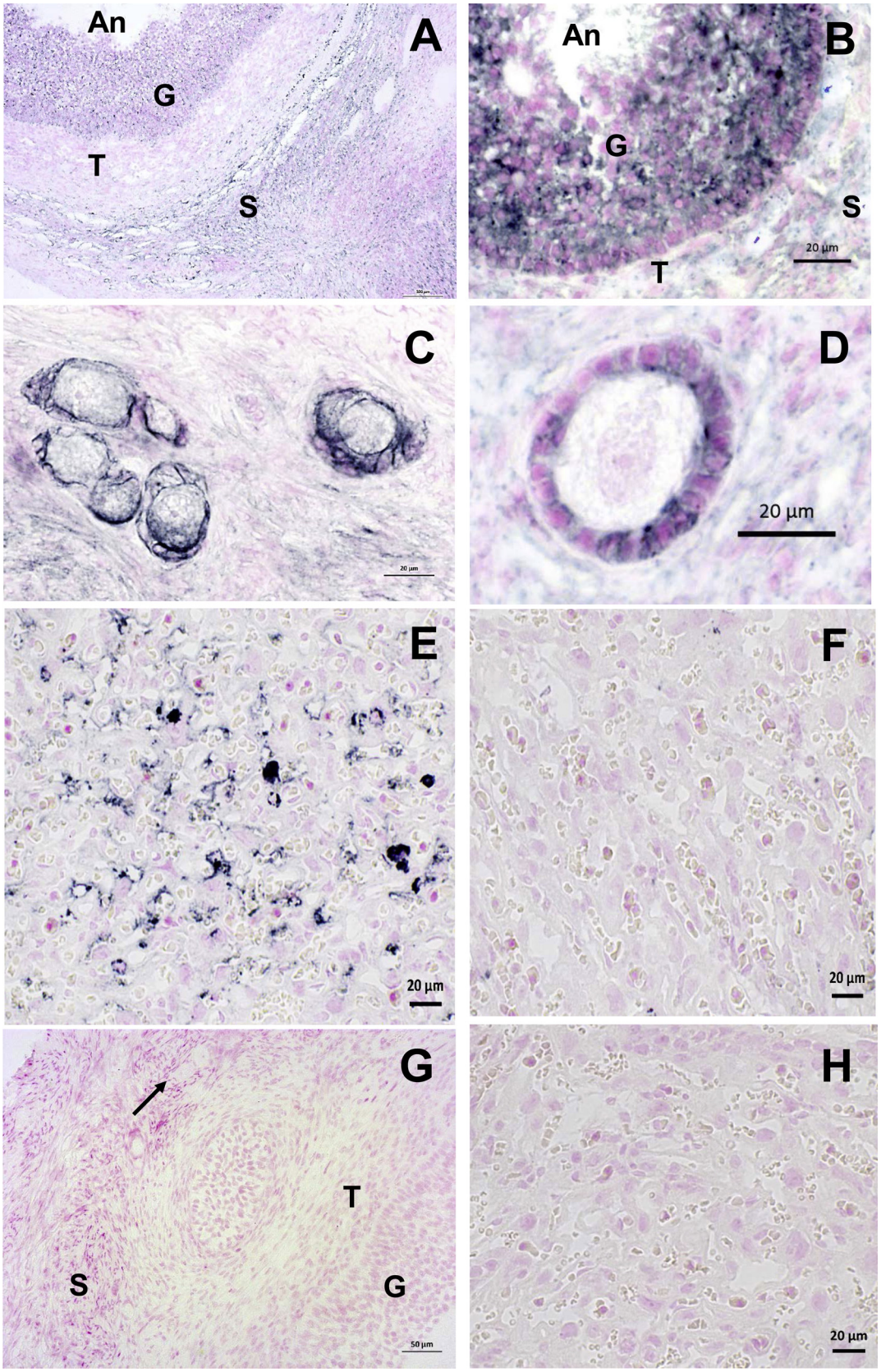

Fig. 1. Representative images of FSHR staining (dark color) in ovary from a non-pregnant ewe (A, C), human ovary (B, D) and placenta from wild-type (E), and *Fshr-/-* (F) mice. In A and B, note strong staining in granulosa (G) layer, weak in stromal tissues (S) and no staining in theca (T) layer. In C and D, note strong staining in primary follicles and week or no staining in stroma. In E and F, note strong staining in labyrinth layer of placenta from wild-type, and no staining in placenta from *Fshr-/-* mice, respectively. Antrum = At. Note no positive staining in control ovine ovary (G) and mouse placenta (H) where primary antibody was replaced with rabbit serum. Pink staining (nuclear fast red) indicates cell nuclei (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).