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Fibroblast growth factors and endometrial decidualization: models, mechanisms, and related pathologies

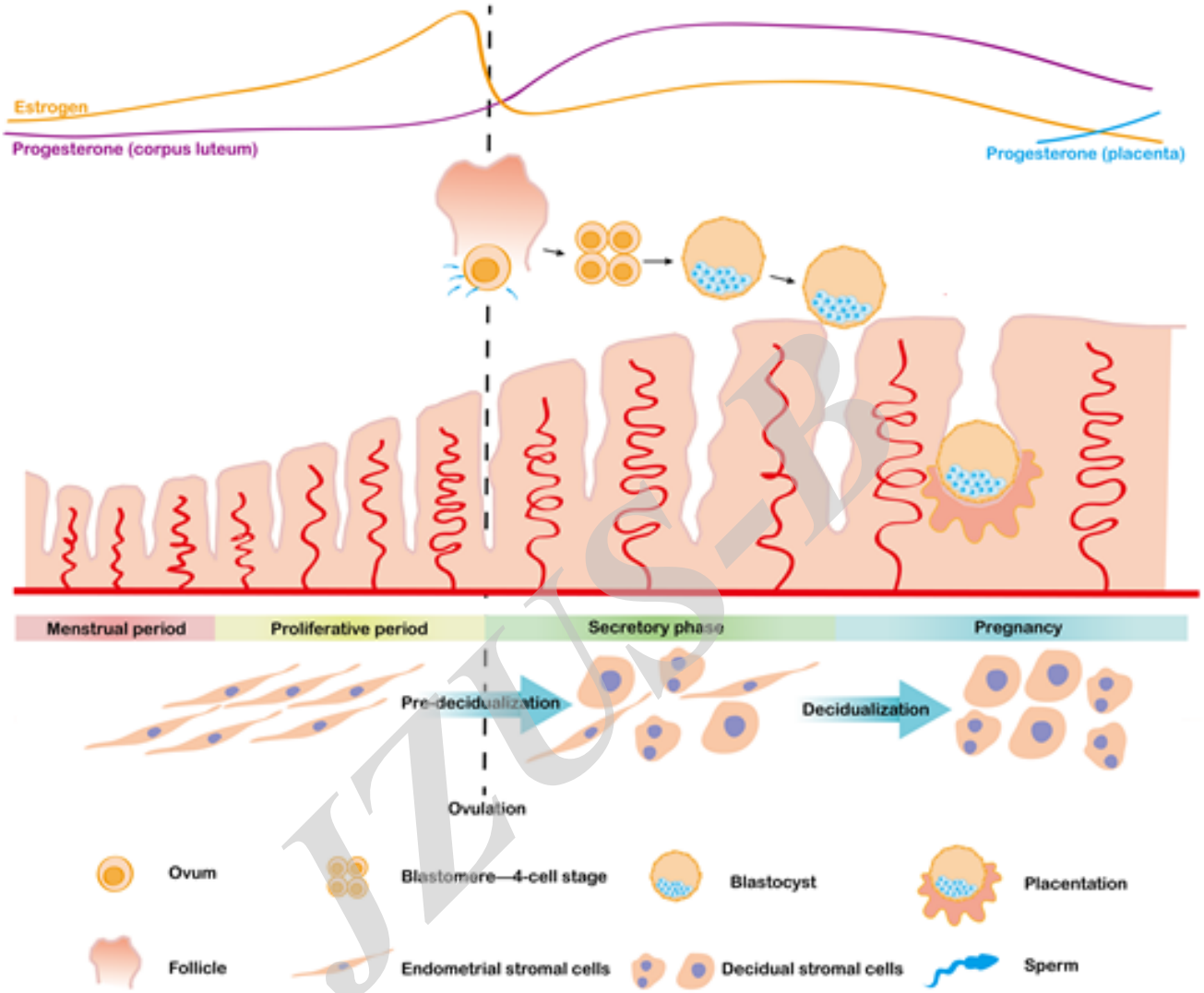
Key words: Fibroblast growth factor; Decidualization; Pregnancy; Adverse pregnancy outcomes

Research Summary

This review focuses on comparing diverse research decidualization models, delineating the regulatory mechanisms of FGFs in decidualization, and providing a synopsis of endometrial disease triggered by FGF dysregulation, and reviews them from the following aspects:

- **Decidualization of the endometrium**
- **Established models of decidualization**
- **Signal transduction during decidualization**
- **Roles of FGFs in endometrial physiology**
- **Diseases caused by disordered decidualization**
- **FGFs and endometrial diseases**
- **Conclusions and prospects**

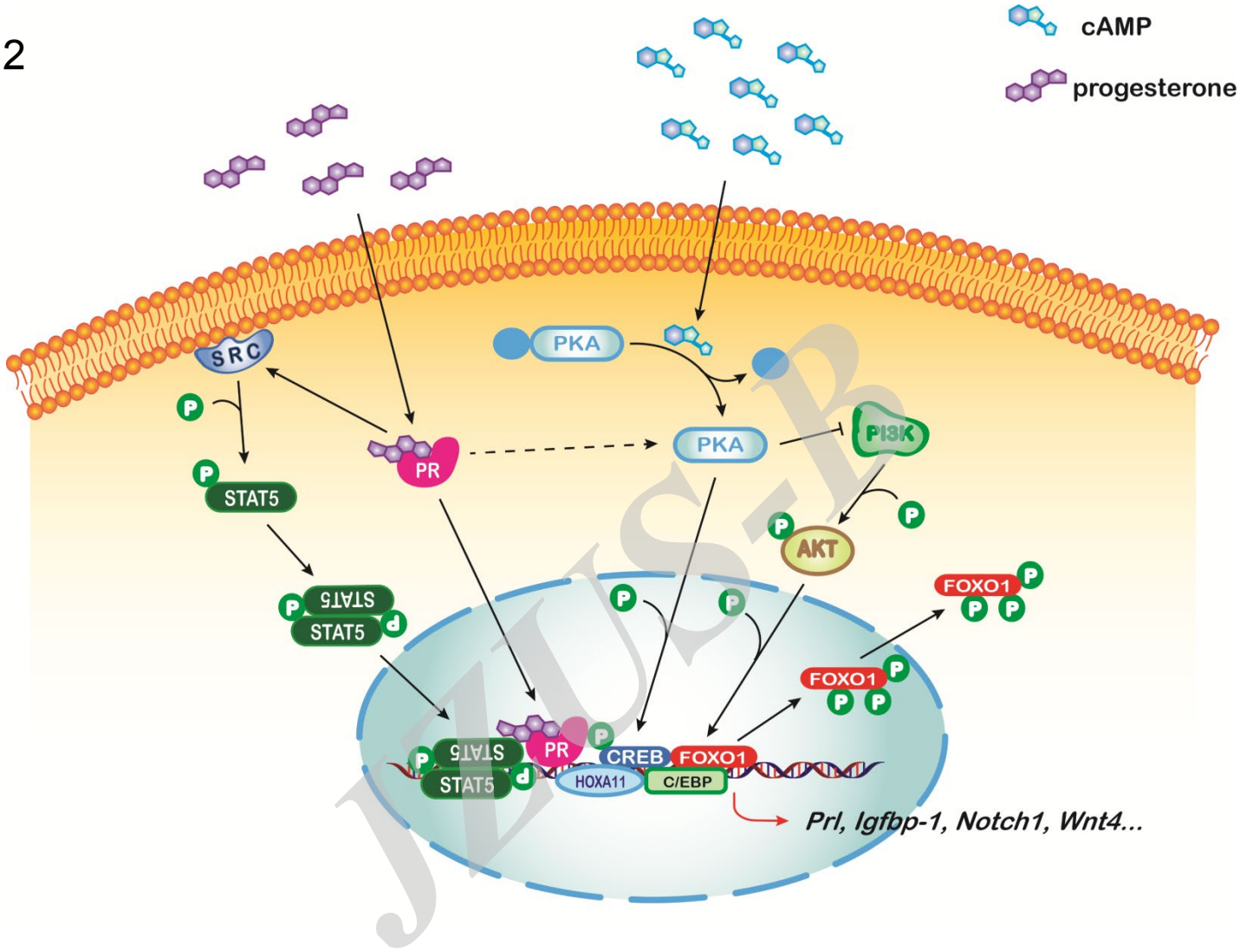
Figure 1



Changes in hormone levels and endometrial stromal cells during implantation

During the menstrual cycle, the endometrium undergoes corresponding periodic changes. In the proliferative phase, estradiol levels continue to rise and the endometrium thickens. From the 14th day of the cycle, estradiol concentrations decrease rapidly and progesterone production increases. At this time, the follicle matures and ruptures, and secondary oocytes are released, marking the end of the proliferative phase and the onset of the secretory phase. With the formation of the corpus luteum, progesterone is continuously secreted, and endometrial stromal cells begin to pre-decidualize in preparation for embryo implantation. On the 7th day after ovulation, the whole endometrium enters a brief period of pre-decidualization that allows the embedding of the embryo. After embryo implantation, the corpus luteum develops into the pregnant corpus luteum that continuously secretes progesterone, while endometrial stromal cells rapidly decidualize. Thereafter, the placenta gradually takes over the secretion of progesterone from the pregnant corpus luteum, while endometrial stromal cells continue to decidualize until the fetus is delivered.

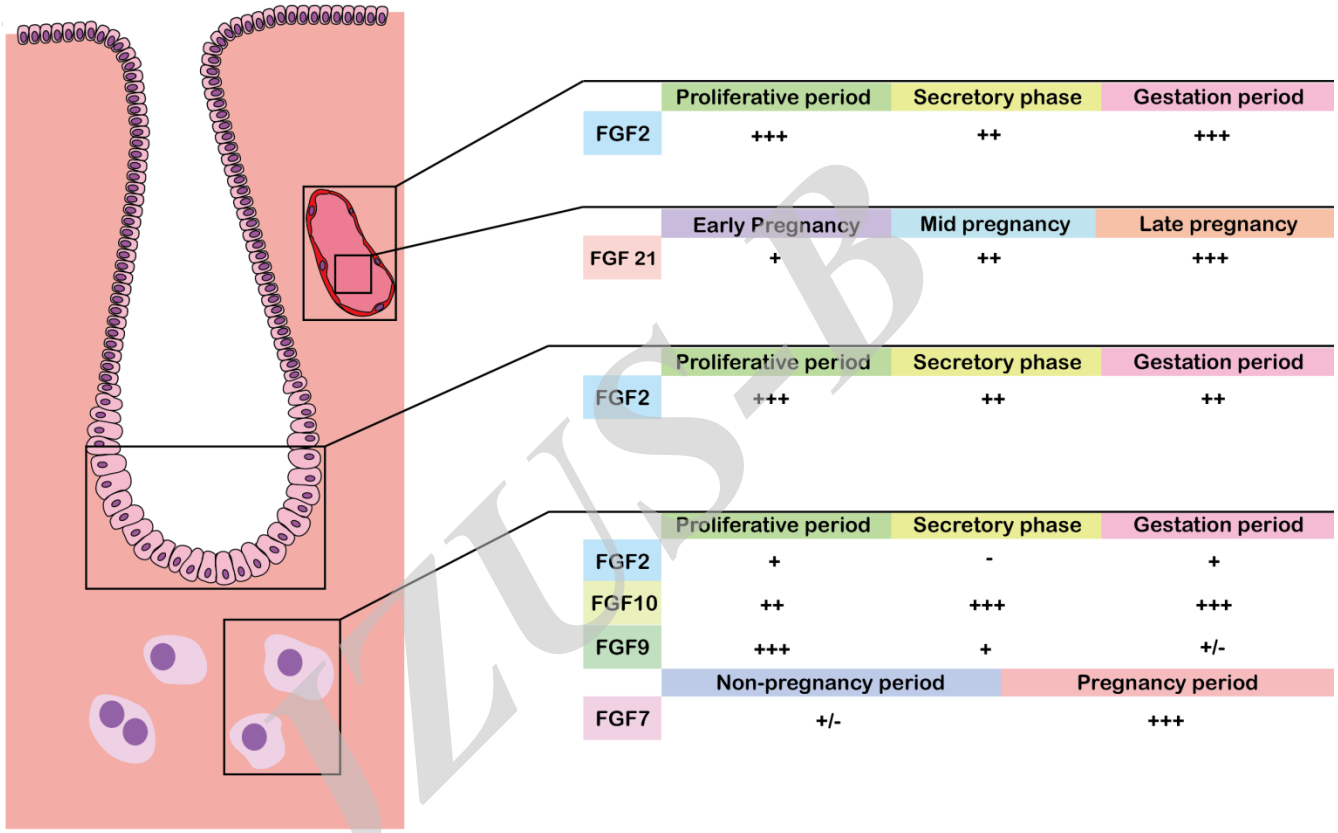
Figure 2



Molecular mechanism of decidualization in human endometrial stromal cells

In humans, progesterone is the principal hormone that induces decidualization in endometrial stromal cells. After bypassing the cell membrane, progesterone binds to and activates PRs in the cytoplasm. The progesterone-PR complex directly enters the nucleus and interacts with other transcription factors to regulate the expression of decidualization-related genes. SRC is a downstream target protein of PRs, which can phosphorylate STAT5 after activation. Phosphorylated STAT5 can bind to regulatory sites and regulate gene expression. In addition, the dashed line indicates that the PR pathway may also regulate the decidualization of stromal cells through the cAMP/PKA signaling pathway; cAMP can directly activate PKA. After phosphorylation, PKA activates the transcription factor CREB, interacts with other transcription factors and DNA-binding proteins in the nucleus, and coregulates the expression of decidualization-related genes. The activation of PI3K/AKT pathway can result in the phosphorylation of the transcription factor FOXO1 and promote its nuclear export.

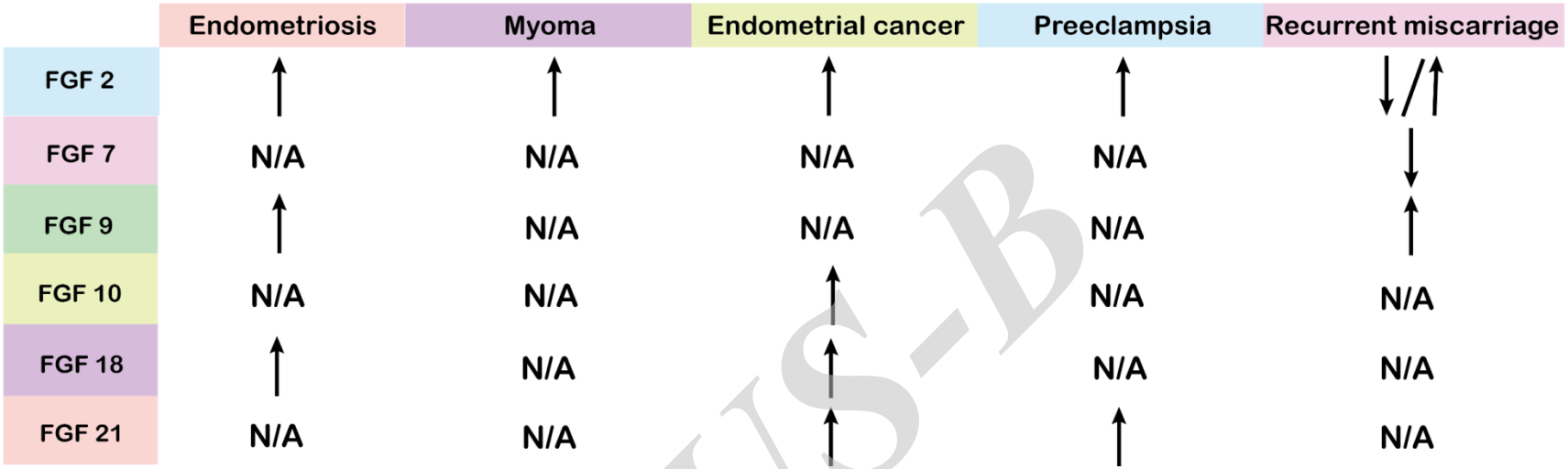
Figure 3 (a)



Expression of FGFs in the context of a normal menstrual cycle, pregnancy, and disease

The spatiotemporal expression patterns of FGF2, FGF9, FGF10, and FGF21 in the context of a normal menstrual cycle or pregnancy. Each table represents a different part of the endometrium, including (from top to bottom) 1) endothelial cells; 2) the serum; 3) the glandular epithelium; 4) endometrial stromal cells. The expression levels of FGFs during proliferation, secretion, and pregnancy are shown. The number of "□" symbols signifies the expression level.

Figure 3 (b)



Expression of FGFs in the context of a normal menstrual cycle, pregnancy, and disease

The trend of changes in FGF2, FGF7, FGF9, FGF18, and FGF21 expression in various endometrial diseases is shown compared with those in healthy endometrium. "↑" Indicates an increase in expression levels in disease compared to healthy endometrium, "↓" indicates a decrease in expression levels in disease compared to healthy endometrium, and N/A indicates not applicable.