CYCLIC DECIDUALIZATION OF THE HUMAN ENDOMETRIUM IN REPRODUCTIVE HEALTH AND FAILURE: A COMPREHENSIVE REVIEW

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Abstracty

Decidualization is a fundamental biological process that transforms endometrial stromal fibroblasts into specialized decidual cells capable of supporting embryo implantation, placental development, and pregnancy maintenance. Human decidualization differs from that of most mammals because it occurs spontaneously during each menstrual cycle under the influence of progesterone and cyclic adenosine monophosphate signaling. This review summarizes current knowledge regarding the cellular, molecular, endocrine, immunological, and stem-cell-mediated mechanisms regulating decidualization. The role of decidual cells in embryo selection, implantation, immune tolerance, angiogenesis, and tissue remodeling is discussed. Furthermore, the clinical implications of defective decidualization in infertility, recurrent implantation failure, recurrent pregnancy loss, endometriosis, preeclampsia, and fetal growth restriction are examined. Advances in transcriptomics, proteomics, and regenerative medicine have revealed complex regulatory networks that govern decidual differentiation and reproductive success. Understanding these mechanisms may facilitate the development of novel biomarkers and targeted therapies for reproductive disorders.

Keywords

Decidualization; Endometrium; Implantation; Reproductive failure; Infertility; Pregnancy; Progesterone; Stem cells

1. Introduction

The human endometrium is a highly dynamic tissue that undergoes cyclic growth, differentiation, shedding, and regeneration throughout reproductive life. One of the most important events occurring during the luteal phase is decidualization, a process in which endometrial stromal fibroblasts differentiate into secretory decidual cells. These cells create a supportive microenvironment for embryo implantation and placental formation.

Unlike most mammalian species, decidualization in humans is initiated independently of embryo implantation. Instead, rising progesterone

concentrations following ovulation trigger extensive structural and molecular remodeling of the endometrium. This evolutionary adaptation is believed to facilitate embryo selection and optimize reproductive success despite the high frequency of chromosomal abnormalities observed in human embryos.

2. Morphological Features of Decidualization

Decidualization is characterized by dramatic morphological changes. Stromal fibroblasts become enlarged, rounded, and metabolically active. The cytoplasm expands and accumulates glycogen and lipid droplets that serve as energy reserves during early pregnancy. Simultaneously, the extracellular matrix undergoes extensive remodeling, generating a tissue architecture suitable for implantation and trophoblast invasion.

The transformation begins around spiral arteries and progressively extends throughout the superficial endometrium. Histological changes include stromal edema, vascular remodeling, increased leukocyte infiltration, and enhanced secretory activity. These alterations establish a receptive endometrium capable of supporting embryo attachment.

3. Endocrine Regulation

Progesterone represents the principal endocrine regulator of decidualization. Following ovulation, progesterone produced by the corpus luteum acts through progesterone receptors expressed in endometrial stromal cells. However, progesterone alone is insufficient to initiate decidualization. Additional signaling pathways involving cyclic AMP, prostaglandin E2, relaxin, and corticotropin-releasing hormone contribute to the induction and maintenance of the decidual phenotype.

Interactions between steroid hormones and intracellular signaling pathways result in activation of transcriptional networks responsible for cellular differentiation, immune regulation, and tissue remodeling.

4. Molecular and Genetic Mechanisms

Modern transcriptomic studies demonstrate that decidualization involves extensive reprogramming of gene expression. Thousands of genes exhibit altered expression during stromal cell differentiation. Key transcription factors include FOXO1, C/EBPβ, HOXA10, HOXA11, and progesterone-responsive regulatory proteins.

Among the most widely accepted markers of decidualization are prolactin and insulin-like growth factor-binding protein-1. Additional mediators include LEFTY2, WNT signaling molecules, transforming growth factor family members, and numerous cytokines and chemokines. Collectively, these pathways

coordinate cellular communication required for successful implantation and placentation.

5. Immune Adaptation During Decidualization

Successful pregnancy requires precise regulation of maternal immune responses. The decidua contains abundant uterine natural killer cells, macrophages, dendritic cells, and T lymphocytes. Rather than promoting tissue destruction, these immune populations facilitate vascular remodeling, trophoblast invasion, and immune tolerance.

Uterine natural killer cells represent the dominant leukocyte population in early pregnancy. They contribute to spiral artery remodeling and regulate trophoblast migration through cytokine and chemokine secretion. Disturbances in immune homeostasis have been associated with recurrent pregnancy loss and implantation failure.

6. Stem Cells and Endometrial Regeneration

The regenerative capacity of the endometrium is supported by resident epithelial and mesenchymal stem cell populations. These cells enable rapid tissue repair following menstruation, miscarriage, and childbirth. Endometrial mesenchymal stem cells exhibit clonogenicity, self-renewal, and multipotent differentiation potential.

Recent studies suggest that defects in stem-cell populations may impair decidualization and contribute to infertility. The identification of stem-cell markers has stimulated interest in regenerative medicine and the potential use of endometrial stem cells in therapeutic applications.

7. Embryo Selection and Implantation

A unique feature of human decidualization is its role in embryo quality control. Decidual cells actively respond to embryonic signals and may distinguish between developmentally competent and impaired embryos. This selective mechanism contributes to reproductive efficiency by supporting viable embryos while facilitating rejection of nonviable conceptuses.

Communication between embryos and decidual cells involves cytokines, growth factors, extracellular vesicles, and metabolic signals. These interactions influence implantation outcomes and early placental development.

8. Clinical Implications

Defective decidualization has been implicated in numerous reproductive disorders. In infertility and recurrent implantation failure, impaired stromal differentiation may reduce endometrial receptivity. Women experiencing

recurrent pregnancy loss frequently demonstrate abnormalities in decidual immune regulation and progesterone responsiveness.

Endometriosis is also associated with altered decidualization pathways and progesterone resistance. Furthermore, inadequate decidual remodeling contributes to placental disorders such as preeclampsia, fetal growth restriction, and preterm birth. Consequently, decidual dysfunction is increasingly recognized as a central mechanism underlying reproductive failure.

9. Emerging Technologies and Future Perspectives

Advances in transcriptomics, proteomics, metabolomics, and single-cell sequencing have revolutionized the understanding of decidual biology. These technologies provide insights into cellular heterogeneity and regulatory networks that were previously inaccessible.

Future research should focus on personalized approaches to reproductive medicine, identification of predictive biomarkers, and development of targeted therapies capable of improving implantation and pregnancy outcomes. Stem-cell-based therapies and molecular interventions represent promising areas for future investigation.

10. Conclusion

Decidualization is a complex and highly regulated biological process essential for human reproduction. Through coordinated endocrine, immune, cellular, and molecular mechanisms, decidual cells establish an environment that supports implantation, placental development, and fetal growth. Disruption of these mechanisms can lead to infertility, recurrent pregnancy loss, implantation failure, and pregnancy complications. Continued investigation of decidual biology will contribute significantly to the advancement of reproductive medicine and maternal–fetal health.

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