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Decidual cell reaction: Insight into mechanisms and regulatory factors involved

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Abstract
Decidual cells represent a morphologically distinct class of cell appearing within the endometrium of mammalian uteri**.** The decidual cell reaction is a complex process that occurs in the endometrium during pregnancy, involving changes in gene expression and cellular morphology. Decidualization is the transformation of endometrial stromal cells into specialized decidual cells, crucial for establishing implantation and maintaining pregnancy. This review explores the intricate mechanisms underlying the decidual cell reaction, focusing on the roles of key hormones such as estrogen, progesterone, relaxin and androgen. Additionally, it discusses the expression of critical genes and proteins like MUC1, HB-EGF, and BMP2 in regulating decidualization. The involvement of immune cells like natural killer cells and the use of animal models to study decidual development are also highlighted.
Keywords: Decidualization, Implantation, Pregnancy, Stromal cells, Decidual Cells,

Introduction

Decidual cells are unique type of cell found in the mammalian endometrium specifically during pregnancy (Kearns *et al*., 1983). The endometrium of mammals undergoes. Uterine decidualization, a key event for successful implantation and is critically controlled by stromal cell proliferation and differentiation. These decidual cells proliferate at the site of implantation surrounding the embryo and provide the uterine contribution to the placenta (Finn et al., 1975). At the time of implantation, the walls of the uterus become tightly apposed so that the uterine lumen is more or less occluded, and changes in the surface of the uterine epithelium make a conductive surface for blastocyst attachment. Blastocyst attachment induces the formation of a uterine crypt and also stimulates the uterine stroma to form a spongy mass of cells known as decidual tissue. The process is known as "decidual reaction" and the mass of decidual cells around single embryo can be referred to as "deciduam", meaning "the thing that falls off". Decidual cells appear during implantation and early pregnancy.

The importance of the decidual tissue for establishing implantation of the embryo and maintaining pregnancy until the stage of placenta formation was first indicated by its physical importance when mice were challenged by blastocyst transfer into the peritoneal cavity and failed (McLaren et al., 1963). The embryonic loss was observed by ovariectomy mediated progesterone withdrawal due to collapse of the deciduas (Deanesly *et al*., 1973). The significance and importance of decidua was described in human when tubal decidual formation was observed in some cases of human ectopic implantation in the ovary or peritoneal cavity (Spornitz *et al*., 1993). Thus, decidualization of uterine tissue is essential to establish successful pregnancy. Decidualization, the process by which the uterine endometrial stroma proliferates and differentiates into large epithelioid decidual cells, is critical to the establishment of fetal-maternal communication and the progression of implantation (Lee *et al*., 2007). The decidua is an important platform of the uterine tissue, which comprises terminally differentiated endometrial stromal cells and newly generated maternal vascular cells for vasculogenesis and angiogenesis. The decidua has been known as maternal uterine tissue, which plays essential roles in protecting the embryo from being attacked by maternal limmune cells and provides nutritional support for the developing embryo prior to placenta formation (Mayumi *et al*., 2006).

In this review paper, we will discuss the decidual cell reaction, investigate the underlying mechanisms governed by gene expression and the various techniques employed to study this phenomenon.

Materials and methods

This review paper provides a comprehensive analysis of the decidual cell reaction, delving into the underlying mechanisms governed by gene expression and the various techniques employed to study this phenomenon. Information for the review was sourced from different digital databases including Google Scholar, PubMed, Medline, Science Direct, ResearchGate, Google Search Engine and NCBI (National Center for Biotechnology Information). A total of 60 articles, comprising research papers, review papers, short communications, and other relevant articles from reputable sources, were analyzed to develop this comprehensive review paper.

Results and Discussion

1. Method of decidualization:

The decidual reaction involves a rapid increase in the permeability of local capillaries, causing the uterine stroma to become swollen and edematous. The stromal cells in the decidual tissue proliferate, increase in size and establish numerous tight functional complexes with their neighbors (Finn *et al*., 1967). One of the earliest of the visible responses of implantation is an increased vascular permeability in the stromal tissue underlying the conceptus, followed by edema and compositional changes in the intercellular matrix & changes in the morphology of the stromal cells and also a progressive sprouting and in growth capillaries. The stromal reaction set in motion by the blastocyst signal is particularly marked in primates and rodents where it is called decidualization and it prepare the major endometrial component of the placenta the decidua. A primary signal from the conceptus has been efficiently transferred through the endometrium to transfer through the epithelium to the stroma but the nature of the signal or massage derived from the blastocyst has not been established yet distinctly. It could be a low molecular weight secretory product of the blastocyst that itself diffuses rapidly through the endometrial tissue. But, more probably the blastocyst stimulates the adjacent uterine tissue to secrete a ‘decidualizing molecule’ which then spread through the stroma. The nature of the decidualizing molecule has been the subject for various considerable experimental work, and evidence is available which suggests that

both histamine and prostaglandin are involved. Both molecules are present in the progestational endometrium and will induce decidualization if injected locally (Kennedy *et al*., 1985).

In mouse, attachment of the blastocyst to the maternal uterine tissue takes place after four days of fertilization. The attachment of the blastocyst to the uterine epithelium initiates the process of decidualization. This phenomenon involves differentiation of the underlying fibroblastic stromal cells into morphologically distinct cells, termed as decidual cells (Jollie *et al*., 1965). The decidual cells have unique biosynthetic and secretory properties. The steroid hormones estrogen (E) and progesterone (P) play a pivotal role in directing early uterine events during pregnancy. These hormones orchestrate the changes in the uterine epithelium that makes it competent to attach to the blastocyst and initiate the process of implantation. Cellular differentiation induced by Progesterone (P) following brief priming with estrogen (E), which is a prerequisite for successful implantation. Decidua begins to develop at the time of blastocyst attachment on day 4.5 of pregnancy. During the next 3 days of gestation, decidual cells surrounded the site of embryo attachment. Decidual cell proliferate, becoming larger often with binucleated or polyploidy status. Stromal cell polyploidy during differentiation eventually results in apoptosis and the latter process is thought to limit the life span of decidual cell which allowing the placental development. In both mice and humans, the identities of the hormone- regulated pathway that controls the decidualization process remain largely unknown but the roles of several key steroid hormone regulated molecule have been identified and are thought to participate in the establishment of early pregnancy by controlling uterine decidualization.

2. Different Factors of decidual cell reaction:

A work on early stages of implantation in mice has done by Finn and Anne McLaren (Finn *et al*., 1965). They studied the changes taking place in the blastocyst and locally in the uterus at the site of blastocyst attachment. Females were paired with males of their own strain and examined for copulation plugs and then mice were killed at interval between 3days 21 hr. and 4 days 16 hr. Fifteen minute before each animal was killed they were injected with 0.25 ml of a 1% solution of Pontamine sky blue 5BX intravenously. The uteri were tested for the presence of Pontamine Blue areas which indicate increased permeability of capillaries and histochemically they examine the presence of alkaline phosphate in the uterine stroma. The activity of alkaline phosphate in the uterine endometrium first appeared as a positive area in

the stroma of the blastocyst. Alkaline phosphate is present in the blastocyst before it can be detected in the uterine stroma and in early specimen, it was found around the entire circumference indicating perhaps the continued presence of zona pelucida. At later stage they found that, alkaline phosphate disappears from the embryonic region of blastocyst, except for an occasional cell. They found that the inner cell mass remains strongly positive. They found W-bodies which were most clearly seen in the epithelium after staining Toludine Blue. Emerging W-bodies were always accompanied by a positive Pontamine Blue reaction, but these are absent in the later stage of implantation reaction, probably are to the difficulty to detecting them once the decidual cell reaction (DCR) started.

Role of cyclic nucleotide in the artificially stimulated decidual cell reaction in the mouse uterus triggering the decidual cell reaction was studied earlier (Shelesnyak *et al*., 1957). The artificially stimulated decidual cell reaction (DCR) is used widely as a model for study of changes occurring in the uterus during implantation (Glasser *et al*., 1975) (Ledford *et al*., 1978) (Bernard *et al*., 1978). .This work involved ovariectomized mice which were treated with estrogen and progesterone to prepare the uterus for implantation. One week after ovariectomy animals were injected with 0.1µg 17β estradiol in 0.1 ml sesame oil subcutaneously for three days continuously, were followed by two days of no treatment. Animals were then given daily subcutaneous injection of 6.7ηg 17β estradiol and 1mg progesterone in 0.1 ml sesame oil. Six hr. after the 3rd estradiol progesterone injection uterine horn were dissected out and immediately frozen for cyclic nucleotide determination. Individual horns were homogenized in 1ml of cold 1% Perchloric acid with a polytron PCU-2 at a setting of a 5 for 10 seconds. Tracer amounts of 19C- cAMP and 3H- cGMP were induced in the homogenization for the determination of cyclic nucleotide recoveries. The specificity of the cyclic nucleotide assay, showed that, the cAMP level in the stimulated form had increased about ten-fold. The cAMP level in the unstimulated horn did not change. They also measured cyclic GMP levels in the same uterine horns. They also measured cyclic GMP levels in the same uterine horns. They found that, the estrogen phase of the priming schedule had no effect on uterine cGMP level; however, progesterone treatment resulted in a six fold increase in uterine cGMP content.

Auto radiographic analysis of DNA synthesis of responsive cellafter stimulating decidual cell reaction artificially showed that, rapid cell proliferation begins approximately 30 hr. after stimulation and by 144 hr. is localized in discrete masses (Bernard *et al*., 1978). They used

sesame oil to stimulate the decidual cell reaction and aim of the study was to identify the population of cells initially affected by the stimulation. 3-H thymidine was given to the animal as an i.p. injection and uterine horns were dissected out and homogenized for DNA determination, uterine DNA increases sharply 13 hr. after stimulation. Auto radiographic analysis was used to identify uterine responsive cells.

The immunological studies of mouse decidual cells especially membrane markers of decidual cells in the days after implantation showed immunoglobulin containing cells are present in mouse deciduas (Raft *et al*., 1969) .This study attempt to define immunologically the cells of mouse deciduas in the dates after implantation. This study showed that, in addition to H-2 antigen, Thy-1 antigen can be detected on a sizable fraction of decidual cells and that an apparently increasing member of cells bearing receptors for the Fc region of immunoglobulin G can be detected in the deciduas as pregnancy proceeds from day 6 to day 8. Thy-1 antigen was previously described on mouse thymocytes (Raft *et al*., 1969), peripheral T lymphocytes (Mirsky *et al*., 1975), brain cells (Scheid *et al*., 1972) , epidermis (Galassi *et al*., 1968). The expression of Thy-1 antigen on about 50% of mouse decidual cells as detected in this study reflects their fibroblastic origin; development of decidual cells from uterine stromal cells was suggested from morphological as well as autoradiographic observations (Anne *et al*., 1984).

A Review of life history of decidual cell reaction on different aspects like – Origin of decidual cell, cytochemical markers of decidual cell reaction, decidual cell surface markers (Zhang *et al*., 1996). For studying the origin of decidual cell they employed radio autographic approach to examine proliferation & differentiation of various cell types in uterus. They used 3-H thymidine in day 4 & 5 pregnant rat. Rats were then sacrificed on day 7 and 9 of pregnancy after the single 3HTdR pulse, the same cells appeared to have transformed into decidual cells. Periodic Acid Schiff (PAS) is a reactive material appears within the uterine lumen as well as within the endometrial stroma in both pregnancy & pseudo pregnancy used as a cytochemical marker. The quantities of these substances are much higher in the artificially induced reaction. A number of alkaline phosphatases have been localized on decidual cell as well as their stromal precursor. In this study decidual cell surface markers were also analyzed. In the decidual tissue of pregnant & pseudo pregnant mice indicates that Thy-1 antigen and Fc receptors are detectable at 72 and 96 hr post stimulation in pseudo pregnancy at 6 to 7 days of gestation or pregnancy.

2.1 Hormones involved in decidual cell reaction

The possibility of estrogen that affects uterine sensitization by altering the ability of E-series prostaglandins (PGs) to increase Adenosine 3′:5′ cyclic-Monophosphate (cAMP) concentration (Yoshida *et al*., 2009). To induce ovulation the rats were injected 5 IU pregnant mare's serum gonadotropin (PMSG; Equinex, Ayerst labs, Montreal). At approximately 1700 hr. on the afternoon of the day before the expected ovulation, they give an IP injection of 7.5 IU human chorionic gonadotropin. To increase endometrial intracellular cAMP concentration they injected cholera toxin, an activator of adenylate cyclase (Tessier *et al*., 2000), 8- Br-cAMP analogue of cAMP and 3 iso butyl-1-methyl xanthine, a phosphodiester inhibitor in to the uterine lumen of immature rats pretreated with progesterone and either 0, 0.5 or 10µg estrogen with indomethacin to inhibit endogenous PGs synthesis. Endometrial vascular permeability, determined using 125I- labeled bovine serum albumin. But they found that, in terms of the hypothesis that estrogen alters uterine sensitization for the decidual cell reaction by effects on the members of adenylate cyclase-linked PGE receptors, their result was inconclusive. They found rats pretreated with different levels of estrogen along with progesterone responded to intrauterine cholera toxin will increase endometrial vascular permeability, but the degree of sensitivity was greatest in animals pretreated with low dose of estrone (0.5µg/day) and found least in those receiving the high dose (10µg/day). Permeability increase was obtained in all groups in response to intrauterine cholera toxin but not PGE2. The results are consistent with the suggestion that, in the non sensitized endometrium particularly of animals receiving high doses of estrogen, the interaction of PGE binding site with the adenylate cyclase complex is deficient. However the effects of estrogen on the dose response relationships between endometrial vascular permeability and cholera toxin imply that estrogen must also have an effect on adenylate cyclase or some subsequent step in the pathway leading to increased endometrial vascular permeability (Tessier *et al*., 2000).

In mouse decidual cell reaction is maintained by hormone androgen with a regimen of estrogen and progesterone (Reese *et al*., 2000). For this study they use adult CD1 mice which were ovariectomized and treated with a regimen of estradiol and progesterone to prime the uterus for DCR and to maintain DCR. Ovariectomized mice received injection of 100 ηg estradiol on day 0, and 1mg progesterone plus 10ηg estradiol (Pe) or 1mg testosterone plus 10ηg estradiol (Te) during days 3-5 to prime uterus for DCR. On day 5, 20µl oil was injected into the lumen of one uterine horn to induce DCR. In days 6-8, treatment with Pe, Te, or 10ηg estradiol (e) alone was given to maintain DCR. After that they found that animals that received 1mg testosterone, instead of progesterone during 3-5, DCR was absent. But, after

priming with standard regimen, daily treatment with 1mg testosterone or progesterone during 6-8 produced similar deciduomal weight in the two treatment groups. In contrast, DCR was significantly diminished in those that received estradiol alone during the maintenance period. But the physiological significance of this androgen action in DCR is not clear.

The hormone relaxin plays important role on decidual cell reaction in the Mongolian gerbil (*Merionesunguiculatus*) by increasing protein content and IL-II expression (Peng et al., 2000). In this study ovariectomized gerbils were treated with estradiol, progesterone and relaxin and uterine horn was stimulated. After day 10 uterine horns were measured for weight, protein concentration and the incorporation of 14C-methionine. They used interlukin -II (IL-II) primers for RT-PCR to confirm decidualization. They have found that the uterine horn weight, protein content, and protein synthesis from 14C-methionine significantly increased in the relaxin treated group, which was confirmed by IL-11 expression.

2.2 Ligand- Receptors involved in decidual cell reaction:

Cell specific expression of estrogen receptor α and β are regulated by steroid hormones and prolactin in rat (Dong et al., 1996). In this study they carried out experiment whether the rat decidua expresses both isoforms of the estrogen receptor (ER) α, and β. In this investigation, they analyze the expression of decidual ERα and ERβ , and their regulation by PRL and steroid hormones and examined the ability of decidual ERβ to transducer the estradiol signal to the progesterone receptor. They used immunocytochemistry, RT-PCR, and Northern blot analysis showed that both ER species are co expressed in the decidua during pseudo pregnancy. But these genes were preferentially found in a cell population localized in the antimesometrial site of the uterus where blastocyst implantation takes place.

Defects in implantation and decidualization in Prolactin Receptor (PRLR)-deficient mice which are mediated by ovarian but not uterine PRLR (Jorgez *et al*., 2004). If prolactin receptor (PRLR) is not there i.e., PRLR-/- artificially induced decidualization was absent in pseudo pregnant mice, but was identical to wild type in P4 treated PRLR-/- mice. Furthermore wild type and P4 treated PRLR-/- mice had similar expression of the implantation specific genes, LIF, amphiregulin, HB-EGF, COX-1, COX-2, PPAR delta, HOXA-10, cyclin D3, VEGF and its receptor FLK-1 and neuropilin-1. Together these results showed that luteal P4 production via ovarian PRLR signaling is required for implantation and early pregnancy. The function of uterine PRLR remain unclear. However, the eventual loss of

pregnancy in P4 treated PRLR-/- mice suggests that uterine PRLR may be essential for the support of late gestation.

Activin receptor-like kinase 5 (ALK5) is the major type 1 receptor for the TGF-β subfamily. Uterine activin receptor-like kinase 5 is crucial for blastocyst implantation and placental development. Transforming growth factor β (TGF-β) superfamily are key regulators in most developmental and physiological processes. Absence of ALK5 leads to early embryonic lethality because of severe defects in vascular development (Clementi *et al*., 2013). In this experiment, they have showed the physiological roles of ALK5 in female reproduction by doing conditional ablation of uterine ALK5 using progesterone receptor-cre mice. Absence of uterine ALK5 resulted in substantially reduced female reproduction due to abnormalities observed at different stages of pregnancy, including implantation defects, disorganization of trophoblast cells and fewer uterine natural killer (uNK) cells. In mammals, members of the TGF-β superfamily are potent regulators of cell proliferation and differentiation in most developmental and physiological processes. Recent studies have defined the key roles of TGF-β signaling in multiple female reproductive events including ovarian folliculogenesis and ovulation (Nagashima *et al*., 2013) (Das *et al*., 1994), embryo implantation (Paria *et al*., 1997). uterine decidualization (Lee *et al*., 2007) , and placentation (Raab *et al*., 1996).

2.3 Growth factors involved in decidual cell reaction

Heparin-binding epidermal growth factor–like growth factor (HB-EGF) stands out to be an important molecular link in mediating embryo-uterine interactions with impending attachment reaction in mice. It is expressed in the luminal epithelium surrounding each blastocyst several hours before the attachment reaction (Hamatani *et al*., 2004). HB-EGF is produced in soluble and transmembrane forms and both forms influence blastocyst function in a paracrine and juxtacrine manner via the EGF family of receptors which expressed on the blastocyst cell surface (Paria *et al*., 2001) (Iwamoto *et al*., 2003). Implantation-competent blastocysts also express HB-EGF, which can induce its own gene (Hegf1) in the uterus in a paracrine manner (Meseguer *et al*., 2001) (Simmons *et al*., 2002). This auto-induction loop is the first known molecular link between the blastocyst and uterus that leads to attachment reaction. Although systemic deletion of Hegf1 causes prenatal lethality(Rahman *et al*., 2006).

2.4 Genes involved in decidual cell reaction

Expression of human endometrial MUC1 in endometrial epithelium has been suggested to create a barrier to embryo attachment that must be lifted at the time of implantation. MUC-1 is up regulated by progesterone and down regulated in vitro by the human blastocyst (Xia *et al*., 2008). This study investigated the hormonal regulation of human endometrial MUC1 in hormone replacement therapy. They found that, endometrial MUC1 mRNA and immune reactive protein increase in receptive endometrium compared to non receptive endometrium. Human blastocyst express MUC1, demonstrated by reverse transcriptase polymerase chain reaction & immune histochemistry. MUC1 is present at the surface of primary culture of human Endometrial Epithelial Cell (EEC). They observed that presence of human blastocyst increases EEC MUC1 protein and mRNA compared to EEC lacking embryo. When they allowed human blastocyst to attach to the EEC monolayer, MUC1 was locally removed on EEC at the site of implantation. Progesterone combined with estradiol priming induces on up regulation of MUC1 at the receptive endometrium. In the adhesion phase, the embryo induces the paracrine cleavage of EEC MUC1 at the implantation site. These findings suggest that MUC1 may act as an endometrial anti adhesive molecule that must be removed locally by the human blastocyst during the adhesion phase.

A novel gene, Uterine Sensitization Associated Gene-1 (UASG-1) within the rat endometrium at the time of uterine receptivity in maximally sensitizatised endometrium is expressed for the decidual cell reaction (Sun *et al*., 2012). In their experiment they identify genes involved in the onset of the receptivity using the technique of suppressive subtraction hybridization. They observed this experiment in ovariectomized, steroid treated and virgin rats. For uterine sensitization and decidual cell reaction, animals were administered estradiol (E2) and progesterone (p4) subcutaneously in sesame oil. Uteri were collected on days 4, 5 and 6 of pregnancy. Day 6 pregnant animals were given an IP injection of 0.5% Evans Blue 15 minute prior to narcotized to visualize the implantation sites. Results showed that, Uterine Sensitization Associated Gene-1 (UASG-1), that is preferentially expressed within the maximally sensitized/ receptive rat endometrium UASG-1 mRNA encodes a putative protein of 206 amino acid that contains a possible N- terminal secretion signal and a c- terminal cysteine knot like motif. Northern blot analysis revealed that induction of USAG-1 mRNA was restricted to the day 5 pregnant or pseudo pregnant uterus.

Hoxa-10 deficiency alters region specific gene expression and perturbs differentiation of natural killer cell during decidualization. The results showed that, Hoxa-10 is a

developmentally regulated Homeobox transcription factor, is highly expressed in decidualizing stromal cells and targeted deletion of Hoxa-10 in mice showed severe decidualization defects (Liu *et al*., 2011). After targeted deletion they observe reduced stromal cell responsiveness to progesterone. Hoxa-10 deficiency results in the aberrant region- specific expression of cdk4, cdk6, growth differentiation factor 10 (Gdf 10), hepatocyte growth factor (hgf) and snail 2. They also showed that, Hoxa-10 deficiency compromises natural killer (NK) cell differentiation without altering trafficking of NK precursor cells during decidualization.

Implantation Associated Gene-1 (Iag-1) is a novel gene which involved in the early process of embryonic implantation in rat (Ema *et al*., 2008). Iag-1 was initially derived from suppressive substracted hybridization of cDNA library of rat uterus, which was used to analyze differentially expressed genes between the peri-implantation periods. In this study the expression of Iag-1 in the uterus of early pregnancy, pseudo pregnancy, artificial decidualization and activation of delayed implantation was detected by Northern blotting, in situ hybridization, Western blotting &immunofluorescene. Endometrial stromal cells (ESCs) were isolated from rat uterus. Then they find out the effect of Iag-1 on ESCs proliferation and apoptosis were determined by MTT assay, TUNEL and Hoechst staining. They found differential pattern of Iag-1 expression were detected in rat embryo and in the uterus during peri-implantation period. Iag-1 was specifically localized in glandular epithelium and luminal epithelium. But over expression of Iag-1 can inhibit ESCs proliferation and induce ESCs apoptosis and P53 and BAX may play role in the process of Iag-1 induced apoptosis.

Another gene necessary for implantation is that encoding Kruppel- like factor 5 (Klf5), a zinc finger–containing transcription factor. Uterine Klf5 is also unresponsive to alteration by ovarian hormones (Wang *et al*., 1990), although it is influenced by estrogen and P4 in human breast cancer cells (Wodarz *et al*., 1998). In mouse uteri, Klf5 is present in luminal and glandular epithelia until decidualization is initiated on day 5. At this time, Klf5 is expressed in proliferating stromal cells around the implantation chamber with down regulation in the epithelium. With differentiation, decidual cell expression decreases, suggesting Klf5's participation in cell-specific proliferation and differentiation during pregnancy. Systemic deletion of Klf5 confers embryonic arrest at the blastocyst stage (Soyal et al., 2005). In contrast, mice with uterine deletion of Klf5 (Klf5d/d) are essentially infertile as a result of defective implantation (Wang *et al*., 1990).

2.5 Proteins involved in decidual cell reaction

Bone Morphogenic Protein (BMP2) is critical for the murine uterine decidual response [6]. Bone morphogenetic proteins (Bmps) was identified as a soluble factor capable of inducing ectopic cartilage and bone formation in vivo when implanted into muscular tissues (Daikoku *et al*., 2004) (Heng *et al*., 2010). They investigated the role of BMP2 by doing conditional ablation of Bmp2 in the uterus using the (PR-cre) mouse. Bmp2 gene ablation was confirmed by real-time PCR analysis in the PR-cre; Bmp2fl/fl (termed Bmp2d/d) uterus (He *et al*., 2015) (Roby *et al*., 1993). Bmp2d/d females are completely infertile. Analysis of the infertility indicates that whereas embryo attachment is normal in the Bmp2d/d as in control mice, the uterine stroma is incapable of undergoing the decidual reaction to support further embryonic development. Recombinant human BMP2 can partially rescue the decidual response, suggesting that the observed phenotypes are not due to a developmental consequence of Bmp2 ablation. Microarray analysis demonstrates that ablation of Bmp2 leads to specific gene changes, including disruption of the Wnt signaling pathway (Roby et al., 1993). Progesterone receptor (PR) signaling, and the induction of prostaglandin synthase 2 (Ptgs2). These data demonstrate that Bmp2 is a critical regulator of gene expression and function in the murine uterus.

Post translational activation of bone morphogenic protein 2 (BMP2) is mediated by proprotein convertage 6 (PC6) which cleaved BMP2. Delation or knockdown of either BMP2 or PC6 inhibits decidualization causing implantation failure and female infertility (Alam *et al*., 2017). It was demonstrated that PC6 was the sole member of PC family significantly up regulated during decidualization. Inhibition of PC6 actively inhibits decidualization, which was accompanied by total blockade of BMP2 activation. PC6 processed BMP2 at the KREKB (282) downward arrow cleavage site and mutating this site which prevented the cleavage.

A protein Rbbp7 Which is required for uterine stromal decidualization in mice. Retinoblastoma binding protein 7 (Rbbp7) is a protein which is reported as a core component of many histone modification and chromatin remodeling complexes (Dommia *et al*., 2013). For this experiment, they have done in situ hybridization and immune staining, stealth RNA transfection, western blotting, RNA extraction and real time PCR, and cell proliferation assay which revealed a spatiotemporal expression of Rbbp7 in the uterus during the peri implantation period. Induction of Rbbp7 in the uterine stromal cells in response to

progesterone nuclear receptor PR signaling pointed toward to its potential physiological significance during post implantation uterine development. They employed stealth RNA knockdown approach combined with primary murine uterine stromal cell culture and in vitro induce decidualization model. stromal decidualization can be induced in culture in response to cotreatment of estrogen and progesterone, as verified by increased mRNA expression of Prl8a2 (prolactin family 8, subfamily a, member 2, previously known as Dtprp), a well-known marker of decidual cells (Cho *et al*., 2003). They further demonstrated that, silencing Rbbp7 compromises stromal cell decidualization via attenuating histone H4 acetylation and cyclin D3 expression. These results collectively suggested that, Rbbp7 is a potential functional player regulating normal histone acetylation, modification and cyclin D3 expression in stromal cells during postimplantation decidual development.

Transplantation of endometrial mesenchymal stem cell (eMSC) stimulates development of deciduas (He *et al*., 2015). The aim of this work was to assay the effect of endometrial mesenchymal stem cell (eMSC) transplantation for decidualization process in pseudo pregnant rat. Mesenchymal stem cells (MSC) have been established from endometrium and menstrual blood (Roby *et al*., 1993). In this study they used adult albino rat which were divided into two groups. In the first group 5×10 eMSC^{5}single cell suspension in 20µl PBS and of 20µl PBS without cells were injected into the experimental uterine horn and contra lateral control horn respectively. In second group 20×10^{6}rBMC single cell suspension in 20 µl PBS and of 20 µl PBS with- out cells were injected into the experimental uterine horn and contralateral control horn, respectively.The artificial decidual response has been induced by electrical stimulation of the cervix during oestrus. They found that injection of human eMSC suspension into the uterine lumen of pseudo pregnant rats facilitated more intensive development of decidua in comparison with phosphate buffer saline (PBS) injection in the control uterine horn. The fact that transplanted human eMSC are xenogenic, they used rat bone marrow cells (rBMC) in the same model and they found that, the weight of decidual tissue in experimental horns three times exceeds the weight of tissue in control in both groups of animals. Their findings imply that, both eMSC and rBMC translation stimulate decidualization in animals.

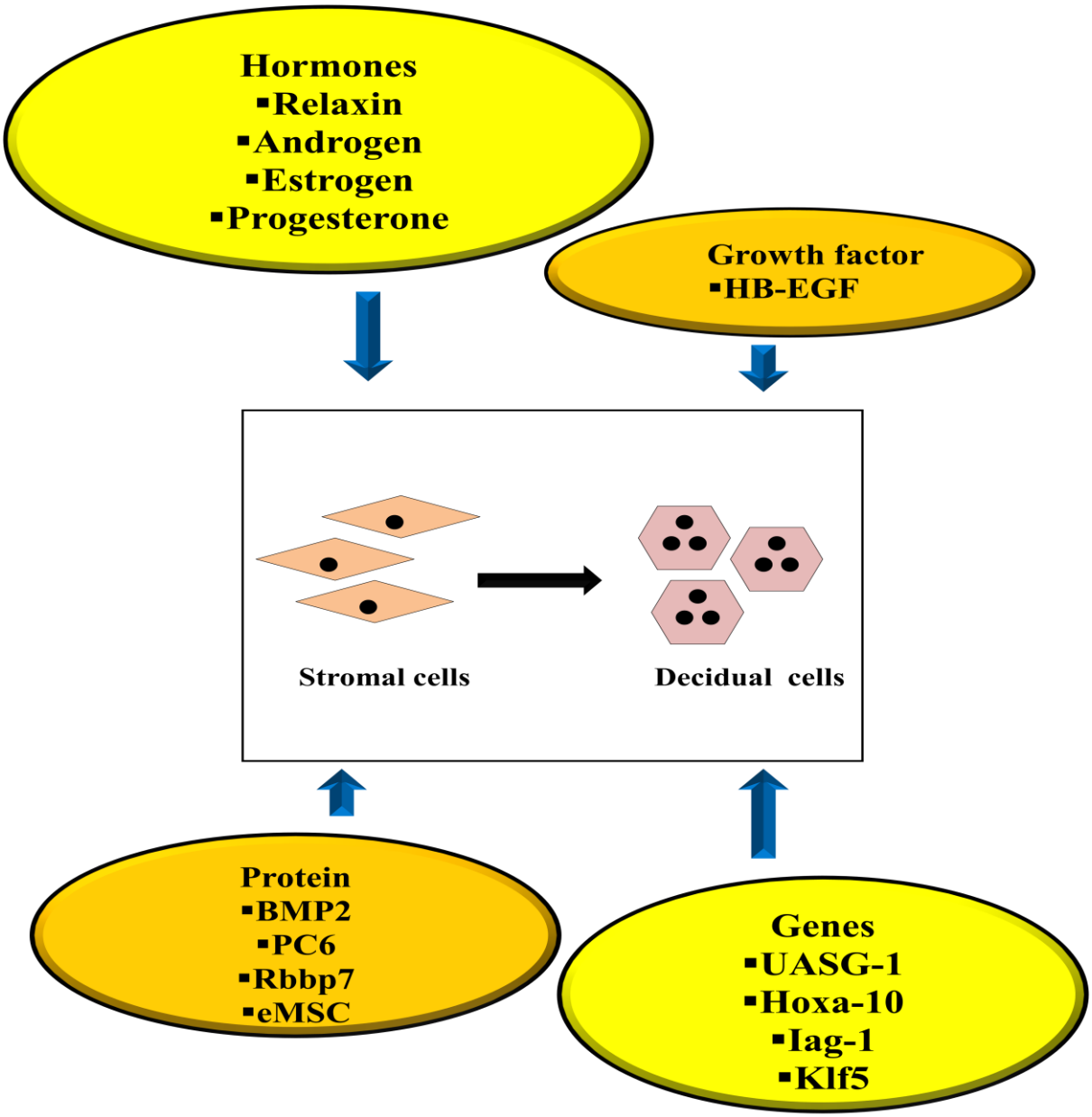

Figure: Regulatory factors involved in Decidualization

Conclusion

Decidual cell reaction (DCR) has a key role during implantation. The decidual reaction involves a rapid increase in the permeability of local capillaries, causing the uterine stroma to become swollen. These stromal cells become larger and formed decidual cell. A number of different factors have been identified which play vital role in the process of decidualization. Works on decidual cell reaction have been started since 20th century but some data of DCR is still remain as paradox. Works have been done on hormone titer, receptors, proteins, growth factors, expression of genes involved in DCR while, recent findings on periimplantation

factors, gene silencing, and implantation failure have exposes a new working field on DCR. This field has facilitated vast improvement in our quality of life and may help in drug designing for reproduction regulation. The significance or aim of this study is to provide some new data of this field of molecular reproduction especially the events of embryonic growth and development in mammal. This comprehensive review emphasizes the complexity of the Decidual Cell Reaction (DCR) and explains the necessity for further research to advance our comprehension of implantation and pregnancy processes.

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Authors' Contribution

This work was carried out in collaboration among all authors. All the authors contributed to the design of the study. Authors Archana Saikia wrote the first draft of the manuscript. Authors Shatabdi Biswas and Dipsikha Mohan analyzed the data and authors Jyotismita Das and Archana Saikia contributed to the management and execution of the study and supervised the whole work. The collective efforts of the all the authors have significantly enriched the quality and depth of this paper. All authors read and approved the final manuscript..

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