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Molecular Mechanisms of Embryo Implantation: The Critical Role of Leukemia Inhibitory Factor and Its Signaling Pathways

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Abstract

The implantation process in mammalian reproduction involves complex interactions between the developing embryo and the maternal endometrium. Leukemia Inhibitory Factor (LIF) has emerged as a crucial regulator in this intricate interplay. This review explores the multifaceted roles of LIF genes in implantation processes, revealing insights into its significance in successful pregnancy outcomes. Key findings highlight the impact of LIF gene polymorphism, gene expression patterns, and LIF receptor complexes on the efficiency of embryo implantation. The genetic variant LIF SNP T/G (rs929271) is being recognized as a promising biomarker that could forecast the success of implantation and the outcome of pregnancy, opening avenues for potential therapeutic interventions. Variations in LIF concentrations during menstrual cycle stages highlight its crucial role in implantation, particularly between fertile and infertile women. This study underscores the significance of LIF in fertility mechanisms.

Keywords: Embryo-endometrial interaction, Implantation, Leukemia Inhibitory Factor (LIF), LIF gene polymorphism, Pregnancy outcomes

Introduction

Implantation is a finely orchestrated interplay involving a receptive uterus and a competent blastocyst [1]. It involves the embryo attaching to the uterine endometrial surface, infiltrating the epithelium, and integrating into the maternal circulation to form the placenta [2]. The combined impact of ovarian hormones E2 and P4 on the uterus supports embryo implantation, while the pro-inflammatory cytokine, leukemia inhibitory factor (LIF), is instrumental in preparing the uterus for this process [3]. It appears that the main function of early E2 is to stimulate the production of LIF. Cheng and colleagues showed that a solitary application of LIF effectively triggered normal implantation and aided subsequent developmental stages, even without early E2 presence [4].

Leukemia inhibitory factor (LIF), categorized as a pro-inflammatory cytokine within the interleukin-6 (IL-6) family, has been consistently associated with various studies [5, 6, 7]. Oliveira et al., noted that the TP53 gene significantly regulates blastocyst implantation by impacting genes within its pathway, among them LIF [8]. Specific members of the HOXA and HOXB genes are thought to play a role in causing leukemia, as shown by their ability to trigger leukemia in murine HSCs

(Hematopoietic Stem Cell) [9]. Wu et al., discovered that inflammatory stress can lead to heightened mRNA levels of LIF expression in uterine tissues at the stage of embryonic implantation [10].

LIF carries out its biological functions by specifically interacting with its receptor, LIFR [11]. The presence of LIFR has been confirmed across various pre-embryonic stages, from the 2-cell phase to the expanded blastocyst [12]. When LIF connects with LIFR, it sets off a receptor complex that includes glycoprotein 130 (gp130). This complex then activates multiple signaling pathways, such as Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3), mitogen-activated protein kinase (MAPK), and phosphatidylinositol-3 kinase (PI3K) [13]. STAT3, identified as a transcription factor, plays a crucial role as a mediator in LIF signaling pathways, serving as a pivotal component in this cascade [14].

Incidence and Prevalence

The recent study by Hassab et al., showcased a notably higher implantation success rate of 32.43% among Iraqi women undergoing IVF, contrasting starkly with a 67.57% failure rate. Examining 74 women dealing with infertility, aged 19 to 45, the research highlighted significant factors affecting success. Abnormal ovulation cases notably increased to 51.35%, surpassing unexplained infertility at 27.03%. Uterine factors were identified in 14.86% of cases, with endometriosis and tubal issues at 4.05% and 2.70%, respectively. The study conducted across various Iraqi IVF centres between December 2019 and November 2020, underlines the prevalence of factors influencing IVF implantation outcomes among this population [15].

Research conducted at a hospital in Rome, Italy, involved the transfer of mosaic embryos to patients and the findings were published. The study revealed that 25% (8 cases) of implanted mosaic embryos resulted in a biochemical pregnancy, while the remaining led to the birth of healthy babies. This percentage closely mirrored the initial rate of mosaic embryos transferred, which was 33.3% [16]. In another study by Fragouli et al., 12% of transferred mosaic embryos ended in miscarriage, and 26% resulted in ongoing pregnancies, although information regarding deliveries and infant follow-ups was unavailable [17]. Both studies demonstrated similar implantation rates, ranging between 38% and 45% [16, 17].

In the study led by Lee et al., the occurrence rates of successful implantation varied significantly based on whether embryos had undergone Preimplantation Genetic Screening (PGS) and the cycle type used for transfer. The implantation rate for chromosomally normal embryos transferred in Frozen Embryo Transfer (FET) cycles stood notably higher at 50.9% compared to unscreened embryos, whether in fresh (23.8%) or FET (25.4%) cycles. The frequency of live births per transferred embryo was significantly greater in PGS-FET cycles (45.5%) than in cycles without PGS, whether fresh (15.8%) or FET (19.0%). The incidences of live birth per implanted sac were comparable across PGS-FET cycles (89.3%), fresh cycles without PGS (66.7%), and FET cycles without PGS (75.0%), showing no significant differences. This study's findings highlight the advantages of employing PGS in enhancing both implantation rates and live birth rates per transferred embryo [18].

Materials and Methods

The research heavily relied on an extensive exploration of scholarly literature through reputable databases like PubMed, Google Scholar, and Sci-hub. Through a rigorous selection process, 90 key articles on the Leukemia Inhibitory Factor gene's role in implantation were carefully chosen from 64,700, ensuring they met high standards of quality, relevance, and research alignment. The use of specific keywords like "Leukemia Inhibitory Factor gene" and "Implantation" ensured that the retrieved articles were precisely relevant to the topic at hand. The methodology upheld stringent criteria, including peer-reviewed publication, alignment with research objectives, and relevance to human adult subjects. The systematic data retrieval strategy methodically arranged important discoveries, including statistical information, experimental findings, and clinical outcomes.

Implantation

Psychoyos, defines that implantation as the phase when the embryo affixes to the uterine lining, infiltrating the epithelium, and subsequently establishes connections with the maternal circulation, leading to placental formation [2]. The restructuring of the uterus for successful implantation relies on hormonal orchestration primarily by estrogen and progesterone, as highlighted by Krege et al., [19]. Progesterone plays a

pivotal role in preparing the uterus for optimal embryo development, a point underscored by Greening et al., [20]. This hormone triggers the creation of pinopodes, altering epithelial cells by reducing cell adhesion and prompting the development of smooth protrusions on the cell surface, as described by Martel et al., and Thie et al., [21, 22]. Notably, studies like those by Simón et al., highlighted that reducing estrogen levels during the preimplantation phase in In Vitro Fertilization and Embryo Transfer (IVF-ET) patients can bolster uterine receptivity [23].

Implantation encompasses three crucial stages: apposition, adhesion, and invasion, as described by Bischof & Campana [24].

(A) Apposition and Adhesion: Implantation initiation occurs with the blastocyst's apposition to the uterine epithelium, typically occurring 2-4 days post-morula entry into the uterine cavity [25]. Van der Weiden et al., and Lim et al., emphasized that implantation is characterized by an inflammatory process, influenced by prostaglandins derived from Cyclooxygenase (Cox), which elevate the permeability of the endometrial blood vessels [26, 27]. The increase of Prostaglandin E2 in both mouse and human implantation sites indicates its involvement in attachment and the localized increase in blood vessel permeability within the endometrium. This particular prostaglandin plays a pivotal role in regulating human trophoblast invasion by activating essential signaling proteins [28].

In the apposition phase, the blastocyst undergoes differentiation into the embryo and placental trophectoderm. Simultaneously, adjacent stromal cells undergo decidualization, transitioning into specialized decidual cells. The link between the blastocyst's outer layer and the endometrial surface relies on various molecules like integrins, cadherins, selectins, and immunoglobulins [29]. This connection is highlighted by Fukuda & Sugihara and McEwan et al., with Lyall observing these molecules on the invasive trophoblasts surfaces. These molecules engage in specific time and location-based interactions with substances expressed by the lining of the uterus [30, 31, 32]. Specifically, Lessey et al., link integrins as specific markers of the menstrual cycle, showing increased levels during the mid-luteal phase, which marks the period suitable for embryo implantation [33].

(B) Invasion: Burrows and colleagues explained that during the initial phase of invasion, cells from the developing fetus move into the lining of the mother's uterus. As part of the implantation process, these cells organize into groups of different types, namely cytotrophoblasts and syncytiotrophoblasts. These specialized cells then alter

the structure of the mother's spiral arteries, changing them from muscular tubes into wider, more flexible sacs covered with fetal cells inside the blood vessels [34]. Hunkapiller et al., highlighted that this invasion serves to transform the mother's spiral arteries, making it easier for blood to flow between the mother and the growing fetus. Essentially, this process replaces smaller, more restrictive blood vessels with larger, less restrictive ones to enhance the exchange of blood and nutrients [35].

Leukemia Inhibitory Factor

LIF is first synthesized as a 202-amino acid precursor, then modified post-translation to a 20 kDa form by removing 22 N-terminal amino acids. Its structure has been determined using X-ray crystallography and NMR [36, 37]. It takes on a compact structure with four helices arranged in an up-up-down-down configuration. The portion identified as Helix A, commencing from Leu44 (equivalent to residue 22 in the mature chain), connects with the N-terminal segment. The area preceding Helix A holds considerable importance because it forms crucial chemical bonds (Cys34-Cys156 and Cys40-Cys153) connecting it to the C-terminal part of Helix 3. Particularly, this N-terminal portion is noteworthy for its involvement in interacting with receptors [38]. Laird et al., found notably lower LIF release in uterine flushings and tissue samples from infertile women during specific phases of the menstrual cycle. Moreover, reported sporadic changes in the LIF gene among women experiencing infertility [39, 40]. Charnock-Jones et al., observed increased levels of LIF in the glands of the uterine lining before the implantation of the embryo, in both mice and humans [41]. This increase could potentially be affected by higher estrogen levels present throughout the menstrual cycle. The widespread distribution of LIF receptors and its diverse activities across various organ systems, particularly in the endocrine and reproductive systems, are highlighted [42]. Nicola and Babon pointed out that while LIF induces similar signaling pathways, such as the JAK1/STAT3, PI3K/Akt, and MAPK pathways, variations in signaling outcomes might result from differing levels of activation within these pathways [43].

Downstream LIF signaling pathways

As per Boulton et al., LIF primarily targets JAK1 kinase, activating the JAK/STAT, MAPK, and PI3K pathways. Among these pathways, STAT3 is considered the main mediator of cellular effects triggered by LIF/LIFR [44]. A crucial downstream target

of STAT3 is SOCS3, identified by Nicola and Babon for its role in providing negative feedback to control the JAK/STAT and MAPK signaling pathways [43]. Nicholson et al. report that SOCS1 can inhibit LIF signaling by blocking the JAK/STAT pathway [45]. Despite the prevailing belief that tyrosine kinase pathways dominate LIF actions, Davis et al., emphasized the significance of alternative pathways associated with LIF and their consequential effects [46].

Table 1: Influence of Modifying LIF Pathway Members in Living Organisms and ESCs

Protein/Gene	**Overexpression in vivo**	**Overexpression in ESCs**	**References**
LIF	LIF is deadly and prevents the development of specialized tissue, disrupting normal embryo formation and gastrulation.	Under typical culture conditions, it's impossible to derive LIF-deficient ESCs.	[47, 48, 49]
gp 130	gp130-deficient embryos survive diapause but fail to maintain the epiblast compartment. However, they succumb to developmental issues and die between E12.5 and E16.	Under regular culture conditions, it's impossible to derive gp130-deficient ESCs. Slight increases in gp130 levels boost self-renewal without external LIF, but higher receptor expression promotes differentiation**.**	[50, 51, 49, 52]

STAT3	Stat3 null embryos initially form and grow the epiblast normally, but their gastrulation process gets disrupted.	Stat3 null ESCs are only obtainable under specific 2i conditions. Overexpressing STAT3 alone is enough to sustain ESCs' pluripotency even without LIF.	[53, 54, 55]
JAK1	JAK1 plays a crucial role in trophoblast differentiation. Jak-deficients will die within the initial 24 hours after birth.	In ESCs, JAK1 is vital for LIF signaling.	[56, 57, 58, 59]
JAK2	Jak2-deficient embryos experience anemia and perish around day 12.5 postcoitum.	Jak2-deficient ESCs respond appropriately to LIF signaling. JAK2 is involved in early lineage determination.	[60, 58]

(A) JAK-STAT Signaling

The JAK-STAT signaling pathway, which relies on the IL-6 cytokine family, involves two receptor types: non-signaling α-receptors and signaling receptors. According to Gearing and colleagues, LIF first binds to its signaling receptor, LIF-R, and then recruits glycoprotein 130 (GP130) to form a complex that facilitates downstream signal transmission [61]. On the other hand, other cytokines in the IL-6 family first attach to specific low-affinity non-signaling receptor parts (like IL-6R, IL-11R, CT-1R, and CNTFR-1). Afterward, they trigger either the formation of GP130 receptor pairs or the coupling of LIF-R and GP130, as explained by Hibi et al., [62]. Protein inhibitor of activated STAT3 (PIAS3) independently oversees the suppression of STAT3, establishing a swift and effective feedback system that manages JAK-STAT signaling, as demonstrated by Chung et al., [63]. The absence of STAT3 leads to severe outcomes, resulting in embryos perishing shortly after implantation [64]. While JAK-STAT signaling isn't necessary for initiating pluripotency after fertilization, it

holds a crucial role in maintaining it. Additionally, GP130 signaling helps maintain pluripotency in the early embryo's epiblast during difficult reproductive conditions termed diapause [65]. Levy and Lee observed extensive instances of JAK-STAT signaling in the later stages of embryo development following implantation [66].

(B) MAPK signaling

Among the numerous intracellular signaling pathways, the MAPK (Mitogen-activated protein kinase) pathway is particularly noteworthy for its involvement in cell proliferation, differentiation, apoptosis, angiogenesis, and tumor metastasis. Eukaryotic cells exhibit four well-known MAPK cascades: the ERK, JNK/stress-activated protein kinase, p38 MAPK, and ERK5 signal transduction pathways. Each cascade comprises at least three tiers: MAP3K, MAPKK, and MAPK [67, 68]. The MAPK pathway plays a crucial role in various aspects of implantation. It stimulates granulosa cell proliferation, cumulus expansion, and, in conjunction with the ERbB pathway, facilitates the resumption of meiosis in the oocyte [69,70]. In humans, a significant portion of extracellular vesicle miRNAs is anticipated to influence targets that govern the WNT, ErbB, MAPK, and TGFβ signaling pathways. These pathways operate throughout various sections within the ovarian follicle and play roles in follicular development, the resumption of meiosis, and the process of ovulation. This insight, shared by Sohel and colleagues in their study, highlighted the potential impact of these miRNAs on crucial mechanisms governing ovarian functions. This pathway's involvement in implantation underscores its significance in orchestrating key processes necessary for successful embryo implantation [71].

(C) P13K Signaling

The PI3K-PKB signaling pathway's key downstream element is mTOR, as highlighted by Rohde et al., [72]. This mTOR pathway is pivotal in embryo implantation with Martin et al., emphasizing its significance [73]. Gangloff et al., observed that mTOR deficiency led to embryonic demise shortly after implantation [74]. Martin et al., also stressed the critical role of the PI3K/PKB/mTOR pathway in amino acid signaling and its importance in embryo implantation [73]. Riley et al., noted that inhibiting the PI3K/PKB pathway affected blastocyst physiology and hatching [75]. Wortmannin, identified as a PI3K inhibitor, hinders the

phosphorylation and activation of PKB, as discussed by Riley et al., and this inhibition resulted in fetal resorptions and unfavorable pregnancy outcomes [76].

Vanhaesebroeck et al., identified three distinct classes of PI3Ks, namely class I, class II, and class III, each exhibiting specific substrates and unique effectors beyond Akt [77]. Class I PI3Ks, crucial in cancer development, modulate downstream effectors shared among serine/threonine kinases from the AGC kinase family, tyrosine kinases seen in hepatocellular carcinoma (TEC family), and guanine nucleotide exchange factors [78]. Class II PI3Ks possess additional protein-binding domains and an elongated N-terminal segment, influencing their intracellular localization [78].

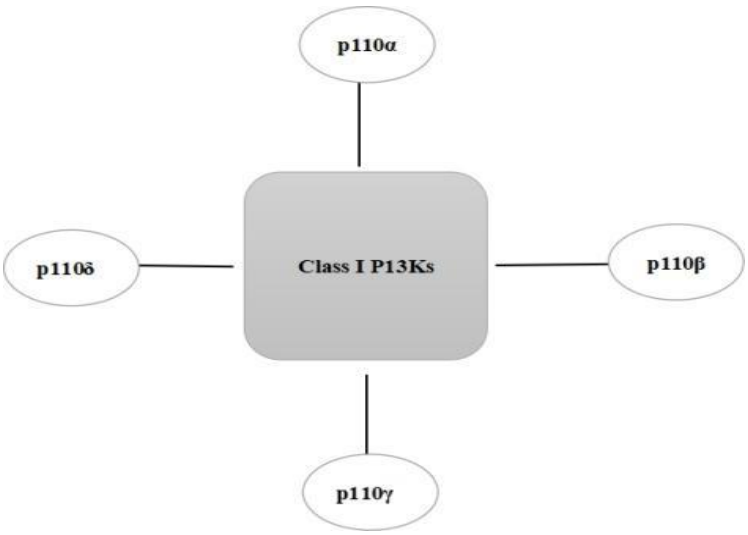

Fig.1: Catalytic isoforms of Class I P13K

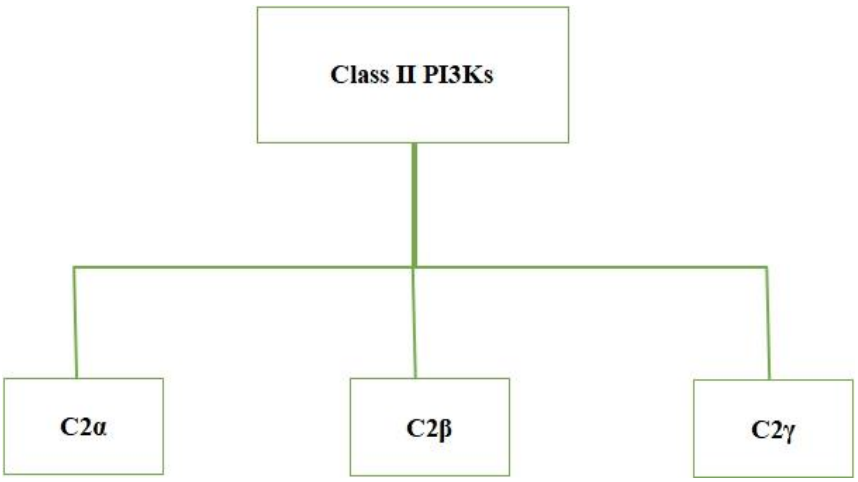

Fig.2: Catalytic isoforms of Class II P13K

Notably, unlike class I and III PI3Ks, class II PI3Ks do not produce PIP3 in vitro but can generate PIP2 from PIP, presenting a significant functional disparity [79]. On the other hand, class III PI3K VPS34, also known as PIK3C3, holds a unique role in regulating autophagy and macrophage phagocytosis. Its function involves binding to a protein complex composed of a regulatory and catalytic subunit [80].

LIF Gene Polymorphism

The LIF gene, essential for various human functions and produced by diverse cell types like hepatocytes, fibroblasts, osteoblasts, monocytes, macrophages, and T cells, plays a crucial role in successful human pregnancy [81, 82, 83, 84, 85, 86]. Increased LIF levels in follicular fluid correspond to improved embryo quality, underscoring its significance in ovulation and early embryonic development [87]. LIF governs the preparation of the uterus for blastocyst implantation and influences trophoblastic function by stimulating proliferation, invasion, and differentiation, as highlighted by Fitzgerald et al.,. These findings are outlined in the studies conducted by these specific researchers [88] .

Investigations into the SNP rs929271 (T/G) located in the 3′ untranslated region of the LIF gene have revealed intriguing associations [89]. Kang et al., noted a significant prevalence of the G allele among individuals under 35, particularly those utilizing fertility treatments, linking this allele to infertility in younger patients [90]. Ucisik-Akkaya et al. suggested a gender-specific effect of the LIF T/G genotype on embryo survival, while Fraga et al. found no association between the LIF SNP T/G (rs929271) and recurrent pregnancy loss [91, 92]. Similarly, Paskulin et al. reported no link between this SNP and conditions like endometriosis or IVF failure [93]. Tagliani-Ribeiro et al. also found no differences in the allelic or genotypic frequency of LIF T/G (rs929271) between dizygotic and monozygotic twins [94].

LIF's Crucial Role in Embryo Implantation: Insights and Implications

Studies by Tian et al.,; Mariee et al.,; and Salleh & Giribabu collectively highlight how crucial endometrial Leukemia Inhibitory Factor (LIF) is in aiding embryo implantation [95, 96, 97]. Reduced LIF protein activity due to changes in the LIF gene, particularly in a heterozygous state, has been associated with implantation difficulties and infertility in women who haven't conceived before [98]. Functional variations in the LIF gene have been observed notably in women experiencing

unexplained infertility, suggesting their potential involvement in the causes of infertility [99].

Specifically, the single nucleotide polymorphism (SNP) rs929271/c.1414T > G located in the 3′ untranslated region (3′ UTR) of the LIF gene has drawn attention due to its link with recurrent fetal loss in women with low levels of this gene [100]. When the LIF receptor is activated in the endometrium, it initiates multiple signaling pathways such as Jak/STAT, MAPK, and PI3-kinase pathways. Across the menstrual cycle, both LIF protein and mRNA display consistent expression patterns, reaching peak levels during the mid- and late-secretory phases and early pregnancy [101, 102].

Notably, LIF mRNA is prominently expressed in human decidual leukocytes at the implantation site, indicating its potential role in facilitating interactions between maternal decidual leukocytes and invading cytotrophoblasts during implantation. These connections emphasize the pivotal role of LIF in the process of embryo implantation [103].

LIF and Its Significance in Maternal-Fetal Interaction

Implantation marks the close connection between the developing blastocyst and the maternal endometrium (decidua), shifting the blastocyst's growth dependency to the maternal environment. Both embryonic and maternal factors contribute to successful implantation. While not fully comprehended, research highlights the crucial involvement of autocrine and paracrine factors like CSF-1, interleukin (IL)-1, and LIF. These factors, along with other peptides and steroid hormones, orchestrate a complex interplay to prepare the uterus for implantation, crucial for the progression of a pregnancy [104].

LIF is crucial for embryo and endometrium growth, aiding in blastocyst formation, attachment, and penetration into the endometrium [105]. LIF and LIF-R levels decrease during cell proliferation but rise after ovulation, peaking during the mid-luteal phase and remaining high until the end of the cycle [106, 107, 108]. Laird et al., Aghajanova et al., and Lass et al. report that LIF levels peak between days 7 and 12 post-ovulation, while LIF-R and gp130 levels peak between days 19 and 25 of the menstrual cycle [109, 110, 104].

Role of LIF in Follicular Fluid and Ovarian Cell Dynamics

The microenvironment within human follicles plays a pivotal role in fostering normal oocyte development, folliculogenesis, and timely ovulation. Within this context, follicular fluid emerges as a crucial factor shaping the environment for oocyte maturation, thereby impacting their potential for fertilization and subsequent embryonic development. Notably, in assisted reproductive technologies, follicular fluid has demonstrated its capacity to enhance human pre-embryo development in vitro, positively correlating with resulting pregnancy rates [111, 112].

Cytokines, as diverse signaling molecules, play a crucial role in regulating ovarian function, including gonadal steroid secretion, corpus luteum activity, embryonic development, and implantation [113]. Research from two independent groups has examined LIF in human follicular fluid and ovarian cells, enhancing our understanding of its impact on these functions [114].

Variations in LIF Expression across the Endometrial Cycle and its Impact on Implantation

Successful blastocyst implantation depends on complex interactions between the developing embryo and the endometrium, which undergoes constant and rapid remodeling. Throughout the menstrual cycle and early pregnancy, the endometrium responds to steroid hormones, locally produced growth factors, and cytokines [93]. Vogiagis et al., and Chen et al., delved into LIF expression within the endometrium by analysing uterine tissue across different menstrual cycle phases. Employing immunohistochemistry to pinpoint LIF cellular localization and Northern blot for mRNA analysis, they observed low LIF levels during the proliferative phase. However, following ovulation, LIF levels rose, maintaining a relatively high presence until the cycle's end before dropping to baseline [115, 116].

Remarkably, LIF mRNA was only observable during the later stages of secretion, specifically from day 20 onwards during the menstrual cycle. This heightened occurrence of LIF and its transcripts in the human endometrium corresponds to the anticipated period for implantation, hinting at a potential involvement of LIF in endometrial function, possibly acting in a paracrine or autocrine manner, as suggested by [104].

Modulating Factors Influencing Endometrial LIF Expression and Biosynthesis

Research by Arici et al., revealed that specific factors such as IL-1, tumor necrosis factor-α, platelet-derived growth factor (PDGF), transforming growth factor, and epidermal growth factor play significant roles in inducing LIF expression in endometrial stromal cells cultured in a manner dependent on dosage and time. Interestingly, interferon-γ demonstrated an inhibitory effect on LIF expression. Surprisingly, steroid hormones like estradiol and progestin did not exhibit the same enhancing effect on LIF expression in cultured endometrial cells. This timing of LIF expression within the endometrium suggests a potential role in implantation, hinting at its regulation playing a crucial role in both physiological and pathological processes associated with human implantation [117].

Contrastingly, Hambartsoumian et al., showcased a different facet, illustrating that endometrial LIF production is governed by sex hormones. Their study indicated that progesterone administration in women without ovarian function inhibited the capacity of explants to produce LIF in culture [118]. This finding contradicts the observations of other researchers in normally menstruating women [116, 117]. Furthermore, Piccinni et al., demonstrated in their recent publication that LIF expression can be up-regulated by IL-4 and progesterone [119]. They suggested that the regulation of LIF secretion in women with regular menstrual cycles might be influenced by ovarian growth factors, absent in patients without ovarian function. This points to a multifaceted regulation of LIF in the endometrium, influenced by various factors and hormonal dynamics [120].

Localization of LIF in Reproductive Tissues: Insights into Implantation Dynamics

Kojima et al., revealed substantial LIF mRNA expression in human first-trimester pregnancy decidua and endometrial tissue, presenting estimated sizes of 4 kb and 1.8 kb. Interestingly, the secretory-phase endometrium showed higher levels of LIF mRNA compared to the proliferative phase. While the first-trimester chorionic villus and term placenta displayed detectable yet low levels of LIF mRNA, differences in LIF expression were observed between epithelial-enriched and stromal-enriched fractions in both secretory and proliferative-phase endometrium [121]. Particularly, epithelial-enriched fractions exhibited more abundant LIF expression than stromal-enriched fractions. Furthermore, in the fallopian tube, high and constitutive levels of

LIF were observed in the ampullary section, suggesting a potential role for LIF during early embryonic development, as highlighted by Keltz et al., [122].

Additionally, the heightened LIF expression in cases of ectopic implantation, coupled with cytokine-induced secretion in the tubal stroma, hints at potential connections between inflammation, LIF, and tubal ectopic pregnancy. Collectively, these findings underscore the significant role of LIF within the local reproductive tract environment, implying its potential influence on implantation outcomes [104]. .

Role of LIF Receptor Complex in Early Embryonic Development and Placental Function

The LIF receptor complex consists of two subunits: the LIF-specific LIFR-α subunit and the gp130 subunit, shared by cytokines like IL-6, IL-11, among others. This complex, composed of LIFR-α/gp130 heterodimers, can respond to oncostatin M, ciliary neutrophic factor and cardiotrophin, aside from LIF [85]. Van et al., demonstrated the expression of LIF receptor component transcripts from the oocyte stage through early preimplantation stages, with subsequent confirmation of expression in blastocysts [123, 124, 108]. However, not all blastocysts showed detectable messages, possibly correlating with arrested or developmentally limited blastocysts. The direct correlation between receptor component expression and successful growth remains uncertain [125].

While non-LIF cytokines using the gp130 receptor, like IL-11, play crucial roles in mouse implantation, evidence for functional LIF receptors (LIFR-α/gp130 heterodimers) on human embryos was established through observations showing increased blastocyst formation rate and improved quality (reduced fragmentation) when cultured in the presence of LIF [126]. Moreover, the presence of LIFR-α in trophoblasts suggests its importance in proper placental function and vascularization, potentially contributing to conditions like pre-eclampsia. These findings emphasize the significance of LIF receptor expression in oocytes, preimplantation embryos and placental tissues, hinting at its pivotal role in early embryonic development and placental function [104].

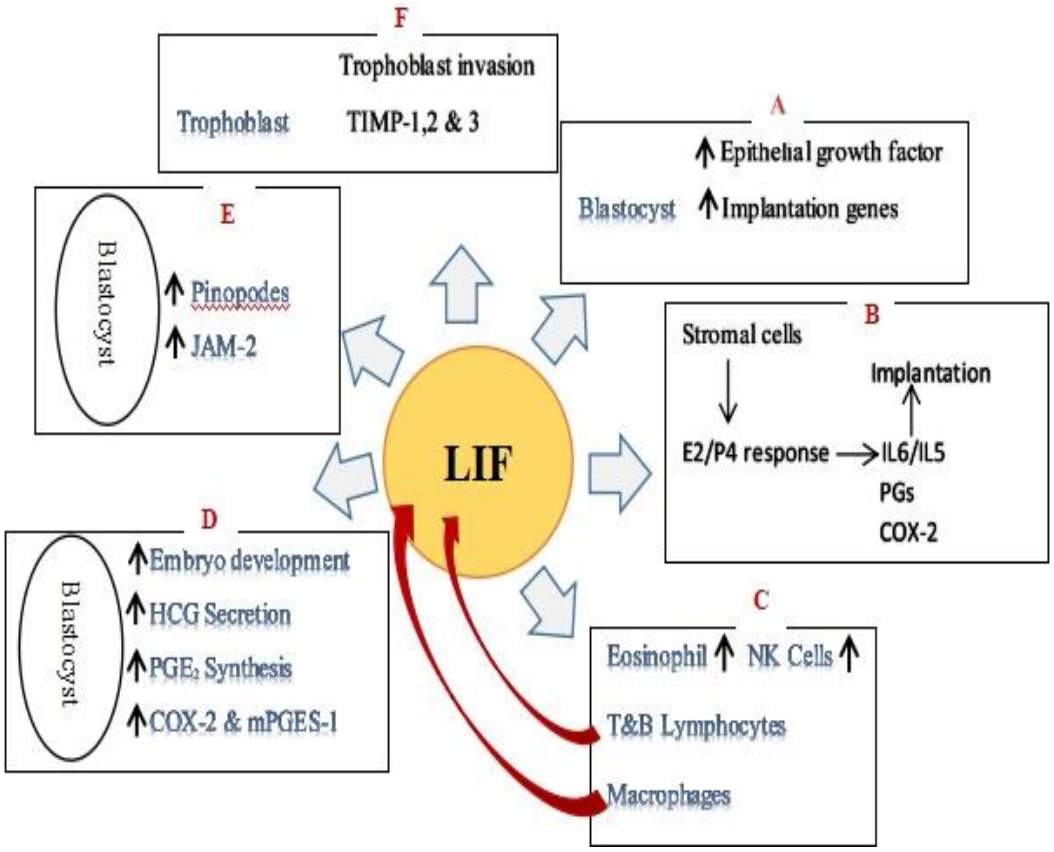

Figure 3: LIF's multifaceted role in embryo implantation and placental development depicted in sequential steps.

Therapeutic Implications of LIF

LIF holds a critical function within the stem cell environment, ensuring the balance and renewal of various somatic tissues like the intestine, neurons, and muscles. Additionally, it plays a pivotal role in regulating immunity, acting as a safeguard against several immunopathological conditions such as infection, inflammatory bowel disease (IBD), and graft-versus-host disease (GVHD) as indicated by Wang et al., [127].

Lass et al., found that in the endometrium, LIF expression varies across the menstrual cycle, peaking during implantation. LIF levels in uterine flushing are notably reduced in women with unexplained infertility compared to fertile women. Unlike fertile women, most infertile women do not exhibit an increase in LIF production during the secretory phase, and there are considerable fluctuations in LIF levels during the proliferative phase. This suggests potential clinical implications of altered LIF expression in human reproduction, particularly in understanding infertility in women [104].

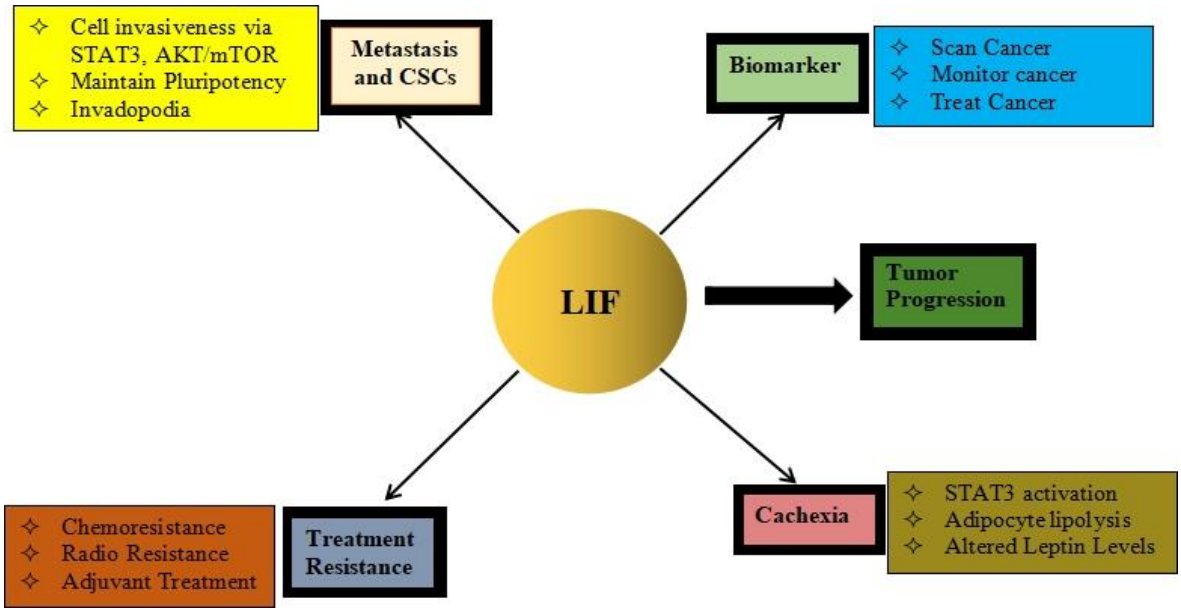

Figure 4: LIF in cancers

Conclusion

The research underscores the pivotal role of Leukemia Inhibitory Factor (LIF) genes in implantation processes, revealing compelling insights. The LIF SNP T/G (rs929271) has surfaced as a potential indicator for forecasting implantation success and pregnancy results. This suggests promising implications for utilizing LIF in infertility treatments or conversely, exploring LIF antagonists for contraceptive purposes. Additionally, associations between LIF gene polymorphism, gene expression, and implantation outcomes have been delineated, highlighting their impact on success or failure. The study accentuates LIF's indispensable function in initiating and regulating embryo-endometrial interaction, crucial for successful implantation. Decreased levels of LIF in maternal plasma were notably linked to increased risk of early pregnancy loss, highlighting the crucial function of LIF in ensuring successful implantation. Additionally, the observed moderate to high LIF expression during certain menstrual cycle phases in fertile women, contrasted with lower expression in infertile women, underlines the importance of LIF in supporting effective implantation. These findings collectively underscore the multifaceted and critical involvement of LIF in the intricate process of implantation, opening avenues for potential therapeutic interventions and enhancing our understanding of fertility dynamics.

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Conflict of Interest

The authors assert that they do not have any conflicts of interest to disclose.

Author's Contributions

Each author participated in data analysis, manuscript drafting, and revisions, collectively contributing to all facets of this research.

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