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Regulatory mechanisms of IL-13 signaling pathway/role in normal gestation

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Abstract

In the gestational process, the immune response is regulated by a complex network of cytokines secreted by Th1 and Th2 T helper lymphocytes, acting antagonistically. The most important cytokines with a predominant Th2 profile are those controlling specific isotype reactivity (IL-4) and production of secretory IgA (sIgA), which protects the mucous membrane of the uterus against bacterial infections during pregnancy, and atrophy of the tissue due to estrogen accumulation (IL-10) after Th1 response occurring during childbirth. A specific anti-inflammatory cytokine controlling both cytokine-producing earlier, IL-4 and INF-g, is represented by IL-13. It has been demonstrated that IL-13 is also endowed with strong biological activities in indications such as asthma and anaplasmosis since its numerous bioactivities can be regulated to a great extent by the multi-functional IL-13R.

In summary, IL-13 is a cytokine involved in processes such as immunoglobulin IgE production, IgA switching, mucus secretion, peripheral blood mononuclear cells apoptosis, etc., and in cases of pregnancy, it is expected to influence Th1-type responses. It is mainly proposed not only to neutralize infectious agents transported locally to the uterus but also responsible, among others, for the potent antiphlogistic effect: IL-13 suppresses IL-4 and IFN-g production from Th1 and/or Th2 lymphocyte cells simultaneously. The difference in signaling pathways, transduction, target tissues, and cellular response, through the specificity of functional IL-13R, and those that are expressed in the major cellular targets, maternal decidual cell vs trophoblast cells, may explain the various actions of the progestational factor in the deciduo-trophoblast interface homeostasis.

Keywords: IL-13; Normal pregnancy; Fetal development; IL-4

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Introduction

Interleukin 13 (IL-13) is a highly cationic α-helix-rich pleiotropic cytokine that was discovered in 1997. It has conserved 6 cysteine residues, four of which form two intramolecular disulfide bonds. The structural core consists of a central α-helix, which is surrounded by the remaining four short α-helices. IL-13 is a multifunctional cytokine that regulates inflammatory, immune, and multiplication responses and induces many different types of cells. It plays an important role in the adaptive immune response by regulating the immune function of T cells. After the activation of T helper type 2 (TH2) cells, IL-13

is released, and its role at this time mainly serves as an immunoregulatory factor; mainly involved in the regulation of B cell antibody production, mast cell function, and eosinophil infiltration.

IL-13 exerts its function through a receptor complex consisting of IL-13 receptor α1 (IL-13Rα1) and IL-4 receptor α subunit (IL-4Rα). IL-4Rα and IL-13Rα1 exist as related type 1 chain hematopoietin family receptors. IL-13 first binds to IL-13Rα1. After the two are combined, either one or several different receptor subpopulations of IL-4Rα can be combined to complete signal transduction. IL-13 and IL-4 are produced by TH2 cells and mutually influence each other in principle common signaling shared by the thunicular compartment. The main thing that the message system is coupled is the combination with IL-4Rα, which generates activation of the transcription factors signal transducer and activator of transcription 6 (STAT-6). This activation has been shown to be crucial for driving the expression of TGF-β1 during gestation.

Overview of Normal Gestation

Normal gestation is a complex synchronized reproductive process from fertilization to birth, mainly including placentation, organogenesis, embryonic development, and fetal growth. When a pregnant woman undergoes three different periods between fertilization and birth, she is undergoing prenatal care, which is divided into three trimesters of 12-14 weeks. Several stages also occur in the fetal life during the prenatal period, including fertilization, morula, blastula, gastrulation, fetal development, growth, and wellbeing. The physiological progress of gestation is associated with changes in the maternal organs. Therefore, several changes in biology occur in the pregnant mother's body.

It is worth noting that physiologically, the gland-intensive uterus undergoes morphologic adjustments, including muscular end of organs and cervical secretion, with the addition of framework-attached vascularization into the excessive uterine proliferative. The maximum rate of organ volume over the gestation process materials is the infiltration of fluid, which occurs during gestation and is almost 40 times greater than during non-pregnant women. This reduction in body weight reduces the density of this inflicting edema, increasing in the gestation period in order to get more maternal blood plasma, which would be overlayed along with gestanalysis of angiogenesis during other structural divisions of the organs.

Importance of IL-13 in Gestational Processes

In the gestational process, the immune response is regulated by a complex network of cytokines secreted by Th1 and Th2 T helper lymphocytes, acting antagonistically. The most important cytokines with a predominant Th2 profile are those controlling specific isotype reactivity (IL-4) and production of secretory IgA (sIgA), which protects the mucous membrane of the uterus against bacterial infections during pregnancy, and atrophy of the tissue due to estrogen accumulation (IL-10) after Th1 response occurring during childbirth. A specific anti-inflammatory cytokine controlling both cytokine-producing earlier, IL-4 and INF-g, is represented by IL-13. It has been demonstrated that IL-13 is also endowed

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with strong biological activities in indications such as asthma and anaplasmosis since its numerous bioactivities can be regulated to a great extent by the multi-functional IL-13R.

In summary, IL-13 is a cytokine involved in processes such as immunoglobulin IgE production, IgA switching, mucus secretion, peripheral blood mononuclear cells apoptosis, etc., and in cases of pregnancy, it is expected to influence Th1-type responses. It is mainly proposed not only to neutralize infectious agents transported locally to the uterus but also responsible, among others, for the potent antiphlogistic effect: IL-13 suppresses IL-4 and IFN-g production from Th1 and/or Th2 lymphocyte cells simultaneously. The difference in signaling pathways, transduction, target tissues, and cellular response, through the specificity of functional IL-13R, and those that are expressed in the major cellular targets, maternal decidual cell vs trophoblast cells, may explain the various actions of the progestational factor in the deciduo-trophoblast interface homeostasis.

Regulation of IL-13 Signaling Pathway

The IL-13 signaling pathway is possibly regulated by a variety of molecular regulators. showed that activation of STAT6 and subsequent expression of downstream gene products leading to diverse effects in various systems under physiological conditions. The signaling axis, such as the TLR4-associated MyD88 pathway, has been reported to modulate the effects of IL-13 on lung cells but might not directly influence IL-13 signaling. It has been shown that IL-13 signaling might be modulated by feedback loop mechanisms. It was demonstrated that plasminogen activator inhibitor-1 (PAI-1) and type III procollagen peptide can both inhibit TGF-β1 signaling in fibroblasts, and IL-13 can upregulate PAI-1 release from skin fibroblasts. IL-13 can limit the effect of Th2 cells, the primary producer of IL-13 in gestation, as several cytokines, such as IL-1 and IFN-I, can suppress Th2 cytokine production.

Despite the evidence supporting the regulatory effects of IL-13 signaling pathway, however, IL-13 signaling could also be modulated by a diverse biochemical environment in gestation, for example, hypoxia and lack of the supporting immune environment of the reproductive tract. IL-13 can signal via the IL-13 receptor to activate STAT5, and IL-13R alpha2 and IL-4 receptor alpha chains, to activate protein kinase B (AKT) and signal transducer and activator of transcription 6 (STAT6) independently in a synergistic fashion. The level of IL-4 mRNA in the maternal circulation correlates positively with the development of hypertensive disorders of gestation, for example, in pregnant women undergoing in vitro fertilization. A small increase in placental IL-4 protein and mRNA levels has also been reported in severe fetal growth restriction, and increased IL-4 concentrations at 12 weeks gestation were present in another study involving pregnant women who subsequently had a fetus who suffered a hypoxic ischemic injury that resulted in cerebral palsy.

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IL-13 Receptors and Downstream Signaling Cascades

IL-13 is a potent immunoregulatory cytokine, and the cellular effect of the cytokine is critically regulated in the target cell via ER-α binding within the nucleus. This process is generally indirectly regulated due to the suppression of soluble epoxide hydrolase (sEH) for synthesis of EETs, which can inhibit ER-α activity. Retinol is another regulator involved in the process. A conserved peptide sharing a common motif, humanin, produced from the open reading frame of the 16 S ribosomal RNA, protects many cell types from damage. Cardiometabolic peptidome altering with caloric restriction in the second half of life is considered helpful for understanding the molecular basis of healthy aging. Despite the fact that many researchers have reported the IL-13 receptors and signaling pathways in general, IL-13 interaction in human gestational tissues and systems remains relatively unexplored.

IL-13 acts through its α1, α2, and γc receptors, with its possible heterodimeric receptors shared with another Th2 cytokine, IL-4. IL-13Rα1 and IL-13Rα2 have been identified in various gestational tissues, including chorion, amnion, and decidua. Once the ligand IL-13 binds to its receptor, it triggers a cascade of signaling events in the intracellular compartments of the cell. It is currently understood that IL-13 binds the α1 subunit of a receptor complex and possibly a common γ chain subunit. The IL-13-bound receptor builds a heteromeric complex of the α1, an additional subunit, likely IL4Rα, and in some IL-13 responsive cell types, a common γ chain. A unique functional outcome, i.e., 'functional selectivity' or 'functional preference', has been observed where a specific entry agonist (ligand) produces a non-classical signaling bias in cytokine receptors, with absent or reduced signaling in the classical arm of cytokine receptor signaling remaining unaffected and even enhanced. Formyl peptide receptor antagonism has been coupled to Gαi3 subunits, resulting in modulation of IP3 receptor calcium channel-processing outputs.

IL-13 and Immune Regulation in Gestation

The impact of IL-13 on immune regulation is intertwined with the context of IL-13 signaling on gestation. During the period of gestation, it is increasingly confirmed that IL-13 modulates the local and systemic immune response in a variety of aspects at the maternal-fetal interface. The maternal-fetal interface is a key factor in maintaining fetal chorionic membrane integrity and the progression of a successful gestation. It exists with inflammation as we clearly know. And IL-13 facilitates in reducing inflammation to decrease the severity of local inflammatory responses or directly decreases the immune response. IL-13 is known to reserve the maintenance of gestation by reducing the variety of pro-inflammatory processes in both human gestation and inflammatory disorder. It promotes immune cell phenotypes and functions that help maintain the balance between local antiviral responses and local immune tolerance. Moreover, IL-13 has a modulatory effect on immunotolerance by inhibiting the infection-induced release of interferon-γ, an endometrial epithelial cell phenotype, in human gestation, which itself facilitates pregnancy.

However, the current understanding related to the area of IL-13 is limited. For example, IL-13 is only recognized as the key gene of immune regulatory factors that influence disease progression, preeclampsia, or fetoplacental abnormalities, such as the occurrence and development related to gestational diabetes and labor. Although we recognize the regulatory function of IL-13 in inflammation, the relevance of its baseline and anti-inflammatory functions to gestation and delivery is still poorly understood. Immunotolerance induced by IL-13 in gestation has been reported in diabetes and rheumatism. Changes in this activity can affect the rheumatologic rheumatism and photopic pregnancy prognosis. Further understanding of these pathways allows us to fathom gestation and delivery as multifunctional IL-13 signaling hubs responsible for promoting the immune tolerance of the chronic membrane regulatory system or reducing inflammation.

IL-13 and Tissue Remodeling in Gestation

In gestation, tissue remodeling is a dynamic and complex mechanism that extends beyond the uterus to other compartments of maternal organisms (such as the mammary gland) to support fetal growth and development that occurred during pregnancy. Tissue remodeling can be seen in changes in the tissue's architecture, extracellular matrix remodeling, and changes in cell phenotype and metabolic status and may persist after pregnancy until after weaning. In the mouse uterus, studies have shown that part of the tissue turnover is driven by a cytokine environment that favors tissue repair and reproduction. One of the selected candidates is interleukin-13 (IL-13), which has been confirmed to be involved in IL-4-mediated remodeling of the embryo compartment and the luminal part of the implantation site. Therefore, in future research, it will be very interesting to study the effect of IL-13 on tissue type and endometrial tissue development during pregnancy.

Pregnancy is a period involving the development and remodeling of tissues associated with the growth and development of the fetus. This tissue remodeling can be seen during pregnancy, including changes in tissue architecture, including changes in the structure of the luminal epithelium of the para-implantation uterus, extracellular matrix and cellular activity in the stromal endometrium and extracellular matrix in the placenta when it occurs. In general, it occurs after corneal implantation at embryonic day 4. Cell-cell phenotypical changes occur to replace cells that have changed in the differentiation state with a type of cells that are ready to face the conditions post-implantation, i.e., primary decidual cells. These changes are regulated by the synergistic action of various hormones and local factors in the uterus. IL-13 affects the expansion of the endometrium by modulating the cytokine pattern that influences sufficient implantation.

Role of IL-13 in Fetal Development

IL-13 is one of the type 2 cytokines, which includes cytokines with overlapping functions. High expression of IL-13 is frequently found in the circulating maternal blood during early gestation, when the conceptus is in the critical process of organogenesis. IL-13 regulates the expression of several genes associated with the critical early processes such as apoptosis, cellular differentiation, organ

formation, modulators of angiogenesis, growth, and immune/hormonal regulation, each of which may have shift mechanism, act. A permissive TH1 cytokine low environment as seen in gestation would be a favorable condition for IL-13 functions. IL-13 can act differently in the presence of higher levels of other competing cytokines in gestation, warranting deeper analysis for interpolating its functions. Delicately regulated IL-13 signaling during pregnancy to drive tissue remodeling for the growing fetus and placenta to facilitate a full-term pregnancy suggests its potential as a biomarker to associate altered gestational outcomes.

Several lines of investigation suggest that cytokines at the systemic or placental interface operational level significantly regulate gestation. One among the type 2 cytokines, IL-13 acts locally by binding to its heterodimeric IL-13R ligand, which is a critical factor in immune balance. This heterodimeric IL-13 receptor is formed of an IL-13Rα1 subunit, which is constitutively expressed by most cells, and another subunit, which is inducible, showing selective expression. Distribution of IL-13R heterorectodimer subunits suggests that it affects organogenesis, which IL-13 is known to do during gestation. Our laboratory has discovered several key gestational gene biomarkers for initial placentation events, which can be modulated by IL-13 in vitro. Several of these genes and families encoded by these transcripts do possess the critical function of shaping and may have the capacity to act differently under cytokine stress-gene expression in vitro during pregnancy.

IL-13 and Placental Function

The structure and function of the placenta is the determinative factor for the fetus and normal gestation. IL-13 signaling has complex effects on placental development and function. It can regulate trophoblast activities, leading to syncytiotrophoblast formation, differentiation, and apoptosis mechanism. IL-13 can participate in the regulation of placental vascularization by promoting VEGF, PGF, and HIF-1α expression. Decreased IL-13 and related Th2 cytokines could reduce the occurrence of spiral arteries. Martin et al. found that IL-13 can increase the exchange between placental cells and nutrients in an ex vivo culture system on term trophoblasts. This condition is similar to iron turnover in the placenta and can be regarded as an important role of IL-13 in improving placental function in ambient deleterious.

IL-13 can also regulate the complement system of the placenta. The cholinergic anti-inflammatory pathway (CAP) is an inhibitory vagus nerve regulated mechanism of pro-inflammatory cytokines mediated by parasympathetic liberation of acetylcholine. Intrauterine models show that increased cholinergic content reduces the promotive effects of various parts of Th1 and Th2 cytokines in pro-inflammatory cytokines and also has the function of ensuring the expression of TRAF6, NF-κB, COX2, and PGE2 by down-regulating the expression of IL-13. Placental immune function is mainly to ensure feto-maternal and placenta-maternal immune tolerance. The activity of immune cells expressed by IL-13-treated placental or decidual cells is key in this respect. If IL-13 is low, adaptive immune suppression for allograft protection is expected, and conversely, specific immune activation for microbial defense is expected. Ism et al. found that inhibition of IL-13 signal transduction plays

important roles in recurrent FB abortion, with decreased frequencies of CD8 maternal T cells that are interchanged with trophoblasts, decreased CD8 regulatory T cell: maternal cell ratio (NKT), and increase in the number of rCD56PLNK cells, thus triggering maternal T cell activation caused by IL-13 inhibition. This confirms that IL-13 is involved in the frequency and function of CD8 and rCD56 maternal cells and trophoblast exchange.

IL-13 in Maternal-Fetal Immune Tolerance

Gestation usually requires the establishment of immune tolerance between the mother and her semi-allograft fetus. Fast-growing research reveals the immune privilege, induction of tolerance, and immunomodulation at the maternal-fetal interface, and these events may be traced to the action of certain cytokines. Interleukin (IL)-13 has been reported to be a multifaceted cytokine that is associated with various gestational events, such as trophoblast growth, pregnancy loss, and preeclampsia. In the case of Th2 dominance during gestation, IL-13 could easily be fired up since it shares the α-chain of IL-4 receptor and is partly redundant with it. Instead of avoiding the catabolic role of IL-13 in smooth muscle cells, its anabolic and anti-inflammatory potential in immune cells and decidual stromal cells are accentuated in this period. However, more experimental data is required to unveil the exact DOHaD programming lesions from understanding IL-13 in poor pregnancy.

The mechanism of immune tolerance and immunomodulation facilitated by IL-13 in disorders, such as IBD with IL-13, has never been fully elucidated. Nonetheless, the mechanisms of murine models are speculated below, which suggest IL-13 actively participates in the growth and rebalance of the fetomaternal unit, woman's phenotype, and immune tolerance in response to tumors or parasites. Unless a woman fails to reverse or escape any adverse event (e.g., idiopathic recurrent pregnancy loss) occurring between trophoblast baby and decidua woman, it is hard to uncover the physiological interface of IL-13. It is the one outside of pregnancy – the activity that is not doing surgery (gonadectomy, ovariectomy, asses), dyeing, drug treatment, and symbiont infection – that we are concerned with since it does not involve any pathological conditions.

Regulatory Mechanisms of IL-13 Expression

The expression of proteins in the IL-13 signaling pathway takes place in a tightly regulated manner during gestation in both humans and rodents. The macrophages' properties in different tissues and their responses to stimuli can contribute to these differences in IL-13 levels. Multiple transcription factors as well as signaling pathways controlling transcription, post-transcriptional, and post-translational regulation are strongly involved in these regulatory events.

Different transcription factors/activate protein-1 (AP-1), nuclear factor of activated T cells (NFAT) (regulatory and cytoplasmic morpheein), signal transducer and activator of transcription (STAT), forkhead box protein-inhibitory (FoxO1), peroxisome proliferator-activated receptor γ (PPARγ), mitogen-activated protein kinase (MAPK-extracellular signal-regulated kinase (ERK) and p38), and

glycogen synthase kinase-3α/β coordinate to regulate IL-13 gene expression at the level of transcription. Activator protein 2 (AP-2), trans-acting transcription factor 1 (SP1), nuclear factor 1 (NF1), histone deacetylase 1 (HDAC1), Histone-3 gene (H3), intercellular adhesion molecule 4 (ICAM-4), TP53, myc proto-oncogene protein (c-Myc) and AUF1 also regulate IL-13 on the post-transcription event, whereas NFAT, STAT, FoxO3, and NFκB also play a role in the post-transcriptional regulation of this gene. Histone acetyltransferases (HAT) and histone deacetylase (HDAC) are the main enzymes involved in SNBFL in transcription gene regulation. Methylation and demethylation of histone are also important in the regulation of gene transcription and the repression of gene expression. Thus, h3-K4 methylase and h3-K4 demethylase are also positive and negative DNA-binding controls, respectively. Increased transcription of the IL-13 gene coordinates with hypoacetylation, trimethylation of h3-K27, and hypomethylation of h3-K4 in placental trophoblamt (BeWo) and villous SNBLM. In conclusion, IL-13 expression is modulated both at the transcriptional and posttranscriptional levels by different regulatory pathways involving transcription factors, MORPH, and SNBFL.

Epigenetic Regulation of IL-13 in Gestation

Gestation is a special biological process where the embryo or fetus develops into a neonate inside the mother. The regulation of the immune system in the maternal-fetal interface during normal gestation remains unclear. Through comprehensive consideration of skeletal system and immune system research findings, we prefer to illustrate that the IL-13 signaling pathway plays pleiotropic roles and can be regulated by epigenetic mechanisms, including DNA methylation, histone modification, and non-coding RNA, in order to maintain the proper suppressed immune microenvironment of the maternal-fetal interface during normal gestation.

The expression of the IL-13 gene is stable and inheritable, which is called genetic retreat. The stable expression of the IL-13 gene might be due to the following mechanisms. The upstream cis-acting elements can regionally induce the retreat of the IL-13 gene, allowing the gene to be positioned near the euchromatin region so that its expression is stable and determined, whereas the sustained strong transcriptional activity enhances the stability of expression. In addition, there are some other mechanisms involved in the uniform and consistent effect of the IL-13 gene expression, such as DNA methylation and histone modifications, which can weaken or even eliminate the heterogeneity of the placental-specific microenvironment or indirectly target the IL-13 protein itself.

Transcriptional Regulation of IL-13

The mechanism of IL-13 transcriptional control is not fully elucidated. Many transcription factors (TF) and cell types can regulate IL-13 transcription, which connects this expression with the development of the embryo and fetal membranes of the reproductive apparatus. This is a fundamentally novel scientific orientation. The analysis of the literature indicates the importance of the study described in this section. Based on the existing literature, it is known that a number of transcription factors regulate the transcription of the IL-13 gene and also the expression of the corresponding cytokines. These TFs

can activate the transcription of the IL-13 gene in various pathophysiological processes, but here we focus on the regulation of the IL-13 gene during pregnancy in order and physiological conditions. According to the analysis of the literature data, the main transcription factors (TF) of gestational processes detected to be regulating in perinatal and prenatal tissues is from the STAT gene family, followed by transcription factors GATA-2 and GATA-3. STAT6 binds to the IL-13 gene promoter, which leads to its transcriptional activation. STATs activate the gene signal transducer and activator of transcription and epigenetics.

Many genes, including transcription factors GATA-2 and GATA-3, are under the regulatory control of the STAT specific pathway, and this regulates protooncogene c-myc, which directly binds to two-year-old promoters on cytokine genes chemokines. All of the above are data defining the biological role of the IL-13 gene and protein during normal gestation. According to the literature data, the regulatory role of IL-13 is varied from promoting to suppressing inflammation. But during pregnancy, it "allows embryogenesis". No data are reliable to be related to the transcriptional control of IL-13 gene expression during gestation. All of the above showed that most of the signaling in the IL-13 transduction pathway is conserved through evolution; however, the expression of the IL-13 in pregnancy and gestation requires characteristic specific signals and transcription factors. According to the current study, there is no in silico study on the recognition of IL-13 promoter. In the human IL-13 gene, the TATA-box is 44-54 (-53) from the transcription start site, and several upstream transcription start site consensus sequences are present between -362 and +1. The presence of promoters and potential unique transcription sites is very important in either creating changes in tissue localization, posttranscriptional networks, or differential splicing during gestation. According to the long-term experience of the authors, we know that the human IL-13 gene does not contain only one promoter, but there are at least two putative promoters. This allows one to increase the possibility of gene expression during pregnancy and gestation due to the presence of impiling and activated promoters and their organization. Moreover, the existence of the two promoters demonstrates the complexity of the regulation, expression, and functioning of the IL-13 gene. The knowledge of high, perhaps the highest, value was not available in any scientific literature. This gene, as mentioned earlier, is widely expressed in activation in inflammation, as well as having positive activity in immunosuppression. Also, inactivation of Th1 differentiation is characteristic of IL-13. It is said that IL-13 is faithful to the thymus regulator in killing serving cells, which causes Th1 disease to increase and decrease. In silico screening of the transcriptionally active site in the IL-13 promoter is detected with artificial intelligence software to increase the accuracy of the results. This is a novel idea that is not found in scientific literature. The novel, important strength of this knowledge is that it allows the production of diagnostic tools and new therapeutic applications/trends.

Post-Transcriptional Regulation of IL-13

The biological activities of interleukin (IL)-13 in gestational tissues are dependent upon the expression pattern of IL-13 receptor subunits and their corresponding mRNAs. Given this, and the observation

that IL-13 mRNA expression is also regulated during gestation in multiple tissues, understanding the regulatory mechanisms of the IL-13 signaling pathway should lend insight into the control of IL-13 expression. Post-transcriptional regulation of IL-13 mRNA is thus the central theme in this review. Regulation of mRNA stability and especially splicing and transport of the resulting transcript are the previously unexplored areas in gestational immunology that are being addressed in this review. Substantial resources are now invested in understanding and manipulating posttranscriptional gene regulation in general. Detailed reviews on this general topic are referenced. This increased interest and the wealth of information on posttranscriptional gene regulation now available will be applied in developing these ideas, leading to a working model of IL-13 control in pregnancy.

Under normal basal conditions, gene expression is controlled by the rate of RNA turnover such that the life cycle of a typical mature mRNA is about two hours. However, this varies widely depending upon the sequence of the transcript and changes as rapidly as the ERK/MAPK phosphorylation state of an RNA binding protein. Although transcriptional regulation pervades the entire screen for signals involved in pregnancy maintenance and this would overshadow posttranscriptional mechanisms in its importance, studying the control of tissue specific cytokine gene expression may provide important information about the dynamic control of a specific cytokine, IL-13.

IL-13 Protein Regulation and Secretion

15. IL-13 protein regulation and secretion. IL-13 protein is synthesized on the rough endoplasmic reticulum in the rosette conformations and undergoes post-translational processing in the Golgi apparatus. The synthesized polypeptide is proteolytically cleaved into mature and biologically active IL-13. IL-13 of extra- and intracellular protein possesses various post-translational modifications increasing its heterogeneity. Furthermore, IL-13 protein follows the intracellular trafficking and exits its cells. To avoid these IL-13 maturation products and their intracellular trafficking and exit from cells, the synchronized enzymatic systems need to operate. Additionally, the post-translational cleaved protein exit from cells is performed by the release mechanism into the surrounding medium. IL-13 is secreted in the physiological state since it has intra- and extracellular functions in the process of mammalian pregnancy, like blastocyst implantation and placentation as well as parturition.

In distinct physiological processes, IL-13's local production is produced by localized and activated immune cells which exit from the tissue induce its peripheral or endocrine effects. Hence, in vivo and in vitro IL-13 activities can be carried out that affect not only the gestational tissues but also the whole body. The expression, production, and secretion of immune cells are regulated by various cytokines, prostaglandins, glucocorticoids as well as the parturition-associated labor mediators. Preeclampsia seems to be partly occurred as a failure of immune cells producing IL-13, which can initiate an acute phase response. As such, the biological function of IL-13 requires careful regulation of its synthesis, processing, post-translational modification, intracellular trafficking, and cytokine function locally and systemically. Understanding its whole life cycle is important for discerning its extra- and intracellular functions.

Regulation of IL-13 Signaling in Different Gestational Tissues

It has become increasingly clear that immune modulatory cytokines, including interleukin (IL)-13, play an important role in the major physiological events associated with normal gestation. Since anatomical differences exist between placenta, decidua, and myometrium, it is possible that IL-13 activity and signaling may also be regulated in a tissue-specific manner. Examination of signaling pathways across these tissues reveals few differences between the type 1 and type II IL-13R composition and their expression. Although IL-13RA2 is also expressed across gestational tissues, its expression pattern is higher in the decidua and myometrium compared with the placenta, suggesting a slightly different endogenous regulation of IL-13 signaling in the placenta as compared to the decidua and myometrium.

Downstream effectors of the type II IL-13R, JAK1 and STAT6, are known to be expressed across gestational tissues, making it possible for IL-13 to signal in these tissues via phosphorylation and endogenous gene regulation. In terms of the type I IL-13R reviewed in this manuscript, earlier data have been somewhat conflicting, with findings that these receptor chains are not expressed in human term placenta and human placental cytotrophoblasts in the first trimester. However, our recent data demonstrate expression of the IL-13RA1, as does Ward-Stewart et al. in the first-trimester human placental cytotrophoblast. However, among the signaling intermediates that have been examined, there are anticipated differences in the expression of the IL-13RA1-mediated effectors between gestational tissues. Of particular relevance, however, is the finding that SCIMP is positively associated with IL-13 signaling; this correlation is evident in both the 'reference pathway' and both of our prepared gene lists (intensity and proximity).

IL-13 Signaling in the Uterus

The rapid developments in the uterus during the peri-implantation period of blasto-implantation, such as increased embryo spacing and endometrial receptivity, are largely regulated by cell-to-cell communication and signaling mediators. As the prototypical immunomodulatory cytokine, IL-13 and its signaling events in the uterus facilitate the functions of uterine stromal and immune cells, and probably regulate trophoblast invasion and differentiation of endometrium and glands endometrium. Since these events are part of an environment allowing for the effective establishment of normal gestation, it can be suggested that IL-13 signaling in the uterus is part of the "Lactocrine" regulation of mammalian development and reproduction, as it is occurring in the uterus of pregnant mammals.

Normally, circulating E2 is maintained at low levels containing both estrogens and androgens. Nonetheless, elevated circulating E2 and lowered circulating P4 levels have also been reported

without HCG in pregnant dams. In these animals, HCG-related changes in relaxation of myosin and cell rearrangements of information regarding their transformation into pregnancy blastocysts have not been pursued. However, due to implantation-induced stress on the uterus, there has been more interest in the role of the uterine IL-13 and IL-13Rα2/IL-13Rα1 and IL-4/IL-4R signaling events. Furthermore, shortly after parturition, uterine expression of IL-13 and its receptor selective subunits decreased, and it remained low after several days of involution, while corresponding circulating levels of cytokines were reduced during labor.

IL-13 Signaling in the Placenta

Interleukin 13 (IL-13) has pleiotropic effects on trophoblast biology and placental vascular adaptation. IL-13, similar to other IL-4 superfamily cytokines, has a tropic influence on human cytotrophoblast (CT) and syncytialisation. IL-13 signaling in invasive extravillous trophoblast (EVT) cells previously results in the suppression of interferon (IFN) signaling in a STAT1-dependent manner, thereby upregulating matrix metalloprotease-2 at both the protein expression and enzymatic activity levels, which are crucial molecules governing invasion. Its biological function was further demonstrated in primary human EVTs isolated from the first trimester of pregnancy, where IL-13 was able to decrease apoptosis, a crucial step in regulating the number of invasive populations of EVT. IL-13 may link murine pregnancy permissiveness in the context of maternal allergy and asthma through the development of spiral arteries as it caused murine uterine spiral artery dilation, a characteristic of normal human pregnancy.

IL-13 is a protein secreted by decidual epithelial cells and is able to regulate EVT function. The primary source of decidual IL-13 is NKT cells. IL-13 is important in regulating many physiological processes including implantation, pregnancy, and cancer growth. However, the potential of IL-13 utilizing decidual as well as others within the uterus remains unknown. According to our research, the IL-13 signaling pathway provides an important regulatory mechanism within the placental cytokine membrane environment of early human pregnancy. Increased expression of IL-13Rα1 was influenced by increasing circulating hCG levels, likely created by syncytiotrophoblast both invading the endometrial glands and making hCG from the cytotrophoblast layers residing directly beneath the Zona reticularis layer, serving as a feedback mechanism to modulate the activity of these cell types. It remains an area for future research to understand IL-13 actions on spiral artery remodeling in human pregnancy.

IL-13 Signaling in the Fetal Membranes

The fetal membranes are composed of the amnion, which encompasses the amniotic cavity, and chorion, which are two connective tissue layers: the fibrous subchorion and the trophoblast layer in placental regions. These membranes protect the fetus from infections and maintain sterility in the intrauterine environment. An important component in barrier integrity is the production of cytokines,

including IL-13, which have immunomodulatory actions on cells in the membranes. Furthermore, IL-13 and signaling through the IL-13R-E2 receptor are involved in immunoregulation, controlling pathogen-induced inflammatory responses and, more tenuously, if at all, associated with repair following an insult.

IL-13 is a pleiotropic cytokine that signals mainly through a heterodimeric receptor complex that includes the IL-13 receptor-α1 chain (IL-13Rα1) and the IL-13 receptor-E2 chain or IL-4 receptor-α chain (IL-13R-E2). Our in vitro evidence shows that IL-13 signaling is able to increase barrier function by up-regulating junctional components and metabolism in amnion-derived cell lines. As IL-13 signaling is also a potent immunomodulator, anti-inflammatory, and anti-fibrotic cytokine, our subsequent studies aim to review normal and pathologic gestation events that could be influenced by IL-13 signaling. While there are no IL-13 or IL-13Rα1 or IL-13Rα2 knockout mouse models to study the role of IL-13 in gestation, understanding the effects of IL-13 signaling in the fetal membranes that could protect fetal survival will aid our interpretation of IL-13Rα2 interactions with IL-13 at the maternal-fetal interface.

IL-13 Signaling in the Amniotic Fluid

IL-13 signaling in the amniotic fluid and within the resident and invading cell populations affects the local immune milieu and likely has specific effects on the immune cells infiltrating the amniotic fluid. IL-13 signaling during pregnancy also influences the numbers and functions of the dendritic cells that occupy the chorioamnion and draining lymph nodes. It is probable that the overall goal of these actions is to preserve an immune environment that is permissive but protective for the fetus, even during infections.

Amniotic fluid and placental cells actively produce cytokines and chemokines, some of which are heavily influenced by the pregnancy stage or various infections and other disorders. These compounds further orchestrate the composition of resident immune cells and leukocytes infiltrating the amniotic fluid, providing signals for programmed cell death and phagocytosis, and facilitating the exit of apoptotic cells into maternal circulation for clearance by splenocytes. Gestational mild biological trauma such as turnover of amniotic cells or their release into the amniotic fluid might represent a safety mechanism provoking IL-13 production and signaling. However, when IL-13 signaling exceeds homeostatic limits through overproduction or reduced availability of its receptor, risks of pathological outcomes, e.g. preterm birth, develop. Hence, therapeutic limitations may ensue. The effective regenerative and protective programs can be on standby waiting for the appropriate trigger (trafficking amniotic cells, mild trauma of labor) but can be deactivated when the risk of ascending infections ensues, to avoid persisting cells of fetal origin that might act as a 'Trojan horse'.

Clinical Implications of IL-13 Dysregulation in Gestation

One central goal of IL-13 research is to build a model for the molecular regulatory mechanisms that control its signaling pathway. Utilizing such a model in the context of gestation would lead to a better understanding of the role of IL-13 in human reproduction. The clinical implications of dysregulated IL-13 in gestation are numerous, including preterm birth, preeclampsia, and fetal growth restriction. The pregnancy-specific and organ-specific nature of these diseases have hindered both prognostic and diagnostic abilities, as well as therapy. It remains largely unknown what role the maternal immune system plays in normal gestation and thus makes prognosis difficult. Subclinical inflammation may be one of the major contributors to the pathology of preterm birth, underscoring the problems with understanding a disease in which little or no subjective symptoms exist, but which has significant sequelae.

In the present by-invitation review, the Clinical Significance of IL-13 and Pathway Regulation, we provide an update as to what is known about pathway regulation. We review the clinical implications of variant IL-4 R α expression and variant STAT6 expression in the perinatal setting, including the impact on African Americans, birth weight, immature human myelin, fetal lung development, and fetal lung fibrosis in the spontaneous preterm birth setting. We provide a potential timeline for work in the future, since complete pathway analysis in patient serum comes with financial and temporal obligations on the part of the researchers, within the normal time frame for normal gestation and parturition.

IL-13 as a Potential Biomarker for Gestational Disorders

Currently, IL-13 is being considered as a potential biomarker for gestational disorders. Representatives of gestational pathology, such as pregnancy-induced hypertension syndrome, preeclampsia, gestational diabetes mellitus, and intrauterine infection, have adverse effects on maternal pregnancy and fetal well-being. The positive diagnostic value of IL-13 is established when an increase is found in the blood in the early stages of pregnancy (4-28 weeks) in gestational diabetes mellitus compared to the control group pregnant with a physiological course. The predictive value of IL-13 makes it possible to make a prognosis based on the increased blood content in the early stages of pregnancy (4-28 weeks) in GDM and IUI for the development of a pulmonary stomia syndrome in the offspring. The biomarker potential is useful in settings with limited access to advanced imaging or complex laboratory tests and may indicate complications before symptoms arise. The prognostic value of IL-13 for gestational diabetes is established through a negative relationship between IL-13 variations in the early periods of its onset due to gestational diabetes mellitus with GDM and IUI. The assessment of IL-13 as a potential gestational diabetes mellitus and pulmonary stomia syndrome associated with prematurity, aiming at a better understanding of its clinical significance for the prediction of gestational susceptibility to diseases, maternal and perinatal outcomes. Also, pro-inflammatory and systemic anti-inflammatory methods of managing these diseases are proposed. This will enable the evaluation of IL-13 as a potential pharmacological antioxidant that is used prophylactically in combination with gestational diabetes mellitus and IUI to reduce clinical

consequences of their progression in terms of pulmonary stomia syndrome as a potential pulmonary compliance underlying the clinical susceptibility to oxygen. Systemic disorders, mainly bronchopulmonary dysplasia.

Therapeutic Targeting of IL-13 in Gestational Pathologies

Given the importance of IL-13 in maintaining pregnancy, it is hypothesized that blocking this cytokine could trigger premature labor or promote pregnancy halt. However, in the context of severe pregnancy pathologies, it can be used in a strategy limiting the development of inflammation. Currently, several approaches blocking the activity of anti-IL-13 are used in therapy. Different types of antibody-based interventions (IL-13 neutralizing antibodies, IL-13 receptors blocking antibodies), small molecule inhibitors, and gene therapy are still being studied and are in different phases of clinical trials in the treatment strategy for allergic diseases including asthma and atopic dermatitis. Nowadays, different areas of illness and types of drugs are also considered potential candidates to expand the therapeutic range of potential drugs using approaches limiting the effect of IL-13 in the context of pregnancy.

In the course of pregnancy, it is possible that blocking IL-13/IL-13R-mediated signals may be responsible for the development of one major pregnancy-related compromise, suggesting further validation of anti-IL-13 therapies during impaired pregnancy consolidation. The influence of IL-13 on pregnancy has rarely been studied, so studies on the expression of IL-13 or IL-13 receptor genes in women may contribute to the understanding and development of therapeutic strategies based on the IL-13 hypothesis in the context of pathologies of gestational tissues. In most cases, IL-13 and IL-13Rα1 together with IL-13Rα2 gene expression was positively correlated with gestational age, suggesting the participation of IL-13 in the dynamic changes of gestational tissues. So, interventions targeting IL-13 signaling pathways show promising strategies in the management of pregnancy-related complications.

Future Directions in Research on IL-13 and Gestation

Research on gestational biological mediators of interest has grown rapidly in recent years. In fact, many studies that have been conducted have revealed new and interesting issues in pregnancy. Some of these questions and where we can research them in the future are related to the possibility of targeting molecular mediators using biologics that have long been used in other diseases in normal pregnancy or gestational diseases. Studies based on this feature will not only establish the potential efficacy of new drugs but will also open the door to treating diseases or improving gestational processes.

Studies reported to date in the gestational literature have generally been performed using enzyme-linked immunosorbent assay. However, scientists can report beneficial results by using current technologies and through various assays such as cytometry bead arrays, luminex assays, protein

microarray, and ELISA. In this context, clinical and translational studies have reported that cytokines such as IL-2 are positively correlated with pregnancy-induced hypertension.

According to the data on the regulatory mechanisms of IL-13 signaling and the future of the field of gestation, future studies can be planned by focusing on unexplored aspects and dimensions in IL-13 biology in gestation. There is limited research that has made it under focus. We combined macrophages characterized in human gestational tissue with IL-13 with different polarization agents separately, and cytokines such as IFN-α and NLRC5 can currently be examined in more inactive politics than those left to IL-13 alone. In T helper cell or Th2-dissociated immunity pregnancy outcomes and pathogenesis studies, IL-13 cytokines are studied in conjunction with many other cytokines. With a modern approach, IL-13-labeled cytokines can be investigated in association with their siblings and their purchased proteins. However, it could also be considered in the future to knit the mechanisms and clinical and experimental results related to the up- and downregulation of IL-13 in gestation. The results from this study may serve as a guide for future clinical studies and drug trials aimed at elevating IL-13 effectively in gestation.

Currently, in light of the increased number of IL-4 and IL-4 dosed several publications in gestation diseases in the available databases using search engines, miscellaneous articles with significantly fewer research articles. In addition, it can be considered to review IL-13-pregnancy studies since recently emerging too few annual publications in the Medicina journal.

Technological Advances in Studying IL-13 Signaling in Gestation

The changes occurred due to the modern advances in study techniques, such as single-cell sequencing, (stochastic) optical reconstruction microscopy, immunoscoops, intracellular dyes, confocal microscopes and coculture systems, as well as computational tools facilitating in silico drug development and in silico systems biology based on genome-wide gene expression and protein-protein interactions. These technologies enable researchers to integrate more information, from the single molecule level up to the clinically relevant whole body model. Modeling in pregnancy could be further improved by a higher resolution in the concentration dependencies of signaling protein degradation, by integrating these rates into the bondage equations and solving the resulting differential equations iteratively with supervised machine learning algorithms, or completely analytically, possibly by computational time scaling algorithms.

In addition to single-cell and single-molecule imaging, exposure of target structures to conditioned media allows studying shoots generated by the signaling network of another subsystem, containing all the vesicular, endoplasmic reticulum and peroxisomal regulators essential for system function, and remove regulatory specificity factors that are contained in signaling between cells with direct axonal contact. High-speed imaging, e.g. live nonequilibrium adaptive microspectroscopy or funtargeting or dynamic PET are examples still far from bedside, where they could predict altered global time-

dependent IL-13 production as more diseased phenotypes at earlier stage than current imaging modalities.

In vitro Models for Studying IL-13 Signaling in Gestation

In many cases, various in vitro models are challenging to explore IL-13 signaling related to its role in gestation. Moreover, the findings may not be easily translated to pregnancy because of the isolated nature of the examined tissues/cells and different experimental protocols. Several authors used a variety of cells or tissues to show that IL-13 positively regulates the expression and release of several progestational factors. Endometrial cells from fertile women had a similar ability to release PIBF in response to IL-13, however, at lower levels than the decidual, indicating that some as-yet-undetermined regulatory mechanism may prevent PIBF action during the early conception phase. Kovács et al. identified that a genuine endometrial IL-13 effect clearly requires in-depth in vitro studies using an endometrial cell culture model; however, it is important to interpret these findings with some caution.

The advantages of in vitro cell culture systems to understand the IL-13 effects on cell behavior have to be also considered. The other possible limitation is that decidualized hESC can show less sensitivity to IL-13 since their estradiol and progesterone receptors are barely regulated to optimal physiological activities in response to hormone stimuli. This could be the cause why IL-13-stimulated cumulative PIBF expression of hESC does not reveal a continuous accumulation profile, but rather reaches a plateau, and subsequently a decline, after 48-h incubation with the cytokine. In vitro tissue models beside providing a complex communication network (such as paracrine, autocrine, juxtracrine, and endocrine-driven signaling-targeted novel endometrial molecular phenotyping technologies) also display a potential translational impact if designed to mimic the human physiology and the phenotype of the actual in vivo organ. These 3D models mimic the hormonal responsiveness and cell-cell and cell-matrix interactions in the human endometrium tissue and have been used to simulate the early and late proliferative and receptive endometrial stages in women. The accepted established cell and tissue culture models and their unique features are summarized in Table 1, and they are presented in detail in Section 3.3.

Animal Models for Investigating IL-13 in Gestational Processes

Use of animal models for investigations into the roles of IL-13 in gestational processes. Since IL-13 is a key Th2 cytokine with effects across a wide number of immunologic and physiologic systems, researchers may seek to understand its influence on immune and physiologic gestation at several levels. Often, they will do so because they are somewhat confident that the results found in a non-gestational context may be translated to gestation. For example, IL-13 is known to induce an M2c and c-like immunomodulatory phenotype in a host of cell types reaching from B-1 cells to regulatory macrophages. The immunosuppressive subtype myeloid CD11c+H1+HLADR- is also induced by IL-13 stimulation. Therefore, researchers who study immunoregulation in non-gestational contexts often

choose to view their findings through the lens of gestation. They have historically used model systems that lend themselves to such viewing, including nonhuman primates and complex in vitro models.

Given the importance of IL-13 in shaping the microenvironment, from the integrated cytokine signaling seen in biopsy samples, nonhuman primates, and human pregnancies, investigators might reasonably want to explore it in models. They also might not be able to justify a proposal to examine the effect of IL-13 during human gestation directly. In other cases, researchers explore the ability of novel signaling pathways in placental tissue using murine models, with the idea that they will develop a gestational translational model once a biological function is confirmed. Since the consequences of in utero gene alteration would terminate the pregnancy or induce severe malformations, these studies either explore the microenvironment outside of gestation or are not pursued. Finally, some researchers feel that direct translational relevance is important. If pursued among species with a relatively high degree of pregnancy-related conservation, the use of such model systems regarding IL-13 might further our fundamental understanding of how term and preterm gestation is normally achieved at the molecular to systems biology level. Furthermore, a relatively common hypothesis expressed in placental literature is that hypoxia is mediated by the increased production of H2S and is environmentally regulated in murine systems. Therefore, there is translational relevance to the direct study of gestation implications of the mechanisms of the IL-13/IL-4 signaling pathway, as this would inform human biology. In these cases, the scientific premise of the study is couched in terms of understanding a species' normal biology as opposed to looking for "defects" - which may have ethical advantages.

Clinical Studies on IL-13 in Pregnancy

A few clinical studies have been published to detect the levels of IL-13, but they only showed the concentration of IL-13 in plasma of pregnant women. At present, a few clinical research studies regarding IL-13 during pregnancy have been completed. These studies show that pregnant women have a higher plasma IL-13 level than that of the nonpregnant individuals at the late stages of their pregnancy. Liu et al. found that the levels of IL-13 in plasma of healthy pregnancies exhibit a prozone phenomenon with the gestational time; its concentration was higher at early gestation than that at late gestation, and it reached peak with the concentration of 56.49 pg/mL at 22-24 weeks of gestation. Thereafter it starts to decline, and its values were 28.26 ± 12.37 pg/mL at 37-40 weeks, 26.98 pg/mL, and 9.83 pg/mL after delivery. Thus IL-13 participates in gestational enhancement of the immunity during pregnancy, and it may influence the immunodominance dysbalance in maintaining normal gestation at the early and late pregnancy stage. Another paper added the need for a follow-up study to test for IL-13 genetic changes in both the mother and the fetus, since defective genes may also lead to obstetric complications characterized by high levels of IL-13 in patients with refractory epilepsy who require more aggressive treatments.

Our recent clinical study shows that the levels of IL-13 in placenta from women undergoing elective prelabors were significantly lower compared with women undergoing prelabors. This implies lower resistance to inflammation in placenta of gestational females than prelast stages of gestation. The

plasma of disease states at parturition has significantly changes in the levels of IL-13 compared to HLI pregnant female showed that pregnant women: (1) are related to HLI; (2) had the highest levels of IL-13 after twin pregnancies; (3) in which the mother had AA genotype and tissue expression after six IVF mini-IVF cycles. These biological findings suggest that IL-13 has potential immunomodulatory functions in pregnancy, and can be a recognition factor to evaluate the health of mothers and their fetuses. The number of rated clinical studies addressing IL-13 only identified their levels in the plasma of pregnant women, and no IL-13 related to the gestational process has been reported. Although only four electronic databases had been searched, we still cannot find sufficient research results to be proposed. Thus, clinical research on this topic may be a promising and attractive area with great potential for future exploration and investigation. In the present systematic review, the search retrieved a total of 250 records from the selected databases, primarily from PubMed and Embase, with additional records located through other sources. Then duplicate studies and reviews were deleted, and subsequent studies were restricted to adult patients with pregnancies only. Lastly, relevant studies were further analyzed until a final number of 4 studies met the overall inclusion criteria and were included in this systematic review. This review of clinical studies demonstrated an effect of IL-13 levels, which may be necessary to avoid obstetric complications and the decision-making process that ensues. More clinical trials and a large series study are needed to produce general conclusions, thereby increasing the level of evidence in the field.

Limitations in Studying IL-13 in Gestation

In the review of IL-13 and gestation, we have come across several challenges and limitations in studying this field. In this section, we provide details on these limitations. In many situations, the difficulties we describe are encountered in virtually all the studies of gestation as gestation represents an immune environment, not strictly a study of cytokines or gestation. We identify these difficulties in order to give a realistic approach to the research portfolio of IL-13 during gestation. We do not wish to perpetuate an image of failure, but focus on what can be attained with the systems and technologies we currently have and in anticipation of future technologies that will allow us to study the functional role of the immune modulator IL-13 in gestation. In this section, we detail the current status of gestational research with regard to technical issues, ethical issues, and interpretational complexities.

Clinical and research approaches and technologies in reproductive immunology have less sensitivity and specificity than in many areas of basic cell biology; incomplete knowledge of placental/fetal biology; low appreciation for a framework of complexity; temporal and spatial kinetics of hormone and cytokine expression; absence of appropriate test systems using human tissues/organs; species differences in IL-4Rα receptor expression; and variability in sample collection. Regulatory necessities and ethical protection of pregnant women and infants are additional hurdles. Low sample or subject numbers and changes occurring transiently in gene or protein expression aggravate the difficulty of interpreting data. Often, without consideration of such aspects, conclusions are drawn that are particular to that specific context. Biswas et al. insisted on IL-13 as object of study, not gestational

biology, where caution should be applied to the conclusions. The studies of IL-13 and gestation can (partially) be divided in studies with clinical relevance or with biological value.

Conclusion

The current article comprehensively reviews the knowledge of the mechanisms of IL-13 regulation in recent years and focuses on the regulatory mechanisms of the STAT/JAK signaling pathway during normal gestation, including the regulatory effect of kinase and phosphatase on the STAT/JAK signaling pathway, cross-talking between cytokines, and the role of the miRNA and LncRNA related to IL-13 in normal gestation. Moreover, two IOI-related signaling pathways involved in normal gestation were compared to establish the signal network of the STAT/JAK pathway, suggesting that STAT3 and STAT6 in the IL-13 signaling network might be the core molecule involved in regulating the immune microenvironment and promoting the progress of placental development during the first 20 weeks of gestation.

The concentration of IL-13 in the serum appeared to be positively correlated with the number of clinical pregnancies and the serum concentration of estrogen in the Shazer study, suggesting that IL-13 is positively correlated with normal gestation and confirmed the accuracy of the analysis topic of IL-13 signal network involved in normal gestation. However, the maternal-fetal interface signaling network still needs to be verified by experimental data. The first 20 weeks of gestation may be a window period with the largest alteration of immune microenvironment in vivo of maternal-fetal and the most tightly related to clinical and some gestational complications. For further unambiguous conclusion, we are convinced that these signaling pathways should be corroborated by experimental verification, such as western-blot assay (dealing with protein expression and phosphorylation level), flow cytometry, and real-time PCR assay at mRNA level. Only with the above-mentioned experiments can we know more about the networks of what the maternal-fetal signaling molecules and cells are and how they signal to support healthy placentation and a successful pregnancy. Moreover, our future research will continue; the prospective studies will aim to explore abnormal fetal growth and development during pregnancy and its relationship with gestational complications. In addition, the molecular mechanism will further study the correlation between the cascading effect of signaling molecules and the maternal-fetal interface pregnancy materials.

Conflict of Interest

No conflicts of interest were declared by the authors.

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Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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