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Review Article

Role of angiogenic factors in recurrent pregnancy loss

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ABSTRACT

Women with recurrent miscarriage (RM) often have abnormal NK cell activity. Uterine NK cells produce angiogenic factors and various interleukins. Human endometrium that expresses a variety of angiogenic growth factors and cytokines (NK-cell) may play a critical role in the abnormal endometrial angiogenesis which affect both conception and fetal development. Women with RM also have intrauterine growth restriction (IUGR) after conception. It has been shown 12-15% of women in their initial stage of pregnancies miscarry. The occurrence of miscarriage is known as having three or more continues miscarriage. This percentage is from 0.3 to 0.8% of all diagnosed pregnancies. Recurrent miscarriages have multiple aetiology. In this review article we will discuss a number of factors that may link to pregnancy complication. We focus on endometrial angiogenesis, vascular endothelial growth factor A (VEGF-A), human endothelium expresses messenger ribonucleic acids (mRNA) encoding VEGF-C, placenta growth factor (PlGF). The angiopoietins 1,2 and receptor for VEGF-A, VEGF-C, PIGF. The role of NK-cell, Interleukin-2 (IL-2) and IL-15 that may lead to up-regulation of VEGF-C and Ang-2 in secretory endometrium.

Keywords: Recurrent miscarriage (RM), Angiogenesis, VEGF, NK cell

INTRODUCTION

In pregnancy inadequate trophoblast invasion results in high resistance vessels and placental underperfusion result in multiple changes including hypoxia and oxidative stress, and disturbances in the maternal circulation that lead to systemic abnormalities.[1]

Parental chromosomal rearrangements have been Observed in ~9% of recurrent miscarriages[2], and women having experience of recurrent miscarriages due to uterine defects such as myomas, endometrial polyps or intrauterine adhesions at hysteroscopy are account about 20% of all miscarriages.[2,3] Also, any imbalance in the maternal immunological response , e.g. the formation of antiphospholipid antibodies[4] as well as increased sharing of major histocompatibility complexes between couples[5] have been shown as an aetiological factor for recurrent pregnancy loss but there may be many aetiological factors involve that need to be investigated. It is not clear yet, whether abnormal changes in the balance of the utero–placental vascular development and growth would involve in recurrent miscarriages, even though adequate and appropriate vasculo-and angiogenesis are fundamental requirements for the successful continuation of pregnancy. The vascular endothelial growth factor (VEGF) family that involves in formation of new blood vessels are; VEGF-A, VEGF-B, VEGF-C, VEGF-D and placenta growth factor, and their receptors VEGFR-1/Flt-1, VEGFR-2/KDR and VEGFR-3/Flt-4.[6,7] VEGF was first termed vascular permeability factor when it was partially isolated in ascetic fluid in 1983 due to its ability to increase vascular permeability.[8]

They play an important role in fetal blood vessel development. Experimental analysis shown that a mice deficient from the expression of VEGF or receptor for growth factor, die in utero due to inadequate vascular development.[7,9] Expression of angiogenic receptors seen in placenta[10-12] as well as Tie-1(tyrosine kinase with immunoglobulin and epidermal growth factor homology

domains) receptor that consider to act as a promoter of angiogenesis.[12] In pathological terms of stimulation of angiogenic growth factor, hypoxia considers to be a key stimulator for synthesis of VEGF family of growth factors.[13,14]

Lack of Tie-1 or its close relative Tie-2/tek (tunica interna endothelial cell kinase) expression results in vascular mal- development and intrauterine death.[15] The present review article discusses the role of expression of many angiogenic factors and their receptors as well as the role of NK cell as a cytokine on the endometrium and the outcome of these factors on pregnancy related complication.

The role of angiogenic growth factors had investigated beyond the other pregnancy related complication, for example; pre-eclampsia and placenta while there is no much evidence for the role of VEGF-C in pre-eclampsia but PlGF is considered to play a critical role in this process, as it is predominantly produced by the placenta and shown its significant down regulation in pre-eclampsia.[16] Hypoxic condition can cause down regulation of this process and at or even before the onset of pre-eclamptic symptoms[17] it could be a contributory factor to the symptomology of the disease.

In addition, several growth factors including fibroblast growth factor, transforming growth factors (TGF-α and TGF-β), keratinocyte growth factor, insulin-like growth factor 1 (IGF-1) and platelet-derived growth factor, as well as the inflammatory cytokines, interleukin (IL)-1α and IL-6, are also known to up-regulate *VEGF-A* expression.[13]

PLACENTAL GROWTH FACTOR

PlGF demonstrates 42% amino acid sequence identity with VEGF-A.[18] PlGF has been assigned to human chromosome 14 and consists of seven exons.[19] Alternative mRNA splicing of the PlGF primary transcript results in four isoforms, PlGF-1 ($PlGF_{131}$), PlGF-2 ($PlGF_{152}$), PlGF-3 ($PlGF_{203}$) and PlGF-4 ($PlGF_{224}$)[19] differing in secretion properties and binding affinities.[20] PlGF homodimers bind FLT-1 and NRP-1 while PlGF/VEGF-A heterodimers bind KDR and FLT-1/KDR heterodimers in vitro. PlGF is predominantly expressed in the placenta, heart and lungs. The exact physiological actions of PlGF are still not clear, however, evidence suggests a pivotal role for PlGF in regulating VEGF-dependent angiogenesis under pathological conditions.[21] There are few mechanism that is suggested, how PIGF stimulate angiogenesis.

(i) Stimulating endothelial cells via FLT-1.
(ii) Separating VEGF-A from FLT-1, allowing VEGF-A to activate KDR.
(iii) Recruiting monocytes/macrophages which have a crucial role in vessel growth.[20]
(iv) Inducing the secretion of VEGF-A from monocytes.[22]

POLYMORPHISMS IN RECURRENT PREGNANCY LOSS

The VEGF-A polymorphisms, −1154G/A, −2578C/A, +936C/T and−634G/C have been studied in women who have had recurrent pregnancy loss in a few ethnic groups. The VEGF-A −1154G/A polymorphism has been investigated in six studies of which three reported the association of the A allele with an increased risk for recurrent miscarriage[23-25] and the other three reported no association.[26-28]

The VEGF-A 2578C/A, +936C/T and −634G/C polymorphisms have not been associated with recurrent pregnancy loss[29-31] except in a recent study which reported a decreased frequency of the VEGF-A −2578A allele and an increased frequency of the VEGF-A −634C allele in recurrent pregnancy loss.[32] Of these polymorphisms, a recent meta-analysis demonstrated that the VEGF-A −1154G/A polymorphism was significantly associated with recurrent pregnancy loss.

THE PHYSIOPATHOLOGY OF HUMAN EMBRYO IMPLANTATION

The extravillous cytotrophoblast (EVCTs) invade the deciduas before it will capable of modifying the walls of spiral arteries. On the contrary prospective of implantation and inflammatory reaction, time and space are fundamental factor that separates these two processes as implementation occurs in a controlled manner. Any abnormalities that are involved in inhibition and stimulation of these factors may result in pregnancy related complication, such as preeclampsia. In order to invade the decidua, the trophoblast cells need both to recognize (via integrins and cadherins) the numerous constituents of the membrane and the extracellular matrix (ECM) and then break them down (with metalloproteases).

In order to invade the endometrium, the composition of ECM should be altered and this modification occurs by secreting a MMPs, transforming growth factor (TGF) and tissue metalloprotease inhibitors (TIMP). Invasion of trophoblasts can be affected by the production of cytokines that are released from immune system cells (NK cells, lymphocytes and macrophages) that are placed in the decidua.

Extracellular matrix (ECM) is a three dimensional structure that surrounding cell that stabilizes the cell structure and prevent a passive cell migration, adhesion of trophoblast cells to the ECM is require for activation of MMPs that are endo-peptidase and require for degradation of ECM component. Matrix metalloproteases (MMPs) are endo-proteinases that require the presence of Ca++ and Zn++ ions and comprise 13 members in three

families: collagenases (MMPs 1, 8, 13), which break down type I and III collagens; gelatinases A (MMP 2) and B (MMP 9), which break down gelatin, collagen IV and elastin; and the stromelysins (MMP 3, 7, 10 and 11), which have a broader spectrum. TIMP that is secreted by decidua blocks the activities of MMPs hence regulating the enzyme activity. During the first trimester, trophoblast cells secrete a number of MMPs which play a critical role in the invasion but the activity of MMPs balanced by the expression of TIMPs which inhibit its activity and thereby having a preventive effect on trophoblast's invasiveness. Furthermore, integrins can modulate MMPs expression.

Transforming growth factor β (TGF-β) is expressed at the foeto maternal interface from the first trimester through a term and inhibits trophoblast proliferation and invasion. TGF β1 and TGF β2 are essentially expressed by the villi and the decidua, respectively. Tissue growth factor β1 promotes formation of ECM (collagen and fibronectin, in particular), induces TIMP 1 expression and reduces EVCT migration by over expressing a typical subunit of integrin that is a part of plasma membrane receptor (α5β1). This over expression makes the EVCTs adhere more strongly to the ECM and activates the differentiation of the cytotrophoblast into a non-invasive syncytiotrophoblast.

ENDOMETRIAL DECIDUALIZATION

Implantation of the embryo occurs when the endometrial tissue and vascular embedded have reached a receptive level in the course of proliferative phase and the beginning of the luteal phase, under the influence of sex hormones, growth and angiogenic factors.[33]

Thickening of the endometrium depends on the secretion of estrogens during the follicular phase and is necessary but not sufficient for embryo implantation. Ideally, a thickness of 8 to 12 mm between the two outermost endometrial leaflets is required in the peri-ovulatory period. Estrogen level is a fundamental factor for keeping the endometrium thickened.

Except during pregnancy, the ECM is composed of collagens I, III, V and VI, fibronectin and periglandular tenascin deposits. During decidualization, the endometrial stromal (decidual) cells produce a pericellular matrix composed of collagen IV, laminin and heparan sulphate. Substantial hydration of the stroma occurs at the same time. These changes in the composition and hydration of the ECM make it easier for the EVCTs to invade the decidua. The modified ECM also establishes close contacts with the lymphoid cells present in the decidua, thereby increasing the cellular interactions between trophoblast and lymphoid cells. After ovulation, the luteal secretion of progesterone will prompt the endometrium to become progressively hypoechogenic as it moves towards the uterine cavity.[34]

In cases of pre-ovulatory progesterone secretion, the endometrium will display early maturation, which is unfavorable for embryo implantation. Hydrocortisone treatment enabled these women to achieve follicular-phase progesterone rates below 1 ng/ml, re-establish normal endometrial maturation and obtain pregnancies.[35]

This endometrial maturation is also associated with growth of the spiral arteries (branches of the uterine arteries), which will then carry maternal blood toward the intervillous spaces of the placenta. The growth rate and structure of the spiral arteries depend on ovarian hormonal secretions. Under the influence of oestrogens, the spiral arteries' diameter increases as they grow longer and become progressively twisted. This endothelial proliferation continues during the luteal phase and the first few weeks of gestation. Growth factors also play a role in neoangiogenesis, levels of fibroblast growth factor b (FGFb, a powerful angiogenic factor) are increased by oestradiol and inhibited by progesterone, vascular endothelial growth factor (VEGF, stimulated by oestrogens and hypoxia) is mitogenic for endothelial cells and increases vascular permeability, whereas platelet-derived growth factor (PDGF) contributes to angiogenesis and to the growth of smooth muscle cells. This neoangiogenesis can be disrupted by disease states that are associated with microangiopathy, such as insulin-dependent or gestational diabetes and chronic or gestational hypertension after a kidney transplant.

DISCUSSION

Aside from being a potent vascular endothelial mitogen, VEGF Also maintains newly formed capillaries, induces vascular permeability and macrophage chemotaxis.[7] It May thus give a novel aspect to the aetiology of recurrent miscarriages. In tissues of uncomplicated pregnancy, immunoreactivity of VEGF is observed in the placental trophoblasts as well as in the deciduas.[11] However, the cyto-and syncytiotrophoblasts of women with missed abortion (MA) or blighted ovum (BO) shown negative for VEGF, giving support to the hypothesis of the role of VEGF in the pathophysiology of miscarriage. In the placenta, vasculogenesis, i.e. The newly synthesised blood vessels , accounts for the bulk of the new vessel formation during the first trimester, and is initially observed around day19 post-coitum.[36] VEGFR-1 and VEGFR-2 have largely been regarded as specific for vascular endothelial cells, and are essential for embryonic vascular development.[9] Their mRNA signal has been detected in human placenta that have been studied at 9 weeks of gestation.[11] In women with MA, no difference in the VEGFR-1or-2 immunoreactivity in the placental vascular endothelial was observed. It may therefore be speculated that a possible association between recurrent miscarriages and altered expression of VEGFR-1 and-2 in the vascular endothelium would rather relate to the maternal deciduas than to the placenta. Interestingly, in the two trophoblast layers lining the placental villi, VEGFR-2 immunoreactivity was constantly stronger in

the cytotrophoblasts underlying the syncytiotrophoblasts. Such pattern has been shown for VEGF and VEGFR-1[11], whereas for these two antigens its been observed strong staining in both types of trophoblasts. Altogether, these results may implicate a role of VEGF and its receptors in the function of trophoblasts, cells that secrete a wide range of proteins and hormones, and, consequently, have an important endocrinological and nutritional role.[37,38] VEGF-C is a potent cytokine for the lymphatic vasculature, but it is also capable of inducing vascular endothelial cell growth.[6] It is being shown placental expression of its receptor VEGFR-3 in stromal and vascular endothelial cells in the tissues of both women with recurrent spontaneous abortions as well as controls. Interestingly, the endothelium of decidual blood vessels showed negative for VEGFR-3 in all study groups. There are numerous VEGF receptors recently known that involve in the pathology of recurrent miscarriage but earlier both Tie-1 and Tie-2 receptors were considered blood vascular endothelial specific markers.

Interestingly, Tie-1 and Tie-2 were also expressed in a trophoblast population invading the maternal decidua, whereas VEGF or VEGFR-1,-2or 3 were not. Tie-1 and Tie-2 might thus also play a role in implantation, where the trophoblast invasion is a crucial event. Human endometrium expresses mRNAs for VEGF-C, PlGF, Ang1, Ang2, and the receptors like Tie-1, Tie-2, and Flt-4. Cyclic changes in mRNA levels for VEGF-C, PlGF, Ang2, and Tie2 were detected. It is being shown that uNK cells contain high levels of mRNAs for the angiogenic growth factors, VEGF-C, PlGF, and Ang2.

VEGF-C mainly stimulates lymphatic endothelial cell proliferation and migration via the VEGF-R2 and -R3 receptors that are present in the endometrium.[39] Conversely, PlGF acts only through the VEGF-R1 receptor.[40] Expression of both of these angiogenic growth factors are limited to uNK cells. The highest levels of expression were found in the midsecretory phase of the cycle, which is coinciding with increased lymphocytes in the endometrium.[41] Ang2 expression was also restricted to uNK cells. These differential effects are not the direct consequence of progesterone, since uNK cells do not express either of the progesterone receptors.[42] It is clear that factors produced within the endometrium can affect endothelial cells. For example, it has been reported previously that a slight, increase in endothelial migration occurred when cells were treated with supernatants from the cultured midsecretory phase endometrium. Uterine NK cells are characteristically situated just beneath the epithelial glandular layer and around spiral arterioles.[43] The localization of uNK cells suggests a possible correlation between local VEGF-A production and the location of these cells. The highest levels of VEGF-A are found in glandular epithelium and vascular smooth muscle surrounding the spiral arterioles.[44,45] Although most VEGF-A is secreted from the luminal surface of epithelial cells[46] sufficient amounts may diffuse across the epithelial basement membrane to induce a gradient affecting the subepithelial complex of capillaries.

The evident that uNK are strongly participating in vascular remodelling are due to the fact that Ang2 is expressed by uNK cells but Ang1 is expressed throughout the cycle at low concentration.

Ang1 is assumed to function by mediating the dialogue between pericytes and vascular smooth muscle and the endothelium, so as to promote the stability of blood vessels. Ang2 is highly expressed only at the site of vascular remodelling in the adult, notably in the ovary.[47] Ang2 mRNA is found to be expressed together with VEGF at sites of vessel sprouting and in growth or in the absence of VEGF at sites of obvious vessel regression (*e.g.* atretic follicles). NK cell activity is regulated by cytokines, and several induce the differentiation and activation of NK cells. IL-2 and IL-15 are regulators of NK cell activation, and most activated NK cells express cytolytic mediators.[48]

It is being reported that IL-15 is produced by cells in endometrium and decidua and like IL-2, is capable of inducing proliferation and augmenting cytotoxic activity in decidual NK cells.[49] It is been demonstrated that decidual NK cells expressed several angiogenic growth factor mRNAs, but also showed that uNK cells activated by IL-2 increased VEGF-C mRNA expression, but not Ang2 mRNA expression. It has been observed, there was an increase in levels of VEGF-C mRNA expression in decidual NK cells treated with IL-15, but the difference was less than that after treatment with IL-2, and the response was more variable. Cytokines regulate the expression of the lymphatic endothelial mitogen VEGF-C.[50] IL-1b, also expressed in the endometrium, induced a concentration and time dependent increase in VEGF-C. TNFa and IL-1a also elevated VEGF-C mRNA steady state levels, but Ang1 was down-regulated by IL-1b.[51]

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