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Review Article

Beta-2 GPI induced tissue factor and placental apoptosis for the pathophysiology of pregnancy loss in antiphospholipid syndrome

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ABSTRACT

Based on large concurrent studies on human and in vivo results from experimental animals, it is evident that antiphospholipid syndrome (APS) plays a vital role in pregnancy failure in human being. Many underlying pathophysiology including venous thrombosis, thrombocytopenia and placental apoptosis have been demonstrated for the APS-mediated pregnancy loss. On the other hand, Tissue factor (TF) remains considered as a crucial factor for pregnancy morbidity in women with APS globally. Hence, we hypothesize that TF and/or beta-2 glycoprotein – I (β2GPI)-induced TF might play an important role for the increased index of apoptosis in placenta, especially during early stages of fetal development. Further, this could represent as potentially preventable etiology of APS-mediated pregnancy loss in women.

Keywords: Antiphospholipid syndrome, Tissue factor, Placental apoptosis, Recurrent pregnancy loss

INTRODUCTION

Antiphospholipid syndrome (APS), also known as Hughes syndrome, is an acquired autoimmune disease playing a crucial role in immune-mediated reproductive failure in women.[1] It is a phenomenon directing antibodies in blood against anionic phospholipid-protein complexes resulting in recurrent spontaneous abortion, deep venous thrombosis and systemic lupus erythematosus.[2-4]

Even though APS plays a major role in recurrent spontaneous abortion in women, the exact pathogenic mechanism(s) remain to be elucidated. Number of animal models has been developed to understand the mechanism of action of antiphospholipid antibodies in pregnancy failure and demonstrating different manifestation of aPL in APS including placental dysfunction.[5-7] Among the various underlying mechanisms have been suggested for the manifestation of APS, most common phenomenon observed between these diseases is abnormal development and functions of placenta, because, survival and growth of the fetus critically depend on the placental growth and aging.[8-10]

It forms the interface between the maternal and fetal circulation, facilitating metabolic and gas exchange as well as fetal waste disposal. For overall wellbeing of the fetus, placental development is most important and it depends upon the differentiation and invasion of the trophoblast in placenta. The formation of mammalian placenta involves processes required for tissue homeostasis and morphogenesis as well as cell death. Commonly, the homeostasis is managed by the physiological process of apoptosis (or programmed cell death), which is an important phenomenon for the

regulation and aging of the placenta.[11] Experimental researches in APS focusing several issues with regard to the mechanisms that cause the various clinical manifestations are still subject to debate. Placental abnormalities, activation of tissue factor (TF) and placental thrombosis are considered as crucial issues in aPL-mediated pregnancy complication or fetal loss in women.[12]

Tissue factor expressed on neutrophils in response to C5a contributed to the respiratory burst, trophoblast injury and pregnancy loss induced in APS. TF is the major cellular initiator of the coagulation protease cascade but also plays an important role in inflammation too. For many years, the antiphospholipid syndrome was considered as thrombophilic disorder but recent studies on human and mouse have shown the importance of inflammation in the pathogenesis of aPL-induced pregnancy loss.[12,13]

As previously stated, the association between aPL and pregnancy loss have been mediated through various pathogenic mechanisms. Besides thrombosis, evidence indicates that alternative aPL-mediated pathogenic mechanisms impede placental functions, involving direct targeting of maternal deciduas and trophoblast.[13,14]

In human, apoptosis has been described in the placenta of both normal and abnormal pregnancy. Therefore, recent studies elucidated the impact of placental apoptosis in the aspect of placentation and pregnancy complications in autoimmune diseases like APS.[15] Based on the crucial role of TF and inflammation in aPL-induced pregnancy loss, it would be interesting to understand the mechanism of TF in contributing inflammation either by increased index of apoptosis in placenta for aPL-induced pregnancy loss.

Background of hypothesis on role of TF

Numerous *in vitro* and *in vivo* studies for the past few decades support a direct role for aPL in provoking inflammation followed by thrombosis in the placenta by inducing over expression of TF on the surfaces of circulating monocytes and activating complement proteins in feto-maternal interface.[16] It is reported that complement activation is involved in aPL-induced TF expression on neutrophils.[17]

Furthermore, the synthesis and expression of TF on the surface of neutrophil is mediated by complement component C5a through interaction with C5a receptor. Interestingly, neither TF over expression nor pregnancy failure was observed in mice deficient in complement component C5a receptor (C5aR) treated with aPL demonstrating the importance of C5a-5aR interaction in TF expression and fetal death in this APS model.

The role of TF in inducing fetal loss was demonstrated by *in vivo* study; however, the role of TF in fetal loss through the placental dysfunction is not clearly defined. Since the research on autoimmune APS in regard to pregnancy complication and placental inflammation is still under study, the exact pathogenic mechanism involved in this aspect is not yet known and large prospective studies are needed. Therefore, the present hypothesis is aimed to investigate the biological role of TF in the aPL-dependent pregnancy failure through the activation of Toll-like Receptors (TLRs) in trophoblast which in turn to alter the apoptosis in placenta.

Supporting evidence and evaluation of TF-mediated placental apoptosis

The signal transduction mechanisms involved in aPL-mediated cell activation have been the centre of interest for many researchers. How pathogenic aPL recognition of phospholipidbinding proteins on the cell surface elicits a transmembrane signal to modify intracellular events is not completely understood.

Further, monocytes stimulated by monoclonal anti β2GPI antibodies from patients with APS induce phosphorylation of p38 MAPK, a locational shift of NFkB into the nucleus and up-regulation of TF expression. Such activation was not seen in the absence of β2GPI, indicating that the disturbance of monocyte by anti- β2GPI antibodies is started by interaction between the cell and the autoantibody-bound β2GPI

Previous studies demonstrated about placental apoptosis and APS.[11,15] A subsequent study in other pregnancy complications such as intra uterine growth restriction (IUGR), preeclampsia and fetal growth restriction (FGR) reported that a great incidence of apoptosis play a leading role in such complications.

The molecular mechanisms of apoptosis in humans are complex and involve an ever-expanding list of signaling molecules. Those includes immune-mediated central executioner of apoptosis. It is unclear whether the regulators of apoptosis are differentially expressed in placentas of APS and having any significant role in its pregnancy complications.

This hypothesis fits well with the potential involvement of pattern recognition receptors such as TLRs in sensing TF and triggering an inflammatory response as well as apoptosis. As TLR2 and TLR4 have been reported to contribute to endothelial cell and monocyte activation by β2GPI-dependent aPL, one can speculate that the combination of the effect of TF along with the perturbation of TLR function mediated by the autoantibodies overcome the threshold for triggering apoptosis.

As for as we known, TF is expressed on neutrophils in response to C5a contribute respiratory burst, trophoblast injury, and pregnancy loss with positive aPL. TF is the major cellular initiator of the coagulation protease cascade but also plays an important role in inflammation.

Complexes of TF/Factor VIIa (TF/FVIIa) and TF/FVIIa/Factor Xa (TF/FVIIa/FXa) as well as FXa and thrombin induce proinflammatory signals by activating protease activated receptors (PARs) and inducing the expression of TNF-α, interleukins, and adhesion molecules.[18] The main candidate receptors for β2GPI-mediated TF on cell membranes are TLR-2 and -4. Several groups showed that TLR2 and TLR4 are involved in aPL-mediated cell activation, and previous reports have been published on the direct binding of β2GPI/TF to TLR2 and TLR4.[19]

It is documented that the placental trophoblast and decidual cells are expressed these two receptors; however, the putative role of β2GPI-mediated TF in apoptotic regulation is not yet demonstrated on this cell receptors.

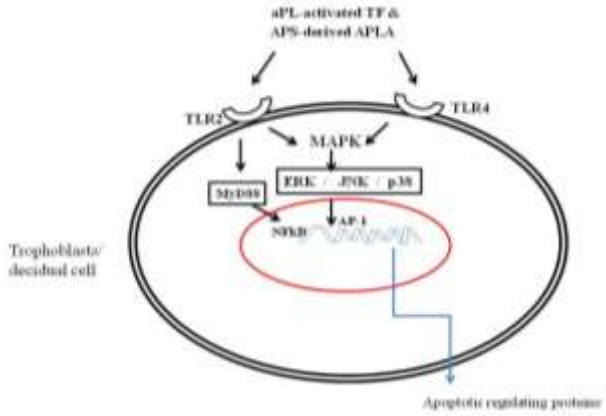

Figure 1: Illustrative diagram of TF-induced expression of apoptosis regulation proteins in trophoblast or decidua of placenta.

As a whole, TF (in particular β2GPI-depedent) bind to trophoblast and decidual via TLRs and initiate the many cellular functions for up-regulation including the apoptosis. By virtue of these potential information, we hypothesize that the β2GPI-induced TF might play a vital role for the impairment of placental apoptosis and could be another etiology for pregnancy failure in APS (Figure 1).

DISCUSSION

Apoptosis has been described in trophoblast and the importance of apoptosis cascade for the normal function of the trophoblast has become obvious. As intrauterine growth restriction proved to be one of the serious conditions in fetal loss, this occurs due to changes in apoptosis regulation in extravillous trophoblast resulting in the shedding into the maternal circulation.[20]

When considering apoptosis in placenta, most previous studies revealed that the abnormal placental apoptosis leads to dysfunction of the placenta, and causes fetal damage and intrauterine growth retardation in women. It is reported that anti- β2GPI reduces the Bcl-2/Bax ratio without clear evidence of apoptosis in human trophoblast *in vitro*.[21] Little is known about the mechanisms of apoptosis and its up-regulation in APS positive placental tissue during abnormal pregnancy.

In addition, the exact mechanism and full complement of regulatory factors involving apoptotic cell death in the human trophoblast layer are unknown. Many molecules are associated with the induction and prevention of apoptosis in different mechanism. Most of the studies revealed that Bcl-2 might be a key factor in evoking apoptosis up-regulation in pregnancy complication.

In complicated pregnancies, a significant increase in the number of apoptotic cells may overwhelm the macrophages and promote macrophage production of pro-inflammatory cytokines, which further enhances trophoblast cell death by affecting the Bcl-2 expression. As described previously, aPL might affect the Bcl-2 ratio like that of anti-beta2 in placenta, which may further promote programmed cell death in placenta.[22,23]

There is also evidence for dynamic balance between inflammation in placenta and pregnancy loss through the activation of intracellular signaling cascade by β2GPI/TF.[18,21] However, there is no direct evidence to know whether the aPL-activated TF involved in over expression of apoptosis in placenta. however, infusion of aPL with or without dimeric β2GPI, altered expression of endothelial adhesion molecules and TF expression have been reported in arterial endothelia which support a key role for aPL in causing vascular abnormalities and pregnancy complications.[24,25]

However, it is not evident that how it activates intracellular signaling pathways to activate apoptotic regulatory proteins such as caspases (-3 and -9), Bcl-2, apoptotic activation factor (AAF) through different receptors in trophoblast and/or decidual cells. There is no sufficient data available to know how these multiple pathogenesis together led pregnancy complication in APS.

The emerging evidence has been demonstrated that various different cell surface receptors and intracellular pathways are activated by aPL and/or β2GPI. These cell surface interactions and activation of intracellular pathways are only partially characterized. These processes are triggered by the interaction of pathogenic aPL with monocytes, endothelial cells (EC), platelets, trophoblast and endometrial cells, as well as plasma components of the coagulation cascade.[16,17,26-28]

Therefore, understanding the proposed hypothesis would stand for a growing evidence for the importance of placental apoptosis through TLRs in the pathogenesis of aPL-mediated pregnancy loss. Pathogenic aPL bind to phospholipid binding proteins of which β2GPI is the best characterized. Hence this hypothesis give an opportunity

to how the β2GPI-mediated TF leads to recruitment of cell surface receptors (TLR2 and TLR4) and perturbation of intracellular signaling pathways that alter the behavior of the cell ultimately causes the fetal damage.

CONCLUSION

Continuing research focused on cell receptors and different intracellular signalling pathways involved in the cell activation mediated by β2GPI, TF and aPL substantially advance the understanding of the pathogenic mechanism in APS.

However, further studies are needed to clarify the biological role of the numerous potential receptors and their activation proposed for cellular modification and function. Potential results would give an idea to how relatively homogenous aPL mediates different pathogenic mechanism for the manifestation in APS. The impact of this study could provide the key for effective therapeutic strategies for the obstetrical complications of APS through different pathogenic mechanisms.

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