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Transforming Growth Factor – B1 and Pre-Eclampsia: Perspectives for Novel Therapeutic Modalities

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Abstract

Breakdown in the immunoregulatory mechanism as well as dysregulated angiogenesis are critical contributors to the obstetric disorder, Pre-eclampsia [PE]. The pleiotropic cytokine, Transforming Growth Factor-β1 [TGF-β1], with its immunosuppressive and angiogenic functions appears to be a promising candidate for prospective therapies in PE, as gleaned from a survey of candidate gene association and biochemical investigations. The current article endows with a background and gives inkling for the plausible therapeutic strategies for PE employing TGF-β1, given the veracity that proper curative procedures are not yet existent for this disorder.

Keywords: Pre-eclampsia; Transforming Growth Factor–β1; Gene Polymorphisms; Therapeutics

Introduction

Pre-eclampsia [PE] is a pregnancy specific vascular disorder resulting in considerable maternal and perinatal morbidity and mortality. Clinically and symptomatically PE is characterized by hypertension and proteinuria after the 20th week of gestation. The incidence of PE in the United States and European countries ranges from 2-5% and the incidence are much higher in the developing nations, 8-10% of all pregnancies in India [1]. PE is estimated to be the leading cause of maternal mortality in Latin America [2-4].

Descriptions of various pregnancy related physiological abnormalities were made as early as the 4th century and it was only during the 18th century, that eclampsia was distinguished from epilepsy. Since then (circa. 19th century), classification of eclampsia continued to be refined and the term Pre-eclampsia was introduced in medical textbooks after 1903 [5]. The present classification of PE is based on the report published in the year 2000 by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [6].

Manifestation of PE is deemed to be a complex disease process encompassing interplay of genetic, environmental, and immunoregulatory factors [7]. Foremost among a host of factors to beget PE are dysregulated angiogenesis and accentuated maternal systemic Th1 type of inflammatory response. In an effort to comprehend the genetic basis of PE, a recently performed genome-wide analysis suggested TGFB1 as one of the key candidate genes for PE [8-10].

Further, a growing body of evidence confirms that TGF-β1, a25KDa homodimeric protein gains prominence in the pathogenesis of PE, by virtue of its pleiotropic nature. TGF-β1 is believed to control proliferation and differentiation of several cell types including foetal cytotrophoblasts and regulation of trophoblast invasion. It also influences embryonic growth, development as well as apoptosis of endothelial cells. Fundamentally, this gene is considered as one of the master regulators for monitoring the number ofFOXP3+ regulatory T cells [Tregs], which play a crucial role in the maintenance of self-tolerance, physiological immune responses and moreover mediates maternal tolerance to the paternal antigens of the foetus [11-13].

A recent report by Goske et al., with an impressive sample size showed an association of two specified polymorphic variants of TGFB1 gene with PE and emphasized the importance of carrying out further follow-up studies taking multiple immunoregulatory markers into consideration [14]. Investigations of such nature concurrently might provide insights into the underlying pathophysiology of the disease and novel drug targets.

Polymorphic variants of TGFB1 gene and serum levels of TGF-β1 in PE

Genetic polymorphisms in TGFB1 gene, which is mapped to human chromosome 19 [19q13.1-13.3] [15], have been studied for their association with PE. A couple of SNPs each in the promoter [-800G>A and -509C>T] and in the coding region [+869T>C and +915G>C] of TGFB1 gene were the widely explored variants for their influence on PE, among various ethnic groups [16-21]. Owing to their location and significance, these gene variants were experimentally demonstrated to impact the circulating levels of TGF-β1 [22-23]. The latest association study of Goske et al., has reported a significant link between TGFB1 T-T and C-C haplotype blocks [corresponding to -509C>T and +869T>C polymorphisms] and PE in south Indian women.

Analyses of circulating concentrations of TGF-β1 have been performed in patients with PE, which however, have engendered inconsistent results perchance due to variation in the sampling methodology and/or gestational age [24-31]. Two current publications dealing with populations of varying ethnicities, point out towards reduced levels of TGF-β1 in the second trimester of pregnancy and increased levels during the third trimester and post-delivery in PE women, whereas the scenario is reported to be opposite in normal pregnancies [32,33] (Figure 1a).

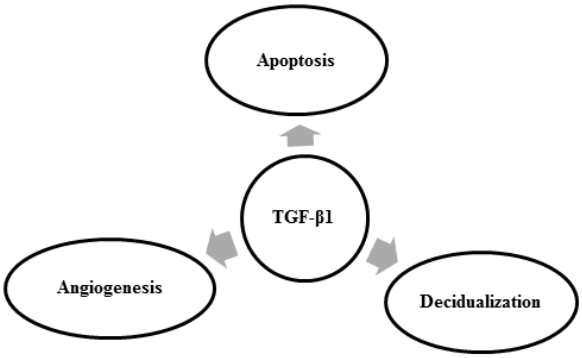

Figure 1a: Major functions of TGF-β1 signalling in pregnancy.

In the light of the existing literature and based on the functional significance of the SNPs studied, Goske et al., argue that the intermediary levels associated with heterozygous genotype confer a selective advantage and might protect women from PE, though their study did not involve measurement of serum TGF-β1 levels [22,23]. Their hypothesis was based on the premise that, elevated levels of TGF-β1 might predispose the pregnant women to infections in an environment of high prevalence of infectious agents, whereas, reduced levels could cause impaired angiogenesis, therefore, they proposed that both the extremities might have their impact on the pregnancy as well as its outcome. Further, they stated that women who are heterozygous for the two studied polymorphisms have intermediary levels of TGF-β1which confer a selective advantage over the disease. Nonetheless, they proposed that systematic studies on the circulating and local concentrations of TGF-β1 levels in relation to genotypes may clarify this aspect (Figure 1b).

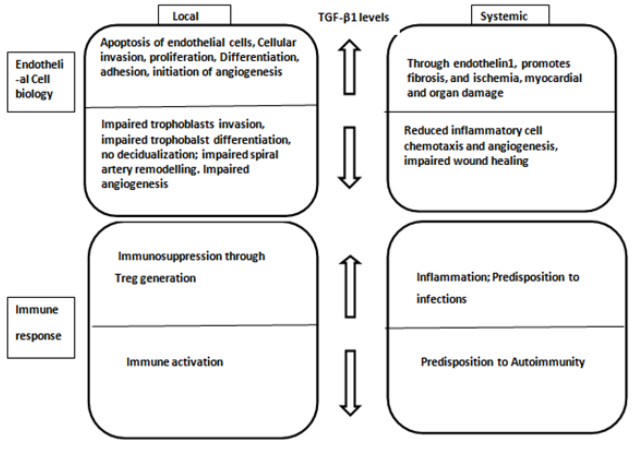

Figure 1b: Local vs. systematic effects to TGF-β1 in endothelial cell biology and immune response.

Current therapeutic interventions for PE

PE as a malady of feto-maternal health has been in existence for several centuries and the etiology of the disease is still unexplained. It is only in the late 20th century that a model for the disease pathophysiology has been proposed. However, the treatment even now remains symptomatic [5]. Contemporary treatment modalities vary based on the time of onset of PE and its severity. The only existing cure accessible for late onset PE is to proceed for delivery of the foetus to avoid further complications to either of the lives involved. Early onset PE presents a difficult situation for the health care provider who has to balance the risk of delivery of a premature child with that of the life-threatening obstetric complications of maternal physiology. Milder version of early onset PE would involve recommendation of simple relaxation and bed rest along with certain dietary supplementation. Dealing with severe early onset PE which is accompanied by seizures, is more challenging and usually involves close monitoring of blood pressure accompanied by administration of anti-hypertensive and anti-convulsing medications. These drugs, however, need judicious administration allowing for their possible teratogenicity effect and potential interference with lactation [34].

Therefore, there is an extremely pressing necessity to develop novel alternative remedial modalities for PE. In line with this notion, a recent study suggested an apheresis based treatment for reduction of plasma levels of a placental protein Flt-1, whose elevated levels are detrimental for normal pregnancy [35]. The statement of Goske et al., raises hopes about enhanced treatment options for PE, relative to the present situation of administering drugs with potent side-effects.

TGF-β1 and therapeutics

Thus far, TGF-β1 as clinical therapeutic target has shown promise in a multitude of diseases such as cancers, autoimmune associated inflammatory conditions and cardiovascular disorders. Monoclonal antibodies like GC-1008 and Metelimumab (CAT 192), small molecule inhibitors like Ly550410 and Ly580276 targeted for blockading the activity of TGF-β1 and TGF-β1 kinase respectively, have been evaluated in phase I and phase II clinical trials of various carcinomas [36].

Likewise, systemic administration of exogenous TGF-β1 protein and TGFB1 based gene augmentation therapy have shown to be fine impending therapeutic targets in animal models of a wide range of autoimmune and chronic inflammatory diseases [37]. In addition, TGF-β1 inhibition and antagonism has been researched upon in combating diverse cardiovascular ailments such as arrhythmias and cardiomyopathies [38].

Additionally, the viability of systemic TGF-β1 administration is challenging, given the pleiotropism of the immunomodulatory molecule. However, extensive investigations on the mode of delivery and dosage, and the possible spin-offs of TGF-β1 therapy in animal models are warranted for realizing the therapeutic potential of TGF-β1 (Figure 2).

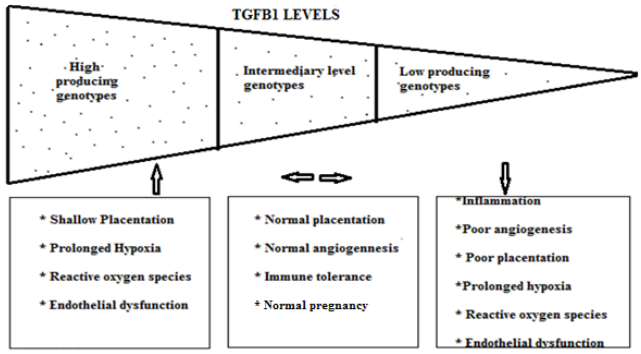

Figure 2: Depicting the impact of TGF-β1 gene polymorphisms on PE. The intermediary levels associated with heterozygous genetypes confer a selective advantage and protect women from PE.

A host of published articles established that, seminal fluid induced immune tolerance towards the foetus by activating Tregs, mainly due to the presence of the cytokine TGF-β1 [39-41]. The substantial decrease of Tregs in women with PE could most likely be ascribed to the lack of optimal TGF-β1 [42,43]. Differential TGF-β1 secretion during diverse stages of pregnancy has been demonstrated to influence optimal angiogenesis and placentation for successful pregnancy outcome [8,44]. Hence, TGF-β1 shows great promise as a potential therapeutic candidate for PE. Exogenous administration of TGF-β1 could hold hope of rectifying the optimal concentrations in a scenario of abnormally low levels. Alternatively, in the setting of elevated TGF-β1 levels, therapeutic intervention could involve employing monoclonal antibodies for blockade of TGF-β1 signalling. In addition, a further strategy would be to have a cell-based therapeutic procedure by employing Tregs, for achieving immunoregulation in PE.

Future Directions

As mentioned earlier the levels of TGF-β1 in healthy individuals are maintained in a delicately poised manner not only during pregnancy, but also at various stages of life. Carefully designed studies for elucidation of the fine fluctuations in serum TGF-β1concentrations would be of paramount use in equipping us to realise, appreciate and utilize the therapeutic potential of TGF-β1. Future studies must also take into account the consequences of the dichotomous actions of this pleiotropic cytokine before embarking on therapeutic endeavours.

Furthermore, emerging evidence points towards the potentiality of employing members of the TGF-β superfamily of proteins, soluble endoglin [a co-receptor for TGF-β1], proangiogenic and antiangiogenic proteins like placental growth factor and soluble fms-like tyrosine kinase 1 (sFlt1) respectively, as prospective diagnostic and therapeutic biomarkers [45-47]. Investigations on these additional biomolecules would facilitate generation of novel attractive therapeutics for PE.

In conclusion, the findings of Goske et al., propose that TGF-β1, the potent immunoregulatory cytokine, might be considered as one of the possible key players of PE pathogenesis. Their study raises multiple avenues for further research on immunomodulatory molecules and their role in PE. This would pave the way for novel therapeutic modalities in the future.

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Author Contributions

Parveen Jahan conceived the manuscript, helped with manuscript drafting and gave critical inputs. Goske Deepthi and Kamakshi Chaithri Ponnaluri together drafted and shaped the manuscript. Komaravalli Prasanna Latha provided valuable insights for drafting the manuscript.

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