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Hepatocyte growth factor and epidermal growth factor in HIV infected women with preeclampsia

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ABSTRACT

Objectives: Epidermal growth factor (EGF) and Hepatocyte growth factor (HGF) both have tyrosine kinase receptors (EGFR and c-Met) which upon binding, activates and regulates many important cellular processes such as cell survival, growth, proliferation, differentiation, invasion, repair and so forth *via* the RAS/MAPK/ERK1/2, PI3K/AKT and JAK STAT3 pathways. These processes are crucial for the development of a placenta and other functions in order for a normal pregnancy to occur. Hence, this study determined the concentrations of HGF and EGF to find the correlation between HIV and preeclampsia (PE).
Study design: A total sample size of n = 80 was used, n = 40 preeclamptic women and n = 40 normotensive women these were further stratified into HIV-positive and HIV-negative women. Analysis of the growth factors were done by using the multiplex Bio-Plex immunoassay method.
Results: Irrespective of HIV status, based on pregnancy type, EGF in PE women displayed an upregulation compared to normotensive women. However, for HGF no variance was found between pregnancy type. Based on HIV status, regardless of pregnancy type, both HGF and EGF levels were significantly increased in HIV-positive women compared to HIV-negative women.
Across all groups for HGF, significant difference was found between HIV-negative normotensive women (lower) *vs* HIV-positive normotensive women (higher).
Nevertheless, for EGF across all groups, a statistically significant decrease was found in HIV-negative normotensive women compared to HIV-positive normotensive women, HIV-positive PE women and HIV-negative PE women.
Conclusion: The study demonstrates that there is a strong association between HIV and PE and that HGF and EGF are promising biomarkers to use as a diagnostic tool for PE.

Introduction

South Africa is home to the largest global human immunodeficiency virus (HIV) epidemic [1]. In South Africa, 13.1% of the total population is HIV-positive, with one-fifth of women in their reproductive ages (15–49 years) being infected [2]. Approximately 30% of South African parturients are co-infected with HIV [3] with the prevalence being the highest in the province of KwaZulu-Natal (37%) [2]. Health care professionals providing maternity care are thus faced with a severe dilemma.

Non-pregnancy related infections (31%), obstetric hemorrhage (24%) and hypertensive disorders of pregnancy (19%) are major contributory factors to maternal mortality with preeclampsia (PE), accounting for >83% of these deaths [4]. Preeclampsia is characterized by new onset blood pressure of greater than 140/90 mmHg and proteinuria (> 300 mg/d) after the 20th week of gestation. In KwaZulu-Natal, the prevalence of PE is 12%. Notably, maternal deaths from HIV infection and obstetric hemorrhage have declined over the period: 2008–2016, however no change in mortality due to hypertensive diseases in pregnancy has occurred [4].

Whilst the exact cause of preeclampsia has not yet been elucidated, it is characterized by inadequate physiological spiral

Abbreviations: cAMP, 3′-5′-cyclic adenosine monophosphate; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinases; HGF, hepatocyte growth factor; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; Ns, non-significant; PI3K, phosphoinositide 3kinase; PE, preeclampsia; AKT, protein kinase B; RAS, renin-angiotensin system; STAT3, signal transducer and activator of transcription 3; Tat, trans-activator of transcription; TGFβ, transforming growth factor beta; cMET, hepatocyte growth factor receptor; VEGF, vascular endothelial growth factor.

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artery remodeling which causes a hypoxic and anti-angiogenic microenvironment [5].

The association between HIV infection and PE is conflicting due to opposing immune responses. Moreover, HIV-infected pregnant women treated with highly active antiretroviral treatment (HAART) have an increased risk for PE development due to the reconstitution of their immune system [6].

Hepatocyte Growth Factor (HGF) and Epidermal Growth Factor (EGF) belongs to a family of receptor tyrosine kinases that are integral to the regulation of cell proliferation, survival, differentiation and migration [7]. The Hepatocyte Growth Factor Receptor (c-Met) also known as tyrosine-protein-kinase-Met, which is a proto-oncogene located on chromosome 7q21-31 [8]. Its ligand, hepatocyte growth factor (HGF) is converted from an inert precursor by a proteolytic cleavage into a bioactive mature form [9]. The HGF/c-Met binding results in receptor homodimerization and phosphorylation of tyrosine residues that mediate a complex signaling network [10]. Hepatocyte growth factor acts as a pleiotropic factor, promoting cell proliferation, survival, motility, differentiation and morphogenesis.

Since HGF promotes epithelial cell migration and invasion, it could play a pivotal role in placentation. In PE, the abnormal trophoblast invasion is associated with a downregulation of placental HGF [11]. Moreover, during development, the HGF/c-MET receptor interaction is important for organ growth [10,12].

Epidermal growth factor acts *via* the epidermal growth factor receptor (EGFR). Both c-MET and EGFR are transmembrane tyrosine kinases, which post binding with their ligand, initiate phosphorylation and activate transcription [13]. In pregnancy, EGF and its receptors are expressed in the placenta [14]. Moreover, the EGFR family activate pathways such as the Renin–Angiotensin System/Mitogen-Activated Protein Kinase/extracellular signal–regulated kinases 1/2 (RAS/MAPK/ERK1/2), Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT) and Janus Kinase Signal Transducer and Activator of Transcription 3 (JAK STAT-3) [15]. Additionally, EGF promotes syncytialization- an integral step in blastocyst implantation and placentation, and when these processes fail to occur in a set sequence, pregnancy complication such as PE occur [5].

In light of the extensive role played by the receptor tyrosine kinases HGF and EGF in placentation, the aim of this study is to compare the level of serum HGF and EGF in HIV associated normotensive pregnant and preeclamptic women using the Bioplex multiplex immunoassay.

Methods and materials

Ethical approval

This retrospective study received ethical approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BCA338/17; 17th April 2018). All women were recruited from the antenatal clinic of a large regional hospital in Durban, South Africa and gave their full informed consent for the participation in this study.

Study population

The study population (n = 80) consisted of 40 normotensive pregnant and 40 preeclamptic women. Preeclampsia was defined as a new onset blood pressure of ≥140/90 mmHg and proteinuria > 300 mg/d after the 20th week of gestation [5].Both groups were further stratified by HIV status into HIV-positive PE (n = 20), HIV-negative PE (n = 20), HIV-positive normotensive pregnant (n = 20) and HIV-negative normotensive pregnant (n = 20) women. All HIV-positive women received dual HAART and nevirapine therapy, a standard of care practice in South Africa.

Exclusion criteria for the PE group were eclampsia, chorioamnionitis, chronic diabetes, chronic hypertension, pre-existing seizure disorders, intrauterine death, abruption placenta, gestational diabetes, systemic lupus erythematous, chronic renal disease, sickle cell disease, thyroid disease, cardiac disease, asthma and an unknown HIV status.

Sample type

Maternal blood samples were collected and centrifuged at 1000 *g* for 10 min at 20 °C. Serum samples were stored at −80 °C until required.

ProcartaPlex™ multiplex immunoassay method

A Growth Factor 45-Plex Human ProcartaPlex™ Panel one was performed according to manufacturer's instructions (Invitrogen by ThermoFisher Scientific, catalog no: EPX450-12171-901). The standards were prepared in a 1:4 dilution series, and no dilution of samples were required.

In a 96 well plate, HGF and EGF capture antibody-coupled magnetic beads were added to each well and washed twice. Standards, samples and blanks were then added into their designated wells and left to incubate before washing three times. Thereafter, a biotinylated detection antibody was pipetted into each well and allowed to incubate. The plate was then washed three times before adding streptavidin-phycoerythrin throughout the wells. Finally, the plate was washed for a further three times, before resuspending each well with assay buffer. The plate was then ready to be placed into the Bio-Plex system for reading.

The Bio-Plex®MAGPIX™ Multiplex Reader (Bio-Rad Laboratories Inc., USA) was utilized to read the experiment plate. Bio-Plex Manager™ software version 4.1 was used to obtain the data from the multiplex analysis.

Statistical analysis

Data analysis was performed using Graphpad Prism 5.00 for Windows (GraphPad Software, San Diego California USA). The Kolmogorov Smirnov test for normality revealed non-parametrically distributed data. A Mann-Whitney U test was utilized to determine statistical significance according to pregnancy type (PE *vs* normotensive) and HIV status (positive *vs* negative). Results are represented as median and interquartile range (IQR). To determine

Table 1
Patient demographics across study groups (n=80). Results are represented as the median (IQR), ns = non-significant, * $P<0.05$ *** $P<0.001$.

	HIV Negative Normotensive	HIV Positive Normotensive	HIV Negative Preeclamptic	HIV Positive Preeclamptic	*P*-value
Maternal Age (years)	24.50 (9.75)	28.50 (9)	24.00 (9.5)	29.00 (10)	0.1601 (ns)
Gestational Age (weeks)	39.00 (3)	38.00 (3)	32.00 (11)	32.00 (6)	<0.0001 ***
Parity	1.00 (2)	1.50 (1)	1.00 (1.750)	1.00 (1)	0.4707 (ns)
Systolic BP (mmHg)	121.5 (16.2)	110.0 (18.5)	158.5 (17)	157.5 (22.3)	<0.0001 ***
Diastolic BP (mmHg)	73.0 (13.75)	70.0 (7.25)	103.5 (19.5)	100.5 (13)	<0.0001 ***
Weight (kg)	76.5 (16.23)	79.5 (19.02)	70.0 (16.17)	79.0 (35.97)	0.3557 (ns)

statistical significance across all groups, a Kruskal-Wallis test in combination with the Dunn's Multiple comparison *post hoc* test was used. Statistical significance was $P < 0.05$.

Results

Patient demographics and clinical characteristics

Patient demographics and clinical characteristics are represented in Table 1 as median and interquartile range (IQR). No significant differences were reported in maternal age ($P = 0.16$), parity ($P = 0.47$) and maternal weight ($P = 0.36$), across all study groups. However, there was a statistically significant difference between gestational age, systolic and diastolic blood pressures across the study groups ($P < 0.0001$).

Serum concentrations of hepatocyte growth factor

Pregnancy type- The concentration of HGF was not statistically different between the normotensive pregnant (median = 6.91 pg/ml, IQR = 20.43 pg/ml) *vs* PE group (median = 8.03 pg/ml, IQR = 9.63 pg/ml), regardless of HIV status (Mann-Whitney U = 382.5; $P = 0.889$; Fig. 1A).

HIV status- However, there was a significant difference in HGF level between the HIV-positive (median = 10.68 pg/ml, IQR = 21.1 pg/ml) *vs* HIV-negative groups (median = 6.44 pg/ml, IQR = 6.35 pg/ml), irrespective of pregnancy type, (Mann-Whitney U = 252.0; $P = 0.0225$; Fig. 1B).

Across all groups- There was a significant difference in HGF concentration between HIV-negative normotensive (median = 4.17 pg/ml, IQR = 5.89 pg/ml) *vs* HIV-positive normotensive (median = 21.78 pg/ml, IQR = 24.74 pg/ml) pregnant mothers (Kruskal-Wallis H = 14.63; $P = 0.0022$; Fig. 1C). No differences were noted across all other groups.

Serum concentrations of epithelial growth factor

Pregnancy type- EGF expression was statistical different between the normotensive pregnant (median = 38.82 pg/ml IQR = 63.63 pg/ml) *vs* PE group (median = 93.13 pg/ml, IQR = 62.3 pg/ml) irrespective of HIV status (Mann-Whitney U = 186.0; $P = 0.0003$; Fig. 2A).

HIV status- The concentration of EGF was significantly different between the HIV-positive (median = 88.85 pg/ml, IQR = 73.14 pg/ml) *vs* HIV-negative groups (median = 49.64 pg/ml, IQR = 72.73 pg/ml), regardless of pregnancy type (Mann-Whitney U = 241.5; $P = 0.0055$; Fig. 2B).

Across all groups- A statistically significant difference in EGF concentration was noted between: HIV-negative normotensive (median = 17.04 pg/ml, IQR = 30.88 pg/ml) *vs* HIV-positive normotensive pregnant mothers (median = 72.25 pg/ml, IQR = 59.88 pg/ml); HIV-negative normotensive (median = 17.04 pg/ml, IQR = 30.88 pg/ml) *vs* HIV-positive PE (median = 96.36 pg/ml, IQR = 80.81 pg/ml) and HIV-negative normotensive (median = 17.04 pg/ml, IQR = 30.88 pg/ml) *vs* HIV-negative PE groups (median = 86.42 pg/ml, IQR = 59.50 pg/ml), (Kruskal-Wallis H = 25.98; $p < 0.0001$; Fig. 2C).

Discussion

HGF: This study demonstrates that serum HGF concentrations were similar between normotensive and PE pregnancies, regardless of the HIV status. Several studies also report similar serum HGF levels between PE and normotensive pregnancies [16]. It is plausible that sample type affects HGF as contradictory studies report a statistically significant increase in the plasma HGF concentration in PE [17]. Martinez-Fierro et al. [18] noted that the urinary concentration of HGF at 20 weeks gestation were elevated in women that developed PE compared to normotensive

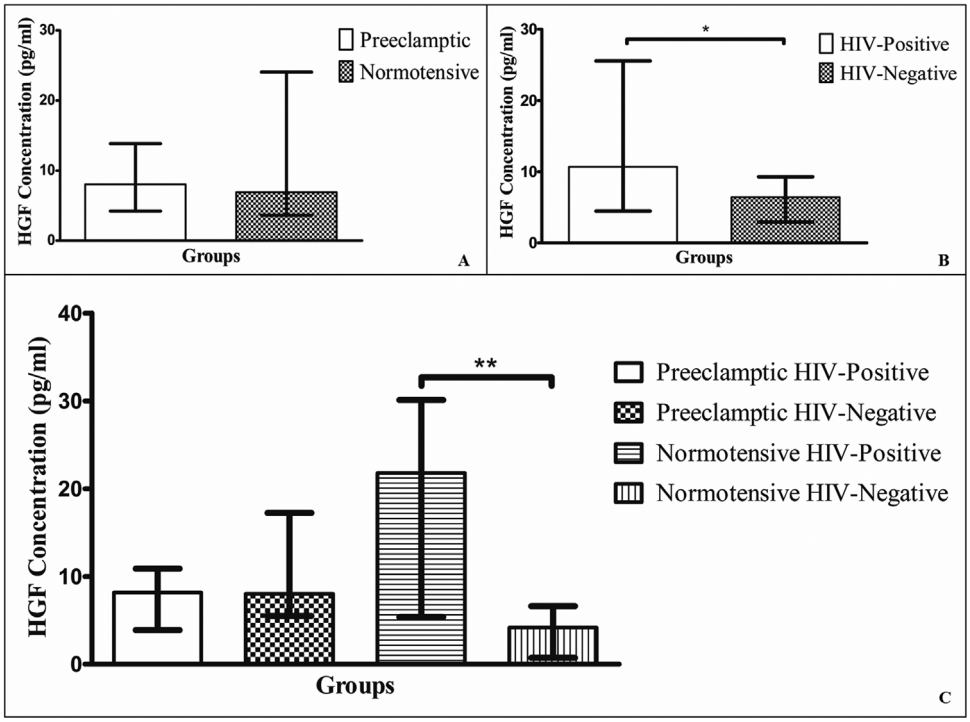

Fig. 1. Hepatocyte Growth Factor: (A) Preeclampsia *vs* Normotensive Groups, (B) HIV infected *vs* HIV uninfected groups, (C) Across All Groups.
*Serum concentrations of HGF are significantly different between HIV-positive and HIV-negative group, $P = 0.0225$. **Serum concentrations of HGF are significantly different between normotensive HIV-positive and normotensive HIV-negative group, $P = 0.0022$.

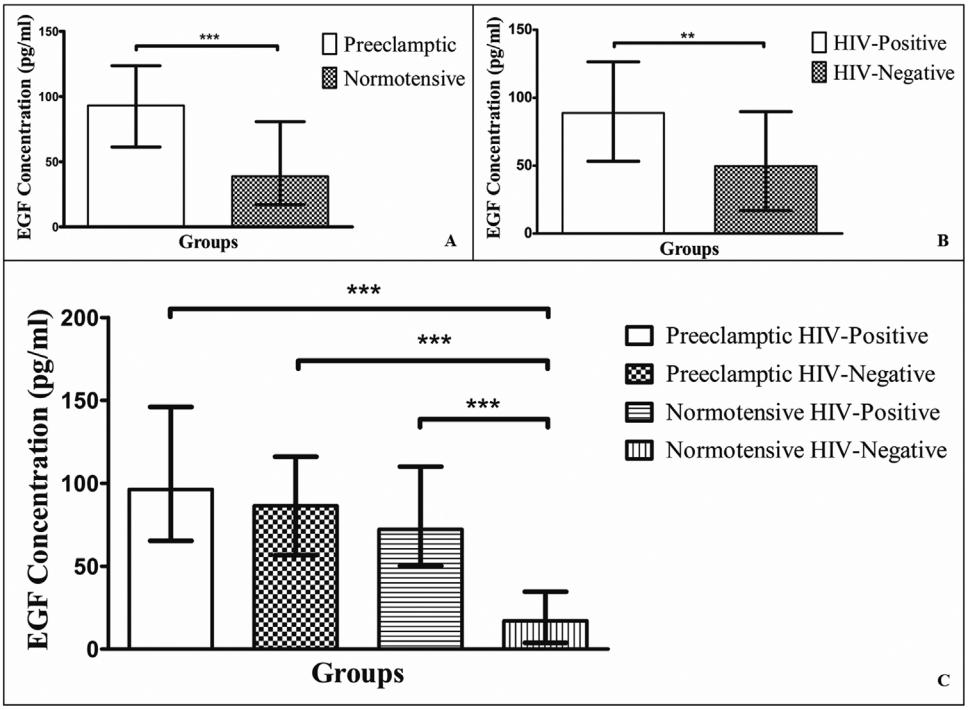

Fig. 2. Epidermal Growth Factor: (A) Preeclampsia *vs* Normotensive Groups, (B) HIV infected *vs* HIV uninfected groups, (C) Across All Groups.
***Serum concentrations of EGF are significantly different between preeclamptic and normotensive group, $P = 0.0003$. **Serum concentrations of HGF are significantly different between HIV-positive and HIV-negative group, $P = 0.0055$. ***Serum concentrations of EGF are significantly different between normotensive HIV-positive and normotensive HIV-negative group, $P < 0.0001$. ***Serum concentrations of EGF are significantly different between preeclamptic HIV-negative and normotensive HIV-negative group, $P < 0.0001$. ***Serum concentrations of EGF are significantly different between preeclamptic HIV-positive and normotensive HIV-negative group, $P < 0.0001$.

pregnancy; suggesting that urinary HGF could possibly have predictive test value for the diagnosis of PE [18].

It is noteworthy to hypothesize that a high production of HGF causes saturation of HGF receptor (c-Met), which results in a reduced level of the free circulating HGF in blood. Nonetheless, Naghshvar et al. [19] investigated c-Met levels in both serum and plasma and found that c-Met levels correlated with severity of PE (Table 2).

Both HGF and EGF are tyrosine kinases which activate signaling to mediate cell proliferation, differentiation, angiogenesis, migration and invasion *via* the JAK STAT-3 and MAPK/ERK1/2 pathways, and proliferation and survival *via* PI3K/AKT cascade [12].The c-MET receptor significantly regulates the activation of cell differentiation, proliferation and self-renewal *via* the MAPK/ERK1/2 pathway [20]. In PE, there is a dysregulation of the latter pathway [20]. This reduced HGF/c-MET axis inhibits trophoblast cell differentiation, proliferation and repair/regeneration of trophoblast cells and may explicate the reduction in trophoblast cell migration that occurs in PE [12]. A recent study by Zeng et al. [21] indicated that HGF was responsible for placental growth and that inhibition of HGF production in an animal model resulted in stillbirth.

The reduction of HGF, albeit non-significantly in PE in the current study may be attributed to the hypoxic micro environment. Hypoxia has been shown to reduce HGF expression, thereby limiting interaction with the c-Met receptor on trophoblast cells [22]. This receptor ligand binding restricts trophoblast 3′,5′-cyclic adenosine monophosphate (cAMP) expression which activates protein kinase A/ Ras-proximate-1 (PKA/RAP1). Subsequently, Serine/threonine-protein kinase (PAK) is inappropriately stimulated leading to integrin β1 down-regulation [23], eventuating in decrease trophoblast invasion (Fig. 3).

Furthermore, c-MET is known for its ability to elicit a cell survival response (anti-apoptotic) *via* the PI3K/AKT pathway. Hepatocyte Growth Factor is needed to regulate this anti-apoptotic response. In a previous report, our research group demonstrated elevated apoptosis of trophoblast cells in PE [24]. Thus, it is plausible that the decline of serum HGF accounts for the increased apoptosis of trophoblast cells, with resultant decline in trophoblast invasion/migration in PE [22].

Our study also illustrated an elevated serum concentration of HGF in HIV-positive women compared to that of HIV-negative women, irrespective of pregnancy type. Tulasne et al. [25] established that stress stimuli transform the anti-apoptotic function of the c-MET receptor to a pro-apoptotic function by a caspase-dependent cleavage. Both PE and HIV infection are well accepted stress stimulant conditions [26]

In an *in vitro* study, the HIV accessory protein, Trans-Activator of Transcription (Tat) is able to activate the intrinsic pathway of apoptosis [27]. Tat induces an upregulation of Transforming Growth Factor Beta (TGF-β) which inhibits HGF production, thus negating its

Table 2
Serum concentration (pg/ml) of Growth Factors across all study groups. Results are represented as median (interquartile range).

	Normotensive pregnant		Preeclampsia		*P* value
	HIV Negative (n = 20)	HIV Positive (n = 20)	HIV Negative (n = 20)	HIV Positive (n = 20)	
EGF	17.04 (30.88)	72.25 (59.88)	86.42 (59.50)	96.36 (80.81)	<0.0001
HGF	4.17 (5.89)	21.78 (24.74)	8.03 (11.75)	8.17 (7.01)	0.0022

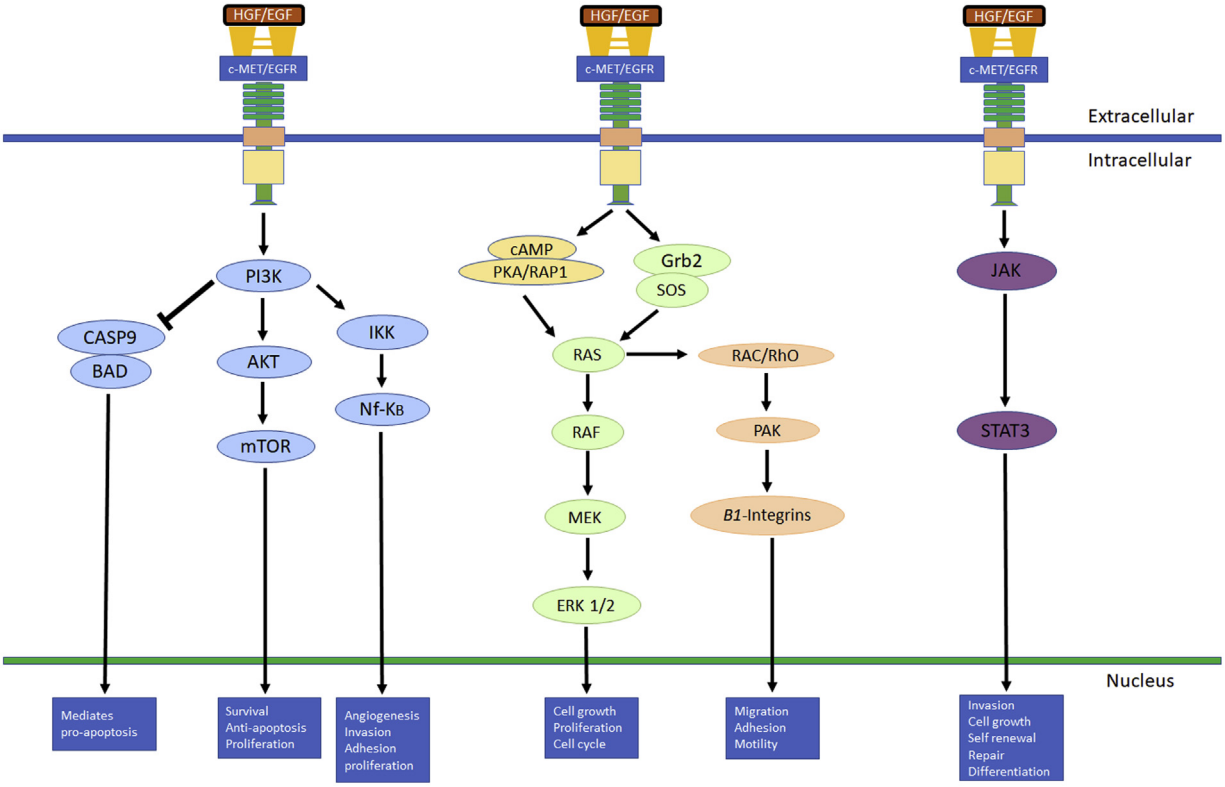

Fig. 3. Cross-link in PI3K/AKT, MAPK/ERK1/2 AND JAK STAT-3 pathways between HGF/EGF upon activation. (adapted from Zhang et al. 2015).
The docking of HGF/EGF to their ligands results in phosphorylation of Growth factor receptor-bound protein 2 /Son of Sevenless (Grb2/SOS). In addition, cAMP/PKA/RAP1 are also phosphorylated, in which both promote the RAS pathway [23]. Henceforth Rapidly Accelerated Fibrosarcoma- Mitogen-activated protein kinase (RAF-MEK-ERK1/2) cascade is stimulated eliciting cell growth, proliferation and cell cycle regulation. RAS also triggers the Ras-related C- ρ - Serine/threonine-protein kinase (RAC-RhO-Pak) pathway which initiates integrin β1 up-regulation for cell migration, adhesion and motility [42].

pleiotropic actions [28]. Moreover, Wiercińska-Drapalo et al. [29] noted that TGF-β levels are greater than twofold in the HIV-positive compared to HIV-negative women. Despite the lack of correlation between HAART and TGF-β in the latter study, HAART is believed to be advantageous during early stages of therapy, with positive HGF production and hepatocyte survival [30]. In the current study, we noted a significantly different HGF concentration between HIV-positive *vs* HIV-negative women, irrespective of pregnancy type. It is plausible that a compromised immune system elicits a compensatory response to produce HGF in order to repair tissues and organs damaged during HIV infection [31].

EGF: Our study also demonstrated an up-regulation of serum EGF in PE compared to normotensive pregnancies, regardless of HIV status. This finding is corroborated by Armant et al. [32], who reported that EGFR- an EGF receptor protagonist, is also overexpressed in PE [32]. Notably, EGFR initiates signal transduction cascades namely the MAPK, AKT and JAK-STAT-3 pathways. This signaling initiates DNA synthesis by modifying cell migration, adhesion, and proliferation. Thus it is possible that the deficient trophoblast cell invasion in PE may be a result of an aberrant signal transduction cascade emanating from the dysregulation of EGFR-EGF binding [7]. Ferrandina et al. [33] further hypothesized that the hypertensive disorders of pregnancy are related to increased placental EGFR concentration. In contrast to our findings, plasma EGF levels were reported to be twofold higher in normotensive pregnant compared to PE women [32].

Epidermal Growth Factor signals *via* the JAK STAT-3 pathway highlighting the fact that EGF influences proliferation and invasion of trophoblast cells [34]. The PI3K/AKT pathway has been associated with many cellular processes such as regulation of the cell cycle, cell death, adhesion, migration and metabolism. Notably, a decrease in EGF reduces AKT phosphorylating of Bcl-2-associated death promoter (BAD), which leads to trophoblast cell death in PE [35]. In PE, the invasive trophoblast cells exits the cell cycle in the G1 phase, leading them to apoptosis rather than passing through into the S phase and mitosis [24].

In this study, EGF was elevated in HIV-positive compared to HIV-negative women, irrespective of pregnancy type. It is plausible that an immunocompromised milieu may affect EGF-EGFR interactions. Burgel and Nadel [36] correlated this upregulation of EGF with an exaggerated innate immune response.

Additionally, preeclampsia is characterized by impaired angiogenesis [24]. The HIV accessory protein Tat is a powerful angiogenic factor, in that it mimics Vascular endothelial growth factor (VEGF) [37]. The Tat protein inhibits EGF-induced processes such as cell proliferation, differentiation, invasion, migration, adhesion and cell survival [38]. Therefore, apart from Tat affecting angiogenesis, it can also affect trophoblast cell migration. In HIV-positive women, Tat would reduce the predisposition to PE development [39]. Since Tat inhibits EGF function, it would negatively impact trophoblast cell migration.

An association between HGF and EGF signaling has been established by Zhang et al. [40], where upon activation, these growth factors elicit the same cellular responses (Fig. 3). The binding of HGF or EGF to the respective receptors induces phosphorylation of PI3K which activates AKT, IκB kinase (IKK) and inhibits Caspase-9/BAD, thus mediating pro-apoptosis. Activation of AKT regulates mammalian target of rapamycin (mTOR) which is responsible for cell survival and proliferation. In addition, IKK promotes nuclear factor kappa-light-chain-enhancer of activated B cells (Nf-K*B*) which triggers cell invasion, adhesion, proliferation and angiogenesis [41] (Fig. 3).

The activation of STAT-3 *via* JAK is a byproduct of the fusion between HGF/EGF and c-Met/EGFR (Fig. 3). This signaling results in the regulation of a number of cell responses, such as: cell growth, differentiation, invasion, repair and self-renewal [34].

One of the limitations of this study was the absence of viral load, which subsequently resulted in no correlation between HGF/EGF based on severity of HIV infection. In addition, all HIV-positive women were on highly active anti-retroviral treatment (HAART), which may have confounded both HGF and EGF levels. Lastly, the heterogeneity of our study population, which was not stratified into early and late onset PE, could be seen as a limitation.

Conclusion

This study demonstrates a significant increase of EGF in the oxidative stressed microenvironment of preeclampsia compared to normotensive mothers, regardless of HIV status. In addition, a significant up-regulation of HGF and EGF was found in HIV infected mothers, irrespective of pregnancy type. Off-note, the HIV accessory protein affects angiogenesis, cell signaling and trophoblast cell migration. Furthermore, HAART may be implicated in the elevation of EGF and HGF in HIV infection. It is thus plausible that EGF may have possible predictor indicator test value for the early detection of PE.

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