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CXCL10/IP-10:

A MISSING LINK BETWEEN INFLAMMATION AND ANTI-ANGIOGENESIS IN PREECLAMPSIA?

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Abstract

OBJECTIVE—Interferon (IFN)-γ inducible protein, CXCL10/IP-10, is a member of the CXC chemokine family with pro-inflammatory and anti-angiogenic properties. This chemokine has been proposed to be a key link between inflammation and angiogenesis. The aim of this study was to determine whether preeclampsia and delivery of a small for gestational age (SGA) neonate are associated with changes in maternal serum concentration of CXCL10/IP-10.

STUDY DESIGN—This cross-sectional study included patients in the following groups: (1) non pregnant women (*N*=49); (2) women with normal pregnancies (*N*=89); (3) patients with preeclampsia (*N*=100); and (4) patients who delivered an SGA neonate (*N*=78). SGA was defined as birth weight below the 10th percentile. Maternal serum concentrations of CXCL10/IP-10 were measured by sensitive immunoassay. Non-parametric statistics were used for analysis.

RESULTS—(1) Patients with normal pregnancies had a significantly higher median serum concentration of CXCL10/IP-10 than non-pregnant women (median: 116.1 pg/mL, range: 40.7-1314.3 vs. median: 90.3 pg/mL, range: 49.2-214.7, respectively; p=0.002); (2) no significant correlation was found between maternal serum concentration of CXCL10/IP-10 and gestational age (between 19 and 38 weeks); (3) there were no differences in median serum CXCL10/IP-10 concentrations between patients who delivered an SGA neonate and those with normal pregnancies (median: 122.4 pg/mL, range: 37.3-693.5 vs. median: 116.1 pg/mL, range: 40.7-1314.3, respectively; *p*>0.05); (4) patients with preeclampsia had a higher median serum concentration of CXCL10/IP-10 than normal pregnant women (median: 156.4 pg/mL, range: 47.4-645.9 vs. median: 116.1 pg/mL, range: 40.7-1314.3, respectively; p<0.05); (5) patients with preeclampsia had a higher median concentration of CXCL10/IP-10 than those who delivered an SGA neonate (median: 156.4 pg/mL, range: 47.4-645.9 vs. median: 122.4 pg/mL, range: 37.3-693.5, respectively; p<0.05).

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CONCLUSIONS—Patients with preeclampsia have significantly higher serum concentrations of CXCL10/IP-10 than both normal pregnant women and mothers who have SGA neonates. These results are likely to reflect an anti-angiogenic state as well as an enhanced systemic inflammatory response in patients with preeclampsia. Alternatively, since preeclampsia and SGA share several mechanisms of disease, it is possible that a higher concentration of this chemokine may contribute to the clinical presentation of preeclampsia in patients with a similar intrauterine insult.

Keywords

Pregnancy; CXCL10; IP-10; chemokine; chemotactic cytokine; small for gestational age; SGA; angiogenesis

Introduction

Patients with preeclampsia and those with a small for gestational age (SGA) neonate share a number of pathophysiological characteristics including: (1) abnormal physiologic transformation of the spiral arteries [1-8]; (2) chronic uteroplacental ischemia [9-16]; (3) endothelial cell dysfunction [17-24]; (4) an anti-angiogenic state [25-32]; and (5) intravascular inflammation [18,33-37]. Furthermore, a biased Th1/Th2 (T-helper 1/T-helper 2) balance towards a Th-1 response has been reported in preeclampsia [38-46] and SGA [47].

The human interferon-inducible protein 10 (IP-10 or CXCL10) is a chemokine of the CXC family [48]. A unique feature of members of this chemokine family is that they have pro-inflammatory properties and act as modulators of angiogenesis in conditions such as wound healing, ischemia and neoplasia. These dual properties are related to the shared expression of specific chemokine receptors by leukocytes and endothelial cells [49-60].

IP-10 is inducible by pro-inflammatory stimuli such as interferfon-γ (IFN-γ) [61-72], tumor necrosis factor-α (TNF-α) [70,73-79], viruses, and microbial products [66,70,80-85], directly or through activation of nuclear factor-kappaB (NF-kB) [81,82,86-89]. It has been proposed that this chemokine is also involved in recruitment and potentiation of Th1 responses as well as in the pathogenesis of allograft rejection [90-103], multiple sclerosis [104-108], diabetes mellitus type 1 [109,110], Graves' disease [111-114], autoimmune thyroiditis [115,116], pulmonary fibrosis [117-119], and cardiovascular diseases such as atherosclerosis [120], and coronary syndromes [121,122]. Importantly, IP-10 has potent anti-angiogenic activity, *in vitro* and *in vivo* [123-126].

The balance between angiogenic and anti-angiogenic (angiostatic) factors controlled by molecules involved in inflammatory processes may have impact on the pathogenesis of many diseases [54,58].

We propose that IP-10 is involved in the pathophysiology of preeclampsia because this condition is characterized by intravascular inflammation and an anti-angiogenic state. The objective of this study was to compare the maternal serum IP-10 concentrations in normal pregnancy, preeclampsia, and SGA.

Methods

Study design

This retrospective cross-sectional study included patients with preeclampsia (N=100), women who delivered a SGA neonate (N=78), normal pregnant women (N=89) and non-pregnant women (N=49). All patients were enrolled at Hutzel Hospital, Detroit, MI. All women provided written informed consent for the collection of clinical data and biological materials under

protocols approved by the Institutional Review Boards of both Wayne State University and the National Institute of Child Health and Human Development of the National Institute of Health (NIH/DHHS). Many of these samples have been employed to study the biology of inflammation, hemostasis, angiogenesis regulation, and growth factor concentrations in non-pregnant women, normal pregnant women and those with pregnancy complications.

Preeclampsia was defined in the presence of hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on at least two occasions, four hours to one week apart, after the 20th week of gestation) and proteinuria (≥ 300 mg in a 24-hour urine collection, or two random urine specimens obtained four hours to one week apart containing ≥1+ protein by dipstick [127,128], or one dipstick measurement ≥2+) [129]. Severe preeclampsia was diagnosed according to the criteria proposed by the American College of Obstetricians and Gynecologists (ACOG) committee [128]. Patients with preeclampsia were sub-classified as either early-onset (<34 weeks) or late onset (≥34 weeks) disease according to the gestational age at which preeclampsia was diagnosed. A neonate was defined as SGA when the birth weight was below the 10th percentile for gestational age according to the reference range proposed by Alexander et al.[130]. Patients were considered to have a normal pregnancy if they met the following criteria: (1) no medical, obstetrical or surgical complications; (2) absence of labor at the time of venipuncture; and (3) delivery of a normal term (≥37 weeks) infant whose birth weight was between the 10th and 90th percentile for gestational age [130]. The non-pregnant group consisted of healthy volunteers not taking oral contraceptives whose blood was withdrawn in the secretory phase of the menstrual cycle.

IP-10 (CXCL10) determinations

Specific and sensitive enzyme-linked immunoassays were used to determine concentrations of IP-10 in human maternal serum. Immunoassays for IP-10 were obtained from R&D Systems (Minneapolis, MN, USA). Briefly, maternal serum samples were incubated in duplicate wells of the microtiter plates, pre-coated with a monoclonal antibody specific for IP-10. During this incubation step, any IP-10 present in the standards or maternal serum is bound by the immobilized antibodies. After repeated washing and aspiration to remove all unbound substances, an enzyme-linked polyclonal antibody specific for IP-10 was added to the wells. Following a wash to remove excess and unbound materials, a substrate solution was added to the wells and color developed in proportion to the amount of IP-10 bound in the initial step. The color development was stopped with the addition of an acid solution and the intensity of color was read using a programmable spectrophotometer (SpectraMax M2, Molecular Devices, Sunnyvale, CA, USA). The concentrations of IP-10 in serum samples were determined by interpolation from individual standard curves composed of recombinant human IP-10. The calculated inter and intra-assay coefficients of variation for IP-10 immunoassays in our laboratory were 7.99% and 4.12% respectively. The lower limit of detection (sensitivity) was calculated to be 5.01pg/mL.

Statistical analysis

The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. The Spearman's correlation test was used in assessing the relationship between maternal serum concentration of IP-10 and gestational age at blood draw in patients with normal pregnancies. Comparisons among groups were performed using Kruskal-Wallis tests with post-hoc analysis for continuous variables, and Chi-square or Fisher's exact test for categorical variables. A p value <0.05 was considered statistically significant. The statistical package used was SPSS v.12.0 (SPSS Inc., Chicago, IL, USA).

Results

Three hundred sixteen patients were included in this study. The demographic and clinical characteristics of the study groups are displayed in Table I.

Among patients with preeclampsia, 63% (63/100) were classified as early-onset and 88% (88/100) as severe preeclampsia. In 75.6% (59/78) of patients who delivered an SGA neonate, the birth weight was below the 5th percentile. IP-10 was detectable in the serum of all subjects.

Serum concentration of IP-10 in pregnancy

Patients with normal pregnancies had a significantly higher median serum concentration of IP-10 than non-pregnant women (median 116.1 pg/mL, range 40.7-1314.3 vs. median 90.3 pg/mL, range 49.2-214.7, respectively; p=0.002) (see Figure 1). There was no significant correlation between maternal serum IP-10 concentration and gestational age at blood draw (r=0.039; p=0.7).

IP-10 in preeclampsia

Patients with preeclampsia had a higher median serum concentration of IP-10 than normal pregnant women and those who delivered a SGA neonate (preeclampsia: median 156.4 pg/mLl, range 47.4-645.9; normal pregnancy: median 116.1 pg/mL, range 40.7-1314.3; SGA: median 122.4 pg/mLl, range 37.3-693.5; p<0.05 for both comparisons). In contrast, there were no significant differences in the maternal serum median IP-10 concentrations between patients who delivered an SGA neonate and those with normal pregnancies (SGA: median 122.4 pg/mll, range 37.3-693.5 vs. normal pregnancy: median 116.1 pg/mL, range 40.7-1314.3; p>0.05) (see Figure 2).

Among patients with preeclampsia, no significant differences in serum concentrations of IP-10 were observed between patients with early onset and late onset disease (early onset preeclampsia: median 155.6 pg/mL, range 47.5-645.9 vs. late onset preeclampsia: median 165.2 pg/mL, range 64.7-401.1; *p*=0.4). Similarly, there were no significant differences between mild and severe preeclampsia (mild preeclampsia: median 177.7 pg/mL, range 79.4-401.1 vs. severe preeclampsia: median 155.5 pg/mL, range 47.5-645.9; *p*=0.56).

Among patients who delivered an SGA neonate, there were no significant differences in serum concentrations of IP-10 between patients who delivered a neonate with a birth weight at < 5th percentile and those who delivered a neonate with a birth weight between 5th and 9th percentile (SGA <5th percentile, median: 126.7 pg/ml, range: 37.3-693.5 vs. SGA 5th-9th percentile, median: 108.7 pg/ml, range: 40.7-349.5; p=0.2).

Using analysis of covariance (ANCOVA), only diagnostic groups but not storage time had a significant effect on the serum concentrations of CXCL10 (storage time: p=0.5; diagnostic groups: p < 0.001). Storage time did not have a significant effect on the serum concentrations of CXCL10 even when gestational age at blood draw was included in the analysis (storage time: *p*=0.72; diagnostic groups: *p*=0.02; gestational age at blood draw: *p*=0.5).

Discussion

Principal findings of this study

(1) The median serum concentration of IP-10 in normal pregnancy was higher than that of non-pregnant women; (2) there was no relationship between gestational age and the maternal serum concentration of IP-10; (3) preeclampsia, but not SGA, was associated with a higher median

concentration of maternal serum IP-10. These results are novel and suggest that IP-10 may participate in the pathophysiology of preeclampsia.

What is CXCL10/IP-10?

IP-10 (CXCL10) is a chemokine of the CXC family [48], which was first described as the product of a gene induced in response to recombinant IFN-γ in several cell populations, including U937 histiocitic lymphoma, human fibroblasts, mononuclear and endothelial cells [61]. The principal biological activity of chemotactic cytokines, such as IP-10, is regulation and control of the basal homeostatic and inflammatory leukocyte movement [57].

In addition, IP-10 has potent anti-angiogenic properties [54,56,57,59], promotes adhesion, migration and invasion of trophoblast cell [131,132], has an inhibitory effect on early hematopoietic progenitors [133], and regulates intestinal crypt cell renewal in both physiologic conditions and during mucosal regeneration following injury [134].

The biological properties of IP-10 are mediated through the interaction with a transmembrane G protein-coupled receptor, CXCR3 [135,136], shared by two other IFN-γ inducible CXC chemokines—CXCL9 (MIG) and CXCX11 (I-TAC)—whose distinct biological activities are related to different transduction pathways [137-140].

Factors controlling the expression of IP-10 and cell sources

IP-10 gene and protein expression is modulated by pro-inflammatory stimuli. Indeed, IFN-γ is an inducer of the gene, and protein expression of this chemokine by mononuclear cells [61], neutrophils [69,70], eosinophils,[70,141] keratinocytes [61,64,65,67], fibroblasts [61], endothelial cells [61-63], pancreatic β cells [71,72], and animal astrocytes/microglia [66,68], TNFα [70,73-79], IL-1β [70,71], as well as viral [66,81,82], and microbial products [70,80, 83-85] can also stimulate the production of IL-10.

Activation of the nuclear factor-kappa B (NF-kB) pathway [81,82,86-89] through ligation of pattern recognition receptors (TLR4 [83] and TLR3 [89]) can also upregulate gene and protein expression of IP-10. Interestingly, IP-10 is considered an ‘NF-kB responsive gene’[142].

IP-10 in inflammation

The pro-inflammatory activity of IP-10 includes: chemotaxis and endothelial adhesion of activated T cells [143] as well as chemotaxis [144] and enhancement of natural killer (NK) cell-mediated cytolysis [144]. However, this chemokine is a poor neutrophil activator [143, 145] and there is controversy about its effects on both monocytes [135,143] and B cells [146, 147].

CXCR3 receptor expression on T lymphocytes is selective for activated cells [135,143,146, 148-151]. Interestingly, analysis of polarized T lymphocytes using specific monoclonal antibodies has demonstrated high CXCR3 expression (mRNA and protein) on Th1 cells and low on Th2 cells [149,152], and this receptor has, therefore, been proposed as a useful clinical maker of circulating Th1-type cells [149,153]. Further evidence that IP-10 promotes a Th1-like dominance is the observation that, following stimulation with phorbol 12-myristate 13-acetate (PMA) and ionomycin, the production of IFN-γ (a Th1-type chemokine) resides exclusively in CXCR3-expressing memory $CD4^+$ T cells, whereas the production of Th2-type cytokines is mainly observed in those CXCR3-negative [153]. In addition, *in vitro* assays show that, in polyclonally stimulated T cells, recombinant IP-10 selectively enhances IFN-γ protein synthesis, while having no effect on IL-4 production [154]. The capability of IP-10 to enhance its own inducer, IFN-γ, supports the hypothesis that a positive amplification loop between IP-10 and IFN-γ also exists *in vivo*[154].

IP-10 in pathologic states

IP-10 has been implicated in states characterized by prominent T cell response [155,156], particularly when a Th1/Th2 imbalance is involved, including: (1) multiple sclerosis, where the serum and cerebrospinal fluid concentrations of IP10 correlate with the disease activity and CXCR3 expression is detectable on the majority of CNS-infiltrating lymphocytes [104-108]; (2) herpetic encephalitis in mice [157,158]; (3) experimental autoimmune encephalomyelitis [159-162]; (4) inflammatory bowel/colon disease [134,163,164]; (5) chronic hepatitis C, in which IP-10 serum concentrations are related to the inflammatory activity and the response to therapy [165]; (6) Sjogren's syndrome, where the expression of IP-10 mRNA is significantly up-regulated in salivary glands ($p<0.01$) and IP-10 has a potential role in the accumulation of T cells infiltrates [166]; (7) type 1 diabetes, whose immunopathogenesis is likely to be linked to the IP-10 [109,110] property of enhancing the traffic of auto-aggressive cells to the pancreas [167] and imprinting a pattern for the subsequent development of the autoimmune disease [109]; (8) Graves' disease [111-114] and autoimmune thyroiditis [115,116], where high concentrations of IP-10 have been detected in the serum of affected individuals; and (9) systemic lupus erythematosus, where IP-10 plasma concentrations not only are higher than in non-diseased individuals but also correlate with the disease activity [168].

IP-10 as an inhibitor of angiogenesis

IP-10 has potent anti-angiogenic properties [54,56,57,59]. Several mechanisms have been proposed to mediate these activities: (1) interaction with the CXCR3 receptor [169,170]; (2) binding to a cell surface heparan sulfate site shared with platelet factor 4 [124]; (3) interference with the pro-angiogenic activity of basic fibroblast growth factor (bFGF) and IL-8 [124]; and (4) through another high affinity receptor (different from CXCR3 and glycosaminoglycans) [171].

The IP-10 receptor CXCR3 (mRNA and protein) has been localized on the endothelial cells of several human tissues (kidney, gut, liver, thyroid and thymus) [170,172]. Interestingly, the endothelial cell expression is cell-cycle dependent [170]. Indeed, staining is remarkably more frequent in conditions of activation and in the presence of a high proliferative rate (such as in inflamed and neoplastic tissues rather than in normal tissues), particularly during the S/G2-M phase of the endothelial cell cycle [170]. Romagnani et al.[170] suggested that these results represent evidence that CXCR3 is mediating the angiostatic activity of IP-10, thus controlling endothelial cell proliferation. In addition, two distinct isoforms of this receptor, CXCR3-A and CXCR3-B (both products of alternative splicing) are likely to mediate opposite effects on cellular proliferation [173,174].

A specific region of the IP-10 molecule has been linked to its anti-angiogenic effect. Indeed, an aminoterminal truncated form of IP-10, resulting from a post-translational processing, has impaired receptor signaling and lymphocyte chemotaxis, but retains anti-angiogenic properties [175].

Evidence in support of the anti-angiogenic role of IP-10 includes: (1) IP-10, added to human umbilical cord vein endothelial cells (HUVECs), cultured on a matrigel substrate, inhibits their differentiation into tube-like structures in a dose-dependent fashion [125] and reduces the extent of the neo-vascular network [126]; (2) IP-10, both *in vitro*[123,124] and in vivo [123, 125] inhibits in a dose-dependent manner the pro-angiogenic effects of IL-8 and bFGF, including endothelial cells chemotaxis and proliferation as well as neovascularization in animal models of angiogenesis (rat cornea [123] or matrigel injected in the subcutaneous tissue of nude mice [125]); (3) recombinant IP-10 can inhibit [^{3}H]-thymidine incorporation into HUVECs cultured with bFGF [124]. Further support of the anti-angiogenic properties of IP-10 is the role attributed to this chemokine in the pathogenesis of pulmonary fibrosis. Indeed, the

lower production of IP-10 in lung tissue of patients with pulmonary fibrosis, as determined by ELISA, has been proposed to contribute to the greater angiogenic activity observed in these patients [117,119]. Additionally, when IP-10 is administered systemically to bleomycin pre-treated mice, it inhibits fibroplasia and deposition of extracellular matrix through the regulation of the local angiogenesis, resulting in a significant attenuation of the severity of the pulmonary fibrosis induced by this chemical [118]. This experimental evidence indicates that IP-10 has an important anti-angiogenic effect.

Evidence that the anti-angiogenic properties of IP-10 may have therapeutic value is the observation that it inhibits tumor growth. Observations in support of this include: (1) Burkitt's tumors implanted into athymic mice, once injected or transfected with IP-10, show histological evidence of tissue necrosis, capillary damage, intimal thickening and vascular trombosis [176]; (2) high serum concentrations of IP-10 have been reported in patients with lymphoproliferative disorders [177]; (3) tumors derived from IP-10 transduced melanoma cells have a reduced *in vivo* growth compared to those originating from parental or null-transduced cells ($p=0.0002$) and the growth inhibition is associated with a marked reduction in microvessel density [178]; (4) the angiostatic activity of IP-10 in human melanoma cell line appears to depend on binding to CXCR3 [169]; (5) tumors originating from human fibrosarcoma cell lines, secreting IP-10 upon vector transduction, and implanted into mice, have histological evidence of a significantly lower number of microvessels than controls ($p=0.01$) [126]; (6) recombinant IP-10 injection into non-small cell lung cancers grown in SCID (severe combined immunodeficiency) mice reduces their angiogenesis, growth, and incidence of spontaneous metastasis, whilst IP-10 neutralization results in enhanced tumor-derived angiogenic activity. Furthermore, plasma or tumor-associated IP-10 concentrations are inversely correlated to tumor growth. Extracts from these tumors decrease the angiogenic activity in the corneal micropocket assay [179]; and (7) IP-10 contributes to the anti-angiogenic and anti-tumor properties of IL-12 [180-183].

In summary, this evidence indicates that IP-10 plays an important anti-angiogenic role.

IP-10 concentration in serum during normal pregnancy

The observation that normal pregnant women have a significantly higher median serum concentration of IP-10 than non-pregnant women is novel. This observation is consistent with the findings that normal pregnancy is associated with systemic intravascular inflammation [35,184-187]. Additional evidence in support of this view is the observation that pregnancy is associated with higher (serum or plasma) concentrations of IL12 [186] TNF-α [188] than the non-pregnant state.

IP-10, inflammation and preeclampsia

The observation that preeclampsia is associated with a higher maternal serum concentration of IP-10 than SGA and normal pregnancy is novel, as well as being consistent with the view that preeclampsia is characterized by an exaggerated intravascular pro-inflammatory state [18,33-37].

Furthermore, accumulating evidence indicates that preeclampsia is associated with a predominant Th1 immune response, including: (1) high maternal plasma or serum concentrations of IL-2 [38], TNF-α [40,41,189-191], IFN-γ [192], and IL-12 [42,193]; (2) low maternal plasma or serum concentrations of IL-10 [194], and of IL-4 [192] (although this topic is subject to some controversy) [195]; and (3) up-regulation of mRNA and protein expression of IL-1β [196] and TNF-α [196,197] in the placenta. Thus, the high maternal plasma concentration of this chemokine in patients with preeclampsia may represent yet another feature of a pro-inflammatory state or intravascular inflammation or even contribute to the

generation of such state. Some evidence also indicates that SGA may be associated with intravascular inflammation [47]. However, the results presented herein do not implicate IP-10 in such process.

IP-10, preeclampsia and anti-angiogenesis

An imbalance between pro-angiogenic and anti-angiogenic factors is involved in the pathophysiology of preeclampsia [25-27,198-218]. The group of Maynard and Karumanchi has recently made a major set of observations that favor this hypothesis [219]. Evidence in support of this includes: (1) over-expression of s-VEGFR-1 mRNA and protein in placenta of patients with preeclampsia [27,219]; (2) higher median plasma/serum concentration of sVEGFR-1 in preeclampsia at the time of diagnosis than in patients with normal pregnancies [27,219,220], and the plasma concentration correlates with the severity of the disease [28]; (3) preeclampsia is associated with decreased plasma/serum concentrations of VEGF and PlGF [25,211,219,221]; (4) serum of pregnant women with preeclampsia has anti-angiogenic effects in the endothelial cell tube formation bioassay and these effects can be restored by the addition of VEGF and PlGF [219]; and (5) administration of sVEGFR-1 to pregnant animals can induce the clinical manifestation of preeclampsia, including hypertension and proteinuria [219]. Moreover, these animals develop the pathologic finding of glomerular endotheliosis but not pathognomonic of preeclampsia [222,223]. (6) preeclampsia is associated with a higher maternal serum concentration of endoglin at the time of the diagnosis or before the recognition of the disease [31,32].

Given the evidence that IP-10 has anti-angiogenic properties and that this is a feature of preeclampsia, we propose that elevated IP-10 maternal serum concentrations may contribute to generating an anti-angiogenic state along with sVEGF-R1 and endoglin.

IP-10, preeclampsia and allograft rejection

Allograft rejection has also been proposed as a mechanism of disease in preeclampsia [224]. Of note, there is growing evidence that IP-10 is also involved in the process of graft rejection, including: (1) CXCR3 deficient (-/-) mice are resistant to both acute and chronic allograft rejection [91]; (2) grafts from IP-10 (-/-) donors are less likely to undergo graft injury [90]; (3) treatment with anti-CXCR3 [91] or anti CXCL10 [96] monoclonal antibodies results in prolongation of cardiac and small bowel allograft survival in mice; (4) clinical rejection of human renal [92,100], lung [93], cardiac [94,95], small bowel [99], and arteries [102] transplants is associated with intra-graft over expression of IP-10 and/or with intra-graft recruitment of CXCR3 positive T cells; and (5) pre-transplant serum [97,103] and urine [98, 101] CXCL10 cellular mRNA or protein concentrations identify patients at risk for the development of acute rejection and/or chronic allograft nephropaty. Collectively, this evidence indicates that IP-10 is involved in the pathogenesis of allograph rejection. Whether or not this mechanism of disease operates in preeclampsia remains an interesting concept. Our observation that IP-10 is elevated in preeclampsia provides a possible link between preeclampsia and this potential pathologic process.

IP-10, preeclampsia and atherosclerosis

Striking parallels exist between preeclampsia and atherosclerosis (see bibliography for details). Patients who develop preterm preeclampsia are at increased risk of death from coronary artery disease later on in life [225]. Moreover, atherosis of the spiral arteries, a lesion observed in patients with preeclampsia, has striking similarities with that of coronary artery disease [226-228].

The current view of atherosclerosis is that it is an inflammatory mediated process [229-231]. Th1 biased responses are thought to be pro-atherogenic, while Th2 biased immunoresponses

confer atheroprotection [232]. Chemokine-dependent migration of cells through the inflamed endothelium into the arterial intima has been proposed to be critical in atherosclerosis [233-237]. There is evidence of a specific involvement of IP-10 in the pathogenesis of atherosclerosis and cardiovascular diseases. Such evidence includes: (1) patients with stable angiographically confirmed coronary heart disease have a higher mean IP-10 serum concentration than control patients, and the magnitude of the elevation correlates with the concentration of several acute-phase proteins (C-reactive proteins) or cytokines known to be central in the pathogenesis of atherosclerosis [122]; (2) serum IP-10 baseline concentrations are significantly higher in individuals who develop coronary heart disease (CHD) than in those who do not (follow-up of 11 years). After adjustment for cardiovascular and immunological risk factors, however, the observed relationship with IP-10 disappeared, suggesting that the association may be explained by other markers of inflammation and not be specific to IP-10. Nonetheless, this observation is important because it suggests that an elevation of IP-10 precedes the development of CHD, thus strengthening the case that inflammation has a causal role rather being a consequence of atherosclerosis [121]; (3) CXCR3-bearing T cells and chemokines IP-10, I-TAC and MIG (all three IFN-γ induced) are present in atherosclerotic plaques [120].

Conclusion

Preeclampsia is associated with higher maternal plasma concentrations of IP-10 than normal pregnancy and SGA. These results suggest that this chemokine may contribute to both the exaggerated systemic inflammation and the anti-angiogenic state that characterize preeclampsia.

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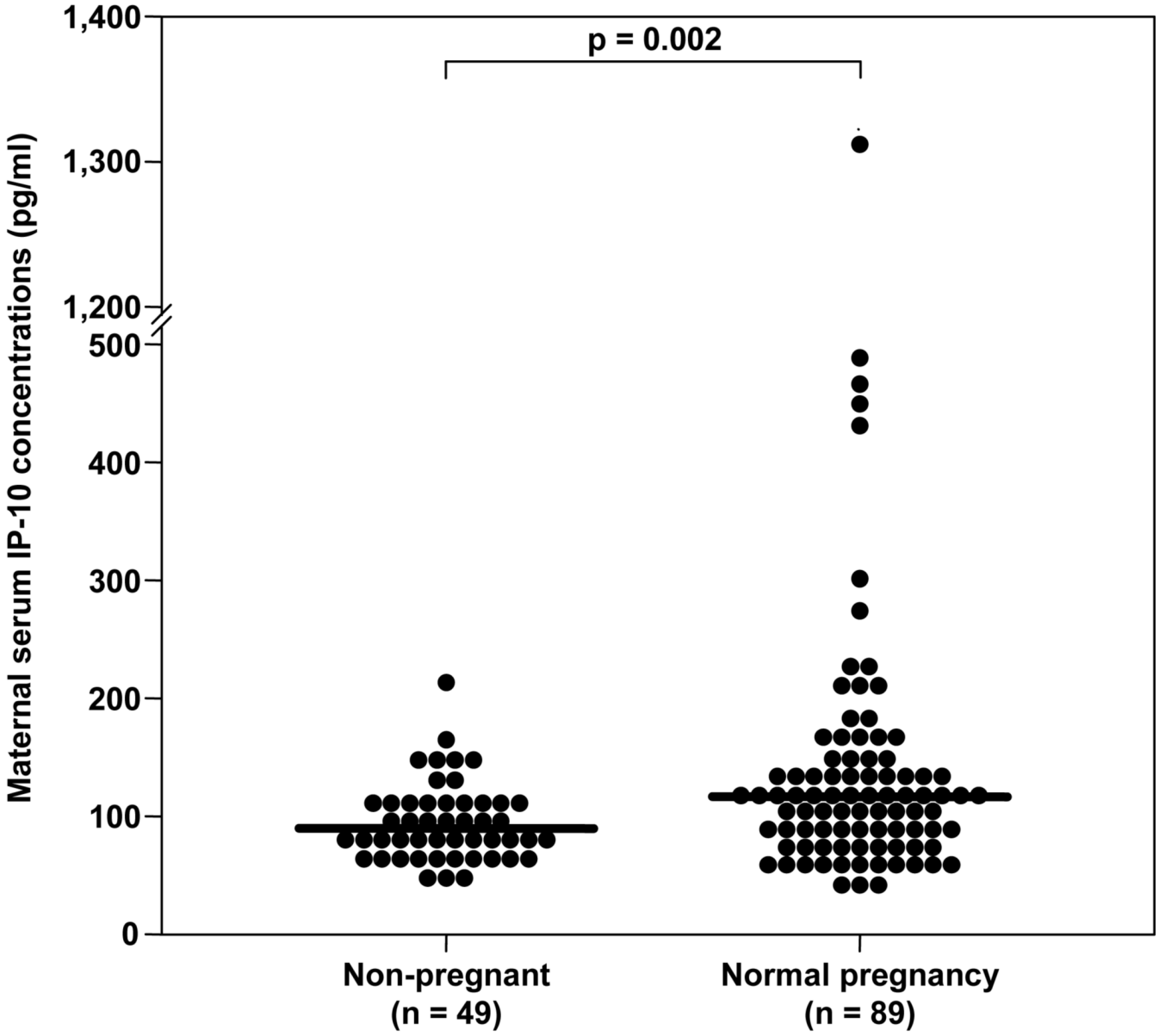

Figure 1.
Serum concentrations of CXCL10/IP-10 in non-pregnant women and in patients with normal pregnancies. Patients with normal pregnancies had a significantly higher median serum concentration of IP-10 than non-pregnant women (median: 116.1 pg/mL, range: 40.7-1314.3 vs. median: 90.3 pg/mL, range: 49.2-214.7, respectively; p=0.002).

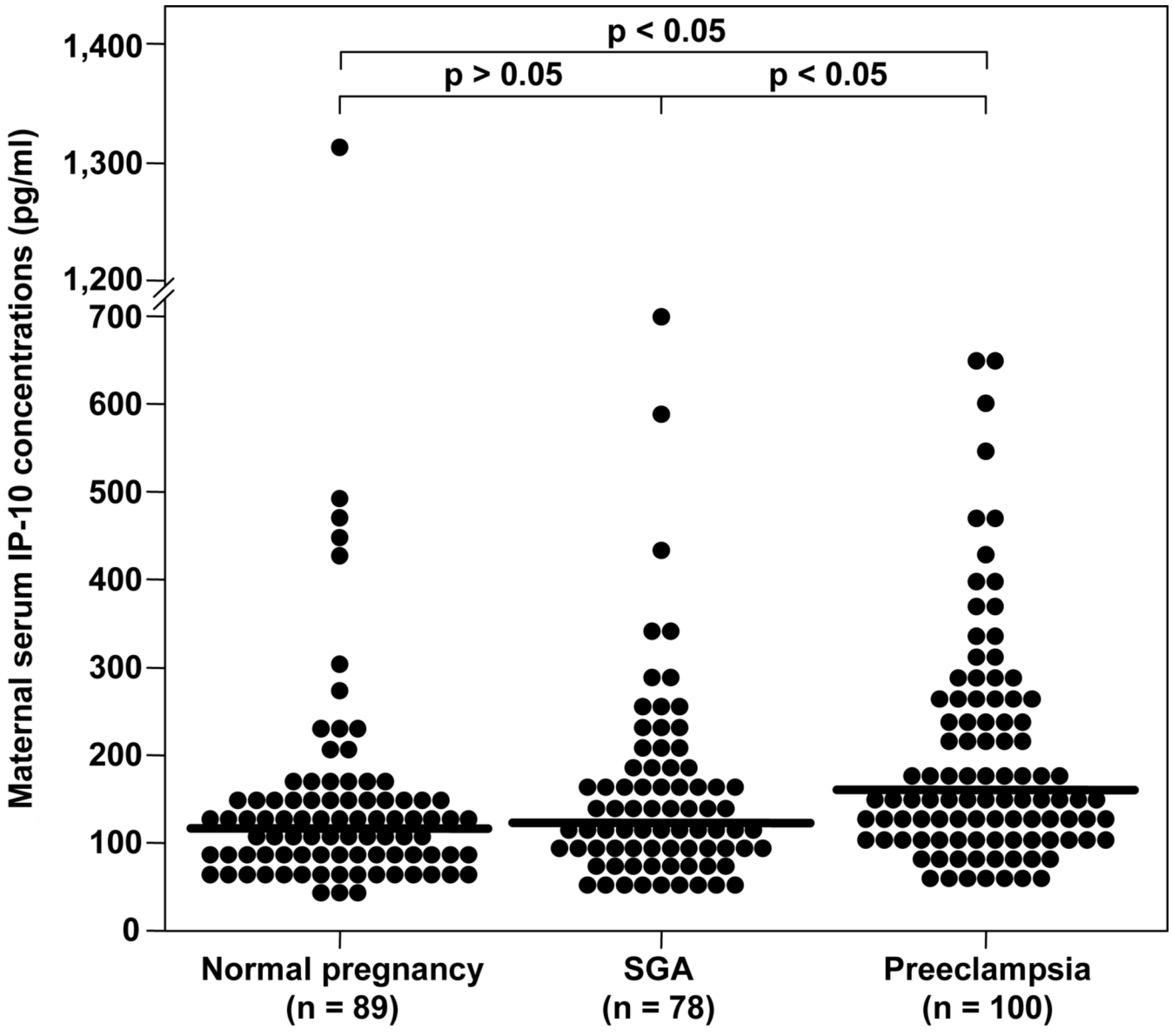

Figure 2.

Maternal serum concentrations of CXCL10/IP-10 among the study groups. Patients with preeclampsia had a significantly higher median serum concentration of IP-10 than normal pregnant women (median: 156.4 pg/mL, range: 47.4-645.9 vs. median: 116.1 pg/mL, range: 40.7-1314.3, respectively; $p<0.05$) and than patients who delivered a SGA neonate (median: 156.4 pg/mL, range: 47.4-645.9 vs. median: 122.4 pg/mL, range: 37.3-693.5, respectively; $p<0.05$). No significant differences were found in maternal serum median IP-10 concentrations between patients who delivered a SGA neonate and those with normal pregnancies (median: 122.4 pg/mL, range: 37.3-693.5 vs. median: 116.1 pg/mL, range: 40.7-1314.3, respectively; $p>0.05$).

TABLE I

Clinical and obstetrical characteristics of the study groups

	Normal pregnancy (N=89)	Preeclampsia (N=100)	p*	SGA (N=78)	p
Maternal age (years) †	23 (17 - 34)	25 (14 - 43)	NS	23.5 (15 - 43)	NS
Race					
African-American	83.1 (74/89)	80.8 (80/99)	NS	84.6 (66/78)	NS
Caucasian	12.4 (11/89)	13.1 (13/99)	NS	10.3 (8/78)	NS
Others	4.5 (4/89)	6.1 (6/99)	NS	5.1 (4/78)	NS
BMI (kg/m^2) †	25.5 (16.3 - 51.6)	26.3 (18.3 - 44.5)	NS	24.9 (14 - 36)	NS
Nulliparity	21.3 (19/89)	29.3 (29/99)	NS	23.1 (18/78)	NS
Smoking	20.5 (17/83)	13.2 (12/91)	NS	28.6 (20/70)	NS
Gestational age at blood draw (weeks) †	31.1 (19.4 - 38.3)	32.6 (20.0 - 40.9)	<0.05	36.6 (24.4-40.3)	<0.05‡
Gestational age at delivery weeks) †	39.6 (37 - 42)	33.3 (20.1 - 40.9)	<0.05	37.2 (24.9 - 41.7)	<0.05‡
Birth weight (g) †	3342 (2550 - 4050)	1700 (220 - 4460)	<0.05	2130 (300 - 2895)	<0.05§

Values are expressed as percentage (number) or median (range).

SGA: small for gestational age neonate; **BMI:** body mass index; **NS:** not significant.

p* comparison between normal pregnancy and PE.

† Kruskal-Wallis with post-hoc analysis.

‡ <0.05 between SGA and normal pregnancy, as well as SGA and PE.

§ <0.05 between SGA and normal pregnancy.