Placenta 78 (2019) 23–28

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Complement receptor-associated CD163$^+$/CD18$^+$/CD11c$^+$/CD206$^-$/CD209$^-$ expression profile in chronic histiocytic intervillositis of the placenta

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ARTICLE INFO

Keywords:
Placenta
Chronic histiocytic intervillositis
CD11c
CD18
CD163

ABSTRACT

Introduction: Chronic histiocytic intervillositis of unknown etiology (CIUE) is a non-infectious, most probably immunologic placenta lesion. CIUE is associated with recurrent miscarriage, intrauterine growth restriction and stillbirth. Among the pathologic-anatomic defined placental lesions this entity displays the highest risk of recurrence in following pregnancies (about 67–100%). The histiocytic cells accumulate in the placental blood space but do not infiltrate into the villi or decidua. Sparsely known is the expression profile of these intervillous cells regarding histiocytic markers.

Methods: We analysed 5-22 markers by immunohistochemistry in a total of 41 placenta samples and evaluated decidual, villous and intervillous histiocytic cells.

Results: In CIUE, intervillous CD163$^+$ histiocytes over-express CD11c/CD18 and down-regulate CD206/CD209, while CD163$^+$ decidual and Hofbauer cells show low CD11c/CD18 and higher CD206/CD209 protein expressions.

Discussion: CD163 expression indicates a M2-like polarisation. CD11c and CD18 form the complement receptor 4 which could be related to a complement mediated trigger for aberrant cell accumulation in CIUE.

1. Introduction

Pregnancy is an immunological challenge for the maternal immune system. Placental fetal Hofbauer histiocytes in the villi and maternal decidual histiocytes are main cellular components which mediate local immunosuppression for preventing rejection of the semi-allogenic placenta, even in case of concomitant inflammation such as intervillous bacteriemia or amnion fluid infection with chorioamnionitis [1]. Usually, maternal leukocytes flow with the blood through the intervillous space of the placenta and do not accumulate or invade the placenta.

In cases of bacterial chorioamnionitis or rare viral villitis maternal leukocytes infiltrate the amnion or the villi, respectively. In this instance, the maternal immune system still tolerates the placenta. Pathologic conditions, which are believed to be based on immunological triggers are chronic intervillositis of unknown etiology (CIUE) and villitis of unknown etiology (VUE) [2–5]. CIUE shows a characteristic accumulation of CD68$^+$ cells in the intervillous space and these cells do not significantly infiltrate into the decidua, chorionic villi or amnion. The initiating factor is unknown but complement activation has been suggested to be one probable pathogenetic factor [2]. The diagnosis can be made only retrospectively, after the pregnancy, by histological examination of the placenta tissue. Recurrent miscarriage, fetal growth restriction and intrauterine death can occur and CIUE has a high risk of recurring in subsequent pregnancies in up to 67–100% of cases [4]. Moreover, many mothers who suffer from CIUE show autoimmune diseases or pathologic autoantibodies in the peripheral blood [6]. Only a few cases have been reported, in which therapy appeared to prevent CIUE manifestation in a following pregnancy [7,8]. Different regimes have been used, including aspirin alone, aspirin in combination with heparin or aspirin in combination with heparin and corticosteroids [7,8].

Approaches to gain insight into the etiologic factors and the pathogenesis of this unique disease are important to develop therapeutic and screening procedures.

In a recent review, Bos and colleagues thoroughly re-evaluated the

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https://doi.org/10.1016/j.placenta.2019.02.007
Received 6 December 2018; Received in revised form 21 January 2019; Accepted 11 February 2019

diagnostic criteria and they found that CD68 is the most commonly used marker to verify monocytic origin of the intervillous infiltrate [9]. Although CD68 is a marker for monocyte-derived cells, it does not discriminate different subtypes. As summarized by Ning *et al.*, decidual histiocytes express CD68, CD14 and CD163 and CD14$^+$ cells are composed of CD206^{high}/CD209^{high}/CD11c^{low} and CD206^{low}/CD209^{low}/CD11c^{high} subtypes [1]. Histiocytic Hofbauer cells in the villi are CD68$^+$/CD163$^+$/CD209$^+$/CD206$^+$ and this observation indicates an immunosuppressive M2-like function in order to maintain materno-fetal tolerance [10–12].

Since the first description of CIUE by Labarrere and Mullen in 1987 there has never been an investigation into which subtype of monocytic-derived cells does accumulate in the intervillosum of the placenta. Due to the lack of significant tissue infiltration and no increased expression of pro-inflammatory cytokines in CIUE [13], M1 polarized cells are unlikely. However, there is more than just one M2 cell type. As summarized by Ning *et al.* [1] and Li *et al.* [14] non-M1 cells include *in vitro*-defined M2a, M2b, M2c, M2d and CD163-negative regulatory macrophages (Mreg) as well as monocytic lineage-derived dendritic cells. This sub-classification has been established for non-placental histiocytes. Histiocytic cells in the placenta are composed of several M2-like subtypes, but the M2a-d sub-classification cannot be directly adopt to placental and decidual histiocytes [1]. In addition, one single marker is not sufficient for characterisation of M2-like polarization. Therefore, for the first time, we performed an extensive evaluation of the CIUE cell phenotype, including up to 22 markers.

2. Material and methods

2.1. Study groups and analytic strategy

Formalin-fixed and paraffin-embedded (FFPE) placental samples were analysed. The retrospective analysis was approved by the local Ethics Committee at Hannover Medical School (#2893-2015).

A total of 41 cases were evaluated: 14 CIUE (median 25.5/range 8–33 week of gestation, median 32/range 24–38 years maternal age), eight VUE (37.5/30–40 weeks, 28.5/18–34 years) and 19 controls without lymphohistiocytic inflammation (31/9–40 weeks, 29/23–43 years). Note that VUE typically manifests in the second/third trimester and not in the first trimester [3]. Controls were matched according to gestational and maternal age to CIUE and VUE.

For screening purposes, we first evaluated up to 22 markers in four CIUE cases (cohort I) and compared intervillous cells with Hofbauer cells and decidual histiocytes as internal controls. After an interim analysis of these result, we selected five markers for re-evaluation (cohort II): CD163, CD206, CD209, CD11c and CD18 (nine CIUE, eight VUE and 19 controls).

2.2. Immunohistochemistry

Automated immunohistochemistry was performed on a Benchmark ULTRA (Ventana Medical Systems, Inc. Tucson, AZ, USA): CD68, CD14, CD163, lysozyme, myeloperoxidase (MPO), CD10, CD11c, CD21, CD23, CD103, CD123, CD80, CD86, annexin A, CD56, S100, CD1a, PDL1, CD4 and Ki67. The following antibodies were stained manually (ZytoChemPlus HRP Polymer-Kit, Zytomed Systems, Berlin, DE): CD18 (pre-treatment with pH 6.0 citrate buffer, 90 °C for 30 min, 1:100, Abcam, Berlin, DE), CD206 (pre-treatment with pH 6.0 citrate buffer, 90 °C for 30 min, 1:300, Abnova, Aachen, DE) and CD209 (pre-treatment with pH 9.0 EDTA buffer, 90 °C for 30 min, 1:1000, Abcam).

2.3. Evaluation and statistics

Percentage of stained histiocytic cells and staining intensity (0–3+) was evaluated per tissue section. Histiocytic cells in the basal decidua and Hofbauer cells were analysed. In addition in CIUE the intervillous histiocytic cells were examined. In VUE, in the affected villi with lymphohistiocytic infiltrates, the histiocytic cells were evaluated. Intermingled non-histiocytic cells were discriminated by morphology.

Results were summarized and descriptive statistics were performed.

3. Results

3.1. In CIUE intervillous cells have a different marker profile regarding CD11c/CD18 and CD206/CD209 than Hofbauer and decidual histiocytes

In cohort I, we found that the majority of intervillous cells co-expressed CD68 (100% of histiocytic intervillous cells, variable 1–3+ staining intensity), CD163 (100%, 2+), CD11c (100%, 2+) and CD18 (100%, 3+); Supplementary Table 1, Supplementary Figs. 1–4. Other markers were co-expressed in variable frequencies and intensities: PDL1 (70–100%, 1–2+), annexin A1 (30–70%, 1+), MPO (10–70%, 1–2+), lysozyme (10–70%, 1–2+), CD4 (5–90%, 1+) and CD14 (< 5–100%, 1–2+). A small subfraction of intervillous cells expressed CD80 (≤10%, 1+), CD206 (≤5%, 1+), CD103 (≤5%, 1–2+) and S100 (< 5%, 1+). The following markers were not expressed in intervillous cells: antigen-presenting cell-associated CD86 and dendritic/reticulocytic cell markers CD209, CD10, CD21, CD23, CD56, CD123 and CD1a.

Intervillous cells, Hofbauer cells and decidual histiocytes showed a similar co-expression of CD163 while we noted that the main difference included CD11c, CD18, CD206 and CD209. Intervillous cells were CD11c$^+$/CD18$^+$ and mainly CD206$^-$/CD209$^-$ while Hofbauer cells and decidual histiocytes had an opposite profile with few or no CD11c/CD18 co-expressing cells but expression of CD206 and CD209 (Supplementary Table 1, Supplementary Figs. 1–4). These five markers were selected for further evaluation.

3.2. Re-evaluation of markers: overexpression of CD11c/CD18 in CIUE

In placentas without CIUE or VUE, most Hofbauer cells and decidual histiocytes were CD163$^+$ and CD206$^+$. CD209 was more variable positive while a smaller subfraction of cells showed staining for CD11c and CD18.

In CIUE, the marker profile pattern in intervillous cells could be confirmed and showed a co-expression of CD163, CD11c and CD18 with no or few CD206/CD209 positive cells (Table 1, Fig. 1). Within VUE lesions, a different pattern was found. Histiocytic cells in affected villi were CD163$^+$ and partially also CD11c$^+$/CD18$^+$ but in contrast to CIUE cells were also positive for CD206 and CD209.

Hofbauer cells in villi without inflammation in VUE as well as in villi in CIUE showed mainly a similar marker profile for CD163, CD18, CD206 and CD209 as in controls. Regarding CD11c, it appears that in CIUE and VUE, Hofbauer cells are mainly negative, while in controls a small subfraction co-expressed CD11c.

Decidual histiocytes were mainly positive for CD163 and variable positive for CD206, CD209, CD11c and CD18 (Table 1). We noted no change of the expression profile of decidual cells in CIUE, VUE and controls.

4. Discussion

Previous studies have focused on the expression profile of decidual histiocytes and Hofbauer cells in non-CIUE conditions [1,10–12]. In our previous studies we have analysed the transcript expression profiles of inflammation-related cytokine and cytokine receptors in CIUE, VUE and placentas without inflammation and found only minor differences [13,15]. For example, in a subfraction of CIUE Toll-like receptor (TLR) 1 transcripts were increased while TLR2-9 were not significantly deregulated [15].

Based on the typical non-destructive CIUE histopathology, it was expectable to find some kind of M2-like expression profile, including

Table 1
Histiocytic marker profile in CIUE (n = 14), VUE (n = 8) and controls (n = 19).

In case of variable percentages of stained cells and variable staining intensity, median/range (%) and range (1-3+, 1-2+ or 2-3+) are listed, respectively. In some cohorts, not all histiocytic compartments could be evaluated (indicated by case numbers). Abbreviations: decidual histiocytic cells (DC), Hofbauer histiocytic cells (HC), intervillous histiocytic cells (IVC), histiocytic cells within the affected villi in VUE (VUE).

Marker	Controls (% cells, intensity)		CIUE (% cells, intensity)			VUE (% cells, intensity)			
	DC	HC	DC	HC	IVC	DC	HC	VUE
CD163	100%, 2–3+ (n = 17/19)	100%, 2–3+	100%, 1–3+ (n = 12/14)	100%, 2–3+	95/30–100%, 1–2+	100%, 2–3+ (n = 6/8)	100%, 2–3+	100%, 1–3+
CD206	100/5–100%, 1–3+ (n = 16/19)	100%, 2–3+	80/30–100%, 1–3+ (n = 11/14)	100%, 2–3+	0/0–5%, 1+	55/10–100%, 1–3+ (n = 6/8)	100%, 2–3+	35/10–80%, 1–3+
CD209	100/70–100%, 2–3+ (n = 16/19)	70/5–100%, 1–3+	20/ < 5–70%, 1–2+ (n = 12/14)	10/ < 5–100%, 1–3+	0%	15/0–30%, 1–2+ (n = 6/8)	15/ < 5–70%, 1–2+	8/5–50%, 1–2+
CD11c	5/ < 5–10%, 1–2+ (n = 17/19)	0/0–30%, 1–2+	0/0–5%, 1+ (n = 12/14)	0%	100%, 1–2+	0/0–5%, 1+	0%	70/10–100%, 1–2+
CD18	15%/ < 5–70%, 1–2+ (n = 16/19)	10/ < 5–70%, 1–2+	80/10–100%, 1–3+ (n = 11/14)	10/ < 5–80%, 1–2+	100%, 3+	10/5–80%, 1–3+ (n = 6/8)	< 5/0–20%, 1+	100/20–100%, 2–3+

CD163 co-expression. In general, the M2 sub-classification is not based on the unique situation in the placenta but on typical types of anti-pathogenic inflammation, scar formation and degenerative conditions. M2 subtypes are not only defined by receptor protein expression but also reaction to cytokine stimuli and cytokine expression [1]. A better understanding of the M2-like expression pattern in CIUE can help to understand the pathobiologic basis of this disease and could be rational for additional diagnostic markers.

Due to the plasticity of histiocytic cells, the classification of M2 subtypes represents a transient state of differentiation and function which can change if needed [1,16–18]. FFPE placental tissue represents a snap shot of the plasticity of the histiocytic cells in CIUE and CD68 as the sole marker is not sufficient for a more precise characterisation. Based on *in vitro* experiments, non-placental M2 subtypes are divided into M2a-d, but, as summarized by Röszer [16], this classification gives emphasis to the activation stimuli, rather than the macrophage functions elicited by the stimuli. In addition, there is some overlap regarding marker expression. For example, in non-placental histiocytes, CD163 and CD206 are expressed in M2a but also in M2c polarized cells whereas CD163/CD206 co-expression is more typical for M2c while M2a cells co-express CD86/CD206 [16,17]. CD209 expression is typically found in dendritic cells [18]. In the normal placenta, all three markers (CD163, CD206, CD209) are expressed by most Hofbauer and decidual histiocytes [1] while CD11c and CD18 are expressed by a smaller subfraction of placental and decidual histiocytes. The CIUE-typical accumulation of histiocytic cells in dense intervillous aggregates resembles dendritic or reticulum-like aggregation patterns but typical related markers such as CD209 are not expressed.

CD163 expression in intervillous cells can be an epiphenomenon of M2-like polarisation (similar to expression of PDL1 and annexin A1), but can also have a particular function in CIUE. CD163 is involved in the clearance and endocytosis of hemoglobin/haptoglobin complexes by macrophages, and may thereby protect tissues from free hemoglobin-mediated oxidative damage [19]. CIUE cells show no increased erythrocyte-derived iron storage or hemophagocytosis but this does not exclude sheer stress and damage of erythrocytes secondary to occupation of the intervillous space by histiocytic cells. In general, one function of non-placental $CD163^+$ M2c cells is not only immunosuppression but also matrix remodelling and tissue repair [1]. We have shown that some CIUE express higher levels of matrix remodelling factor metalloproteinase 9 (MMP9) [13]. However, villous stroma in CIUE appears not diffusely fibrotic and MMP9 could be a reaction to trophoblast cell stress.

CD11c and CD18 are components of the complement factor receptor type 4 (CR4) [20,21]. This is the first time that CR4 expression is demonstrated in CIUE cells. Remarkably, since the first description of CIUE in 1987, activation of complement factors has been discussed as one initiating factor for intervillous cells accumulation [2]. It is still unknown, why complement signalling is triggered and why, for example, complement cascade-associated CD55 is only weakly expressed in CIUE cells [22]. In addition, our results do not clarify, whether CR4 proteins are upregulated after complement aggregation or if the increase of CR4 leads to increased binding of complement or both.

The marker profile of intervillous CIUE cells has some overlaps with VUE but also with normal blood cells. In the normal blood, $CD163^+$/$CD11c^+$ cells are detectable, which are thought to represent a subpopulation of circulating dendritic cells; CD18, CD206 and CD209 were not included in this analysis [19]. In addition to circulating blood leukocytes, $CD163^+$/$CD11c^+$ [23] or $CD11c^+$ [24] histiocytic cells have been found in adipose tissue but also in lymph nodes after infection with *Treponema pallidum* [25]. Without treponemal infection, two populations of $CD163^+$/$CD11c^-$ and $CD163^-$/$CD11c^+$ histiocytes can be found in lymph nodes [25]. This demonstrates the plasticity of histiocytic cells to express these markers in different conditions. Therefore, two mechanisms could be possible which result in CIUE cell accumulation in the intervillous space during pregnancy: i) circulating

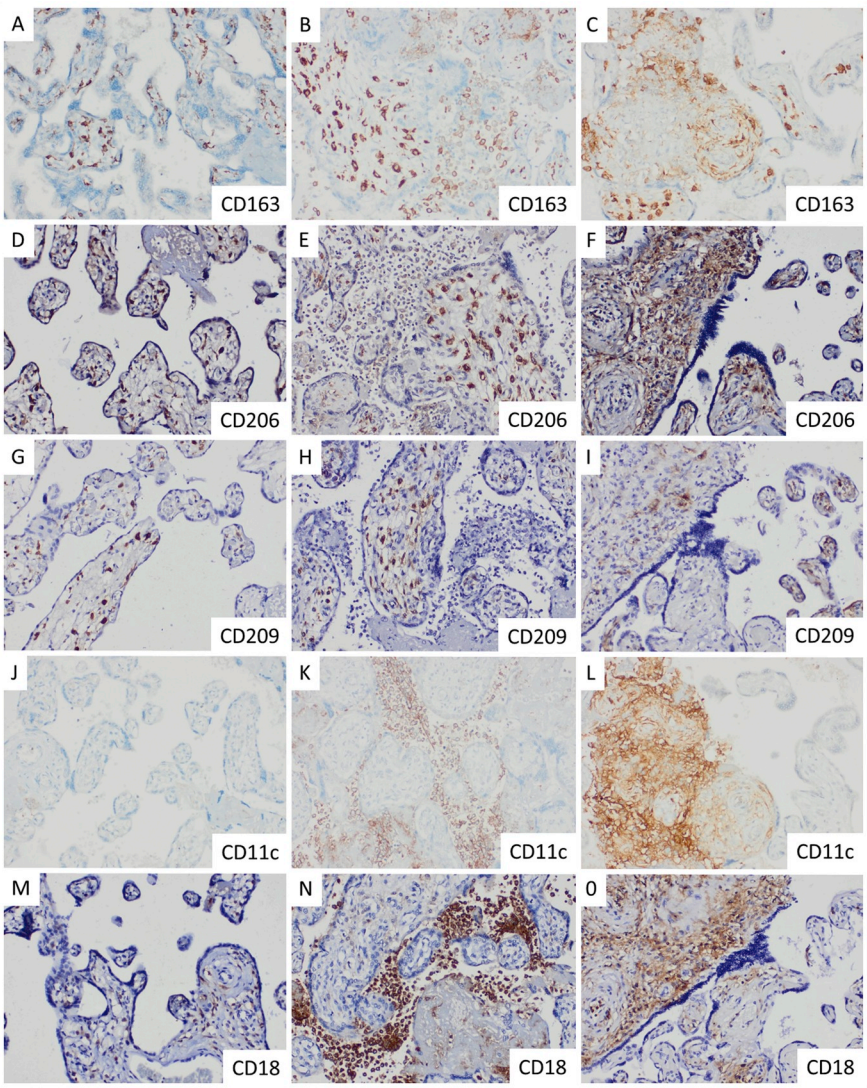

Fig. 1. Aberrant expression of CD206/CD209 and CD11c/CD18 in CIUE. A) Control placenta with $CD163^+$ Hofbauer cells. B) CIUE placenta shows strong CD163 expression in Hofbauer cells and weaker expression in intervillous cells. C) VUE lesions include some $CD163^+$ histiocytic cells. Note $CD163^+$ Hofbauer cells in adjacent unaffected villi. D-I) In controls (D & G), CIUE (E & H) as well as in unaffected villi in VUE (F & I), Hofbauer cells express CD206 and CD209. Intervillous cells in CIUE are negative for CD206 and CD209. In VUE lesions histiocytic cells are positive for CD206 and CD209. J-O) In controls (J & M) few Hofbauer cells are positive for CD11c and CD18 while in CIUE (K & N) and VUE (L & O) almost all villous cells are negative for CD11c and few are positive for CD18. Intervillous cells in CIUE are moderately positive for CD11c and strongly positive for CD18. Within VUE lesions histiocytic cells are positive for CD11c and CD18. Original magnification in all images is 200×.

$CD163^+/CD11c^+$ blood cells are selectively entrapped in the placenta and/or ii) $CD163^+/CD11c^-$, $CD163^-/CD11c^+$ or $CD163^-/CD11c^-$ cells transform after intervillous homing into $CD163^+/CD11c^+$ cells.

CIUE and VUE are both thought to be results of an aberrant immunologic materno-placental tolerance. The differences in pathologic anatomy are paralleled by some differences regarding the monocytic marker profile expression in these two placental lesions. VUE shows increased CR4 expression within the lesions and the surface of the affected villi which indicates complement activation, but the CR4 expression appears to be weaker than in CIUE. In addition, in contrast to CIUE, this CR4 expression is associated with inflammation within the villous stroma and T cell infiltration while CIUE cells do not invade the stroma. In contrast to CIUE, CD209 and CD206 are expressed in VUE lesions, and this could indicate a dendritic-like polarisation in at least a subfraction of histiocytic cells in VUE.

In CIUE, villi show no major stromal changes and in VUE, typically only a subfraction and not all villi are affected. A remarkable finding is that in both CIUE and VUE, the normal Hofbauer cells and decidual histiocytes maintain a $CD163^+/CD206^+/CD209^+$ marker profile expression as in non-CIUE/VUE placentas. This correlates with previous findings, which revealed that inflammatory stress/chorioamnionitis does not induce a M1 polarization in Hofbauer cells [10–12]. This "fixed" M2-like polarisation in Hofbauer cells and decidual histiocytes is likely due to the requirement to maintain the materno-placental tolerance in inflammatory conditions. However, in both CIUE and VUE, CD11c appears to be almost absent in Hofbauer cells which could be a counter reaction to complement activation in both diseases. In principle, this confirms our previous hypothesis: the discrepancy of massive intervillous histiocytic accumulation and the lack of striking up-regulation of cytokines and the maintenance of a Hofbauer and decidual histiocytic marker expression profile are most likely the basis of the non-destructive and non-infiltrating behaviour of the intervillous histiocytes [13].

From a diagnostic point of view, in addition to CD68 [9], CD11c could be a helpful marker for verifying CIUE in placental tissue samples; CD11c is also a diagnostic marker for hairy cell leukemia and therefore established in some immunohistochemistry laboratories. In principle, CD18 could be used, too, but this antibody is rarely, if ever, used in routine diagnostics of hematologic neoplasms. From a purely histological perspective the main histological differential diagnosis of CIUE is placental malaria. In a subfraction of pregnant women with *Plasmodium falciparum* infection a CIUE-like intervillositis manifests [26]. Although this can often be distinguished based on medical history and microbiology it may be a more complex problem in global placental pathology and so additional markers may be beneficial. A previous study has shown that malaria-diseased women with placental intervillositis had significantly higher soluble CD163 placental blood levels compared to malaria-diseased women without placental intervillositis and uninfected women [26]. Remarkably, irrespective of malaria infection status or presence/absence of intervillositis, the maternal peripheral blood

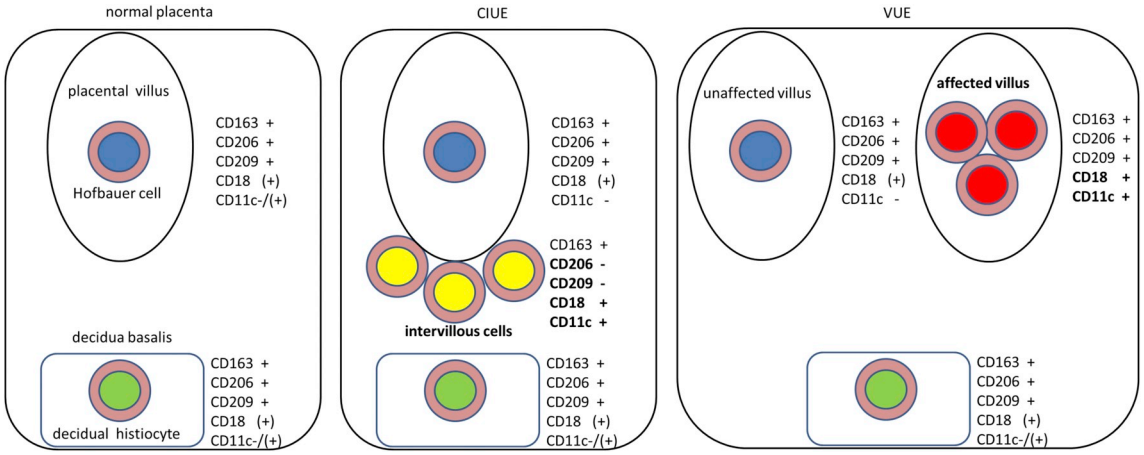

Fig. 2. Schematic overview of the different expression profiles in CIUE versus controls and VUE.

plasma concentrations of soluble CD163 proteins were not different [26]. This indicates some similarities with CIUE, but CD11c, CD18, CD206 and CD209 have not been investigated as yet. A more comprehensive analysis of histiocytic marker expression in placental malaria in comparison to CIUE is pending.

In case of CIUE, maternal serum alkaline phosphatase levels can be elevated while monocytosis is not a typical finding and currently, peripheral blood/serum analysis does not provide reliable information on presence and absence of CIUE [7,27,28]. The normal range of $CD11c^+$ and/or $CD18^+$ cells, the range during non-CIUE pregnancies or pregnancies with other co-morbidities is unknown and therefore as yet no cut-off for the diagnosis of CIUE can be defined. In addition, testing of one single marker is insufficient, e.g. because in particular CD18 is also expressed by granulocytes [20,21].

We know too little on the initiating trigger and the dynamics of intervillous cell accumulation to suggest any CR4-directed specific therapy. Therefore, currently immunosuppressive and antithrombotic agents in a following pregnancy remain the only therapy option [7,8].

In summary, intervillous histiocytic cells in CIUE upregulate CD11c/CD18 and down-regulate CD206/CD209 expression while Hofbauer and decidual histiocytes mainly show no aberrant marker expression profile (Fig. 2).

Funding

None.

Author contribution

KH: design of the study, statistical analysis. ASK, KH: immunohistochemistry. KH, AM, RA, HK, HF: collection of clinical data, sample selection. KH, ASK, AM, RA, HK, HF: interpretation of data, manuscript preparation.

Declaration of interest

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2019.02.007.

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