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1 **Placental macrophages: origin, heterogeneity, function and role in pregnancy-associated**
2 **infections**

3

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28 **Abstract**

29 Placental macrophages are a heterogenous population of immune cells present throughout
30 pregnancy. They are essential for maintenance of the homeostatic placenta environment and
31 host defense against infections. The characterization of placental macrophages as well as their
32 activation have been limited for a long time by the lack of convenient tools. The emergence of
33 unbiased methods makes it possible to reappraise the study of placental macrophages. In this
34 review, we discuss the diversity and the functions of placental macrophages to better
35 understand their dysfunctions during placental infections.

36

37 **Key points:** Macrophages, placenta, M1/M2 polarization, infectious pregnancy.

38

39 **Highlights:**

- 40 • Placental macrophage populations exhibit heterogeneity in terms of fetal/maternal
- 41 origin and phenotype
- 42 • Placental macrophages combine metabolic and immunological functions that enable
- 43 placenta development and maternal immune tolerance
- 44 • The role of placental macrophages in infectious diseases remains obscure opening
- 45 fascinating heuristic and therapeutic perspectives

46 ***Revisit placental macrophages?***

47 The placenta is a chimeric, rapidly growing organ in which fetal and maternal tissues are in
48 close contact [1]. The maternal part of the placenta is composed of the decidua basalis which
49 is directly related to the uterus; this constitutes an intimate connection between the mother
50 and her developing fetus as fetal membranes that are composed of extravillous trophoblasts.
51 The fetal part is covered by the amnion, which is involved in the secretion of the amniotic
52 fluid. Under the amnion, the chorion, a membrane in continuity with the lining of the uterine
53 wall, is required for supplying nutrients to the fetus and preventing fetus rejection by the
54 maternal immune system [1–3]. The placenta is characterized by the presence of an immune
55 system supporting the immune tolerance toward the fetus and the ability of mother to prevent
56 infections. The placental immune system comprises natural killer (NK) cells, macrophages
57 (~20%), T cells (~10-20%) and rarer cell types, such as dendritic cells, B cells, NKT cells and
58 mast cells [3–5]. Although the NK population is the largest during the first trimester (~70%),
59 its number steadily decreases to reach 20% of total immune cells at the end of the third
60 trimester [6]. The number of macrophages follows same kinetics 50% to ~20% before
61 delivery based on immunohistochemical technique [7,8]. In contrast, the use of flow
62 cytometry reveals that macrophage population remains stable during the first trimesters [8]. In
63 contrast, T cell number gradually remains stable thought pregnancy [8].

64 Placental macrophages are composed of two distinct populations, i.e. decidual macrophages
65 and Hofbauer cells; they are detected as early as day 10 of pregnancy and are present during
66 the three trimesters of pregnancy [9]. The lack of convenient tools has limited the
67 characterization of human placental macrophages as well as their functional studies. The
68 diversity of these macrophages has been greatly underestimated, and most studies have been
69 limited to immunohistochemical characterization and inferences from what has been reported
70 in other resident macrophages. The application of single-cell RNA sequencing (scRNA-Seq)

71 to placenta investigation has paved the way for a novel atlas of placental populations,
72 including macrophages [10]. The analysis of placental macrophages publications revealed that
73 the number of reports focusing on placental macrophages has increased steadily since 2000
74 but the number of publications on the role of placental macrophages and infection has not
75 significantly increased (PubMed database).

76

77 ***Placental macrophage investigation: breaking through the barriers***

78 The study of tissue macrophages has been revolutionized by the development of unbiased
79 methods such as multiparametric flow cytometry and mass cytometry. Surprisingly, placental
80 macrophages have been overlooked for several reasons. First, placentation is distinct in
81 humans and rodents, and human and mouse placental macrophages are phenotypically
82 different, thus restricting the use of murine models [11]. Second, their location in a complex
83 and rapidly evolving tissue has favored *in situ* investigations, which precluded functional
84 studies. An *ex vivo* placental perfusion assay might be an alternative to study placental
85 macrophages in their natural microenvironment [12,13]. However, despite its initial
86 description some 50 years ago, placental perfusion assay has been mainly limited to
87 pharmacological investigations [14]. In contrast, the combination of laser microdissection and
88 scRNA-Seq has permitted the characterization of the signature of macrophage populations in
89 their microenvironment [10].

90 The isolation of human macrophages from placenta has appeared as the most convenient
91 approach for macrophage characterization and functional studies. Different methods have
92 been used to isolate placental macrophages [15–18]. The location of macrophages in a
93 complex tissue such as placenta and the lack of pertinent animal models make their study
94 particularly challenging. The investigation of human placental macrophages has mostly been
95 performed on immunohistochemical sections, which excludes functional studies. An *ex vivo*

96 placental perfusion assay might be useful to study placental macrophages in their natural
97 microenvironment in murine models and humans [12,13], but is to-day limited to
98 pharmacological investigations [14]. Isolating macrophages from human placentas is the most
99 convenient approach for functional studies. Different methods have been used: they vary in
100 the use of enzymes (collagenase, DNase and/or trypsin), density gradient type (Ficoll or
101 Percoll), positive or negative selection using anti-CD68, -CD10 or -CD14 antibodies or
102 adhesive properties [15–18]. We have developed a method using Ficoll procedure and anti-
103 CD14 antibodies to isolate human placental macrophages with high purity and yield [18], but
104 this does not discriminate their fetal/maternal origin.

105 We recommend here a method to isolate human placental macrophages using CD14
106 antibodies with high purity and yield [17]. Placental cells obtained by CD14 positive selection
107 exhibit typical macrophage features; despite the fact that they share CD14, the canonical
108 marker of monocytes, they are morphologically, phenotypically and functionally distinct from
109 circulating monocytes. They are of both maternal (30%) and fetal origin (70%) as determined
110 by sex chromosome staining [19]. The introduction of scRNA-Seq on one hand and
111 multicolor flow cytometry or mass cytometry on another hand would have a direct impact on
112 the characterization of placental macrophages. Given the reported differences between
113 Hofbauer cells and decidual macrophages, we will use the term “placental macrophages” for
114 both Hofbauer cells and decidual macrophages, except when their origin is specified.

115

116 *Ontogeny of placental macrophages: an emerging field*

117 It is largely established that resident macrophages in most tissues appear during the pre-natal
118 period, and self-renewal rather than replenishment with monocytes supports their maintain
119 throughout life. In response to aggression, monocytes become the major source of tissue
120 macrophages [20]. The ontogeny of placental macrophages must be analyzed according to the

121 heterogeneity of their origin. Initially, Hofbauer cells were thought to be in the chorionic villi,
122 suggesting a fetal origin, while decidual macrophages were found in the decidua basalis in
123 contact with the maternal myometrium, suggesting a maternal origin (**Graphical abstract**).
124 The sex chromatin staining in the placenta of a newborn boy has shown that X and Y
125 chromosomes are found in macrophages from the fetal part, but only X chromosomes in
126 decidual macrophages [21]. We recently found that CD14⁺ macrophages isolated from at term
127 human placentas are of both maternal (30%) and fetal origin (70%) [19].
128 The lack of convenient animal models for genetic fate mapping methods does not permit to
129 update the knowledge regarding placental macrophage ontogeny contrary to other tissue
130 macrophages. Only fragmentary information concerning the ontogeny of human placental
131 macrophages is available. Some authors proposed that Hofbauer cells originate from
132 mesenchymal cells within stroma of developing chorionic villi at the early stage of gestation
133 [22,23]. For others, Hofbauer cells were originate from monocyte progenitors of yolk sac and
134 migrate to the chorionic villi, whereas decidual macrophages derive from hematopoietic
135 pluripotent stem cells that differentiate into monocyte progenitors; these latter migrate from
136 bone marrow to the bloodstream of maternal side of the placenta where they mature [24]. It
137 is noteworthy that transitional forms between monocytes and macrophages exist during the
138 second and third trimesters, suggesting a differentiation of macrophages from fetal circulating
139 monocytes [25]. The question of self-renewal of placental macrophages is warranted by
140 placenta microenvironment. First, type 2 cytokines such as interleukin (IL)-4 and
141 macrophage-colony-stimulating factor (M-CSF)-1 that are known to stimulate macrophage
142 proliferation are over-represented in placenta [26]. Second, placental macrophages - and also
143 extravascular trophoblasts - likely communicate with placental NK cells through interaction
144 of M-CSF-1 produced by NK cells and M-CSF-1 receptor present on placental macrophages
145 and extravascular trophoblasts [27]. Recently, the study of single cell transcriptomic atlas of

146 maternal-fetal interface has shown that macrophages are able to self-renew [10]. In addition,
147 placental macrophages proliferate in pathological conditions including Zika virus infection
148 [28]. In contrast, Hofbauer cells did not exhibit mitotic activity or expression of Ki-67 marker
149 [29]. In summary, placental macrophages represent a heterogeneous population of embryonic
150 and hematopoietic origins but their ability to renew macrophage placental compartment is
151 debated.

152

153 *Placental macrophage heterogeneity: an increase in complexity*

154 Besides ontogenic heterogeneity, placental macrophages change their phenotype with
155 gestational age (**Table 1**). The phenotypic analysis of CD14⁺ macrophages reveal that seventy
156 percent of them express CD209 (dendritic cell-specific intercellular molecule adhesion
157 (ICAM)-3-grabbing non-integrin or DC-SIGN) and CD206 (mannose receptor), considered as
158 M2 markers (see below). The study of CD209 expression during first-trimester gestation has
159 shown the existence of two subsets of decidual macrophages. The major subset expresses
160 CD209 following CSF-1 stimulation [30] or combined action of CSF-1 and IL-10 [31]. These
161 CD209⁺ cells also express high levels of CD163, CD206, CD304 (neuropilin-1) and CD50
162 (ICAM-3), but low levels of CD11c, suggesting that they rather are M2 macrophages. The
163 minor subset of decidual macrophages that does not express CD209, highly expresses CD11c
164 and class II major histocompatibility complex (MHC) proteins, but not CD163, CD206,
165 CD304 [32–34], suggesting that they are M1 macrophages. Although phenotypically distinct
166 from blood monocytes, the transcriptional profile of these CD209⁺ macrophages is close to
167 that of circulating monocytes [35].

168 The recent use of scRNA-Seq has added an alternative degree in the heterogeneity of
169 placental macrophage populations. Tsang *et al.* identified two clusters of macrophage-like
170 cells that express activation markers of monocytes and Hofbauer cells. The monocyte

171 signature varies during the pregnancy [36]. Vento-Torno *et al.* identified three new
172 macrophage subsets. Two of them are discriminated by the level of expression of integrin
173 subunit alpha X (ITGAX) [10]. Pique-Regi *et al.* identified different myeloid clusters, some
174 of them matching with Hofbauer-type cells [37]. It is likely that the single cell transcriptome
175 approach will allow to identify non-previously identified populations of placental
176 macrophages beyond the classical dichotomy between Hofbauer cells and decidual cells.

177

178 ***Placental macrophage polarization: the limits of such classification***

179 Besides the different subsets of placental macrophages described above, the functional
180 properties of placental macrophages also change during pregnancy. The M1/M2 dichotomy
181 has been largely used to characterize activation changes of macrophages including placental
182 macrophages. Macrophage polarization is crucial for maintaining tissue homeostasis, even in
183 pathological conditions. These two polarization categories lead to the expression of specific
184 surface markers and to the secretion of several key cytokines to respond to
185 microenvironmental stimuli such as placenta tissue modulation throughout pregnancy. When
186 macrophages are stimulated with inflammatory cytokines or bacterial ligands such as
187 lipopolysaccharide, they acquire inflammatory and microbicidal properties.
188 Immunoregulatory cytokines, such as IL-4, IL-10 or IL-13 render macrophages poorly
189 inflammatory and microbicidal, but competent for healing [38]. These polarization profiles,
190 called M1 and M2, respectively, correspond to specific transcriptional, epigenetic and
191 proteomic signatures [38,39]. Throughout pregnancy, a balance of polarization between M1
192 and M2 placental macrophages is necessary for the placenta plasticity and adaptation to the
193 progression of gestation [40].

194 During the first and early second trimesters, placental macrophages exhibit an M1 profile
195 characterized by the expression of pro-inflammatory cytokines including tumor necrosis

196 factor (TNF), IL-12, IL-23, interferon (IFN)- γ and IL-18 [41]. However, Houser *et al.* showed
197 that two subsets of placental macrophages, CD11c^{low} and CD11c^{high}, do not fit a conventional
198 M1/M2 categorization based on the secretion of both pro- and anti-inflammatory cytokines
199 during the first trimester [35]. At the end of the second trimester and during the early third
200 trimester, placental macrophages exhibit an M2 profile characterized by the production of
201 vascular endothelial growth factor (VEGF), IL-6 and IL-10 [42]. At the end of gestation,
202 placental macrophages still exhibit an M1 profile. Indeed, at term, CD14⁺ placental
203 macrophages express a program including the transcriptional expression of several members
204 of TNF superfamily, the expression of chemokine receptors and the secretion of immune
205 cytokines (IL-6, IL-10 and IL-1) [17,41,42]. The M1/M2 dichotomy to characterize placental
206 macrophage populations deserves some criticisms and requires to be rethought. M1/M2
207 markers were found vary according to the studies and are not enough robust to allow
208 characterization of cell subsets. This is illustrated by conflicting results concerning
209 macrophage polarization in preeclampsia, a major inflammatory disease of pregnancy in
210 which we could expect an M1 signature [43]. We recommended to assess macrophage
211 activation by considering agonist and cell types however with a combination of several
212 markers [38]. When this latter approach was used, we were unable to detect M1/M2
213 polarization in at term placental macrophages [17].

214

215 ***Placental macrophages and multinucleated giant cells: a continuum***

216 The originality of placental macrophages is to form multinuclear giant cells (MGCs). Their
217 formation is associated with down-modulation of CD14 and up-regulation of CD68 and
218 CD163, which suggests a maturation process [17]. Placental MGCs exhibit features
219 reminiscent of osteoclasts and foreign body giant cells (FBGCs), other types of myeloid
220 MGCs. Their cytoskeleton is reorganized with podosomes in peripheral ring as in osteoclasts

221 and placental MGCs contain small number of nuclei randomly distributed as in osteoclasts
222 and FBGCs [44]. The ability of placental macrophages to form MGCs may be related to the
223 fusion of cytotrophoblasts into syncytiotrophoblasts, a step required for placenta function
224 [45]. Although placental macrophages have an intrinsic ability to fuse, it is likely that
225 trophoblasts create a microenvironment prone to favor macrophage fusion. Several molecules
226 produced by trophoblasts are candidate to affect differentiation of placental macrophages into
227 MGCs. They include syncytins [46,47], E-cadherin and IL-4, a cytokine that mediates
228 macrophage fusion in an E-cadherin-dependent manner [44,48]. The functions of placental
229 MGCs are still obscure relying on indirect evidence. They exhibit enrichment of genes
230 implicated in cytoskeleton organization, adhesion and immune response, thus highlighting
231 functional diversity [17]. They possess macrophage properties such as phagocytosis and
232 production of reactive oxygen intermediates (ROIs). In the light of what is known in myeloid
233 MGCs, it is likely that placental MGCs are involved in the engulfment of large particles
234 resulting from remodeling of placenta during pregnancy [49]. The profile of cytokine and
235 chemokine production by MGCs rules out a polarized phenotype, but they possess both
236 inflammatory and anti-inflammatory features. We propose that placental MGCs are fully
237 competent macrophages that play a role in host defense and placental homeostasis.

238

239 *Placental macrophages and infections*

240 Placental macrophages are armed to fight microbial pathogens. They express microbial
241 sensors (Toll-like receptors, lectins, complement receptor of the immunoglobulin
242 superfamily) [50–52]. They are competent to ingest inert particles and microorganisms,
243 produce ROIs, but are poor antigen-presenting cells [17,53]. This latter point may be useful to
244 limit deleterious effect of adaptive immunity on pregnancy. As a consequence, placental
245 macrophages are likely involved in the occurrence of placental infections during pregnancy

246 **(Figure 1)**, a major cause of obstetric complications, fetal pathologies and preterm deliveries
247 [54].

248

249 *Bacterial infection*

250 Chorioamnionitis or intra-amniotic infection is an acute or chronic inflammation of fetal
251 membranes [55] causing premature rupture of the membranes that allows the direct
252 introduction of microorganisms during chorionic villi sampling or *via* amniocentesis or
253 fetoscopy. The bacteria mainly found include *Escherichia coli*, group B *Streptococcus*,
254 *Hemophilus* sp. and *Staphylococcus* sp. [56]. Conflicting results have been reported
255 concerning the presence of placental macrophages in chorioamnionitis lesions: decreased
256 number [17,57] and increased number [58] as compared to controls. The activation level of
257 placental macrophages varies according to pregnancy trimesters. In the third trimester, they
258 over-express T cell chemokines (CXCL9, CXCL10, CXCL11) associated with altered villous
259 architecture [59,60]. We found that the balance between TNF and IL-10, as pro- and anti-
260 inflammatory cytokines respectively, is reoriented toward inflammatory response in
261 chorioamnionitis. The expression of CD163, an M2 marker, on placental macrophages is
262 higher in grade III than in grade II chorioamnionitis. We also showed that CD14⁺ placental
263 macrophages from patients with chorioamnionitis are unable to form MGCs. This defect is
264 partially corrected by incubating placental macrophages with control trophoblast supernatants
265 [17], thus demonstrating the role of the placenta microenvironment in MGC formation.
266 Placental macrophages may be also pathogenic through the release of extracellular traps (ET)
267 in group B *Streptococcus* infection [61]. The release of placenta ET depends on actin
268 polymerization and reactive oxygen species. Placenta ETs contain MMPs which are released
269 during infection and lead to breakdown of extracellular matrix and placenta lesions [62]. This
270 way of response of placenta macrophages to infection is shared with other placenta cells.

271 Indeed, we reported the expression of cytonemes, actin-based structures, by placenta mast
272 cells [63,64] in response to infection with anti-bacterial properties [5]. The role in infections
273 by intracellular bacteria that present a placenta tropism is less well documented. During
274 *Listeria monocytogenes* infection, a ubiquitous intracellular gram-positive bacterium
275 responsible of listeriosis macrophages from placenta were found permissive [65,66]. It has
276 been also provided evidence that during *Brucella* sp. Or *C. burnetii* infection, placental
277 macrophages were found infected [19,67,68]. We recently showed that CD14⁺ macrophages
278 from at term healthy placentas infected *ex vivo* by *C. burnetii* eliminate bacteria within 9 days.
279 This elimination is associated with their polarization in M1 cells and is related to the
280 production of IFN- γ [19]. The microbicidal activity of macrophages from at term placentas
281 may account for the fact that the transmission from mother to fetus mainly occurs during first
282 and second trimesters, not during the third trimester. But to date, the factors that govern the
283 mechanisms of infection, the resistance and/or the susceptibility to these bacteria in decidual
284 macrophages are still unknown.

285

286 *Viral infections*

287 Viral infections increase the risk of pregnancy disorders and fetal pathologies, as
288 demonstrated by attention of media for Zika outbreaks. The role of placental macrophages
289 during viral infections has been extensively studied in human immunodeficiency virus (HIV)
290 infection. In placenta from non-emitting mothers, the immune response is effective, but
291 placenta from surrogate mothers have an inflammatory response associated with
292 chorioamnionitis [69]. HIV is detected in placental macrophages that express receptors for
293 HIV including CD4, CCR5, CXCR4 and CD209 [70,71]. CD14⁺ placental macrophages are
294 less permissive to HIV replication than monocyte-derived macrophages [72]. It has been
295 shown that HIV transiently replicates within isolated CD14⁺/CD68⁺ placental macrophages

296 [73]. In contrast, Johnson et *al.* showed that Hofbauer cells assemble and sequester HIV-1
297 without replication in compartments rich in endosomal/lysosomal markers, such as CD9,
298 CD81, CD63 and lysosomal-associated membrane protein (LAMP)-1 [74]. Other placental
299 partners are able to control placental macrophage permissivity to HIV. Hence, decidual NK
300 cells inhibit infection of decidual macrophages by HIV through direct contact and IFN- γ
301 release [75]. These findings highlight the key role of placental macrophages in the mediation
302 of protection of placental tissue during HIV infection (**Figure 2**). The spotlights have recently
303 turned their attention to the ZIKA virus. The ZIKA virus is transmitted by mosquito bites
304 (*Aedes*) that causes ZIKA fever in humans. During pregnancy, ZIKA virus is vertically
305 transmitted from mother to fetus [76]. ZIKA infection in pregnant women is at the origin of
306 adverse pregnancy and birth outcomes causing essentially severe brain malformations [77].
307 Pregnant women infected by ZIKA virus present a chronic placentitis with a chronic villous
308 inflammation, edema and trophoblastic lesions [78]. There is evidence that ZIKA infection
309 compromises mesenchymal and Hofbauer cells in human villi [79,80]. Immunohistochemistry
310 approaches also reveal that ZIKA virus stimulates the proliferation of placental macrophages
311 within the chorionic villous stroma [81]. CD163 or CD68 positive cells are colocalized with
312 ZIKA virus antigens *in vivo* [82,83]. *Ex vivo* models show a higher permissivity of placental
313 macrophages to ZIKA virus than trophoblasts [84]. Recently it has been shown that Abs
314 directed against dengue virus increase ZIKA virus infection of Hofbauer cells, suggesting that
315 pre-existing immunity to dengue affects host response to ZIKA virus [85]. The replication of
316 ZIKA virus within Hofbauer cells induces the production of type I IFN, IL-6, CCL3 and
317 inducible protein (IP)-10 [86]. The blockade of IFN production using Janus Kinase (JAK)
318 inhibitors inhibits the production and the replication of the ZIKA virus in human Hofbauer
319 cells *in vitro* [87]. Additionally, the expression of the co-stimulatory molecules CD80 and
320 CD86 by Hofbauer cells is increased, suggesting that they are potentially APCs *in vivo*. All

321 these studies suggest that the primary tropism of the ZIKA virus for placental macrophages
322 enables the virus to cross the placental barrier and to eventually access to the fetal
323 compartment. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
324 leading to the coronavirus disease in late 2019 (Covid-19) has been associated with a large
325 debate concerning the occurrence of transplacental transmission. Although no transplacental
326 transmission was reported from China, Hosier. H *et al.*, presented for the first time the case of
327 woman with Covid-19 with a SARS-CoV-2 invasion of the placenta and local tissue
328 inflammation and fibrin deposition [88]. They reported an inflammatory infiltrate of immune
329 cells composed of CD3⁺ lymphocytes and CD68⁺ macrophages with only infection of
330 syncytiotrophoblast cells by SARS-CoV-2 virus. The infiltration of CD68⁺ placenta
331 macrophages in SARS-CoV-2 infected placenta was next confirmed [89,90] associated with a
332 M2 phenotype in a case report of an asymptomatic Covid-19 positive woman [91].
333 Interestingly, Facchetti. F *et al.*, reported a strong expression of S-protein in areas with dense
334 monocytes-macrophage inflammation, which suggests a local activation of these cells [90].
335 Thus, to date, although the presence of placental macrophage into placenta lesions was clearly
336 established, their role in SARS-CoV-2 infection of the placenta remains to elucidate.

337

338 *Parasitic and fungal infections*

339 The place of placental macrophages in pathophysiology of parasitic or fungal infections
340 during pregnancy is less documented than bacterial and viral infections. Among them,
341 *Plasmodium falciparum* represents the most virulent of the plasmodial species in pregnancy
342 and is associated with poor birth outcomes and low birth weight [92]. Only *P. falciparum*
343 among plasmodial species is found in decidual macrophages [93,94]. Intravital microscopy
344 has shown that infected erythrocytes accumulate in maternal blood, interact with trophoblasts
345 in a stable manner and are engulfed by placental macrophages [95]. The accumulation of

346 infected erythrocytes in human placenta causes an inflammatory response characterized by the
347 expression of CCR5 [96] and the release of CCL3 [97] by placental macrophages. If the role
348 of placental macrophages in parasite clearance remains uncertain, their contribution to
349 pathogenesis of inflammatory lesions is well admitted. Same conclusions were also attributed
350 to *Tryposoma cruzi* infection an obligate intracellular parasite responsible for the Chagas
351 disease. Chagasic villitis is characterized by inflammatory infiltrates in which CD68⁺
352 macrophages and CD8⁺ T cells are prominent [98]. In addition, there is evidence of the
353 multiplication of *T. cruzi* in CD68⁺ macrophages from placental chorionic villi [99,100].
354 However, the pattern of inflammatory reaction mediated by infected placental macrophages is
355 so far unknown.

356 Although they represent a lower prevalence of chorioamnionitis with 0.3-0.5% [101], fungal
357 infection are ascending infections that may severely compromise pregnancy rarely observed
358 in neonates with preterm birth or neonatal death [102]. Congenital infections leading to
359 preterm infants are mainly due to *Candida* species, including *C. albicans*, *C. glabrata*, *C.*
360 *kyfer* and *C. parapsilosis*. Immunohistological examination of placentas infected by *C.*
361 *guilliermondii* shows the presence of hypersegmented neutrophils and large macrophages
362 with a filled cytoplasm by several 3-6 µm oval bodies [103]. In addition, these infected
363 placentas present edema of the lamina propria and macrophage infiltration. Although the role
364 of macrophages in *Candida* infection is well documented in host defense against deeply
365 invasive candidiasis [104], their role in placental infection has not been investigated to date.

366

367 ***Concluding remarks***

368 Through the focus on pregnancy-associated infections, this review pointed that it is necessary
369 to break down the technical barriers that have long hindered the study of placental
370 macrophages. The results of scRNA-Seq have questioned the dichotomy between Hofbauer

371 cells and decidual macrophages and paved the way for a re-writing of placenta macrophage
372 diversity. The study of placental macrophages in their tissue environment will require the
373 development of *ex vivo* placenta perfusion coupled with intravital microscopy and
374 multiplexed-single-molecule fluorescent *in situ* hybridization. The question of whether
375 placental macrophages are competent to combat microbial pathogens or rather whether they
376 are involved in pathogenicity has not been sufficiently studied. Similarly, the role of placental
377 macrophages in pregnancy-associated infectious diseases is poorly understood and will be a
378 major issue for future research. Nevertheless, placental macrophage characterization could
379 help in prediction of obstetric complications. It might help obstetricians in tricky situations
380 where prolongation of pregnancy generally improves neonatal outcomes but increase
381 infection/inflammation materno-fetal risks.

382 **Authorship**

383 S.M and J.L.M conceived and wrote the manuscript. M.K., A.B.A and F.B provided critical
384 revision of the manuscript.

385

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391

392 **Conflict of interest disclosure**

393 The authors declare no competing interests.

394

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815

816 **Figure legends**

817 **Graphical abstract. Anatomic localization of decidual macrophages and Hofbauer cells**

818 Schematic representation of the maternal and fetal parts of the placenta villi. Decidual
819 macrophages are localized in the decidual at the maternal part, whereas Hofbauer cells are
820 present in the fetal part in the intervillous space.

821

822 **Figure 1.**

823 Number of publications associated with “Placenta macrophage” an “placenta macrophage and
824 infection” (Pubmed database).

825

826 **Figure 2. Responses of placental macrophages to infection**

827 Infection with (a) bacteria, (b) virus or (c) parasites results in the expression of membrane
828 receptors and the secretion of several key proteins by placental macrophages. CC and CXC:
829 chemokines; CD: Cluster of differentiation; HIV: Human Immunodeficiency virus; HLA:
830 Human leukocyte antigen; IL: Interleukin; IFN: Interferon; MHC: Major Histocompatibility
831 complex; TGF: Transforming growth factor; TNF: Tumor necrosis factor.

832

833 **Table 1. Phenotype of placental macrophages during gestation**

Marker s	Functions	1 st trimester	2 nd trimester	3 rd trimester	Refs
CD1	• Antigen presentation to T lymphocytes	Yes	Yes	Nr	[105,106]
CD4	• Interacts with antigen-presenting cells	Yes	Yes	Yes	[71,105,107]
CD11c	• Antigen uptake and presentation	Yes	Yes	Nr	[105,106]
CD14	• Co-receptor for bacterial LPS detection • Cooperates with TLR-4 • Microbicidal functions	Yes	Nr	Yes	[86,105,108]
CD16	• Involved in phagocytosis • Degranulation • Oxidative burst: ROI production • Protective function against fetal antibodies	Yes	Yes	No	[105,109]
CD68	• Binds lectins and/or selectins • Crawling	Yes > than 3 rd trimester	Yes > than 3 rd trimester	Yes	[57,82,110,111]
CD80	• Co-stimulatory molecule • T cell priming	Yes > than 3 rd trimester	Nr	Yes	[112–114]
CD86	• Co-stimulatory molecule • T cell priming	Yes > than 3 rd trimester	Nr	Yes	[112–114]
CD163	• Recognizes and binds bacteria • Host defense • Immunosuppressive barrier between mother and fetus • Innate immune sensor for bacteria	Nr	Nr	Yes	[108,110,115,116]
CD206	• Pattern recognition receptor • Antigen processing • Endocytosis • Phagocytosis • Innate immune response	Yes	Yes	Yes	[112–114]
CD209	• Pattern recognition receptor • Binds CD50 (ICAM-3) • Bind microorganisms through envelope mannose	Yes	Yes	Yes > than 1 st trimester	[117]

	<ul style="list-style-type: none"> • Viral receptor • Innate immune response through TLR modulation • Immune tolerance 				
CCR5	<ul style="list-style-type: none"> • Co-receptor for CD4 receptor • Used by macrophage-tropic (R5) HIV-1 for virus entry 	Yes	Nr	Yes	[96,117–120]
CR3	<ul style="list-style-type: none"> • Pattern recognition receptor • Binds microorganisms • Phagocytosis • Destruction of cells/microorganisms 	Yes	Yes	Nr	[105]
CXCR4	<ul style="list-style-type: none"> • Binds SDF-1 • Chemoattractant for T-lymphocytes • Receptor for HIV 	Yes	Nr	Yes	[117]
HLA-DQ	<ul style="list-style-type: none"> • Binds and presents antigens to T cells • Immune tolerance • Its absence during the 1st trimester leads to the generation of cytotoxic cells • Cooperates with HLA-DR 	No	Nr	Yes	[105,121–123]
HLA-DP	<ul style="list-style-type: none"> • Receptor for self-antigens 	Yes (low expression)	Nr	Yes > than 1 st trimester	[105,121,123]
HLA-DR	<ul style="list-style-type: none"> • Binds microorganism peptides • Antigen uptake and presentation to T cells • Cooperates with HLA-DQ 	Yes (low expression)	Nr	Yes > than 1 st trimester	[105,121,123]
TLR-2	<ul style="list-style-type: none"> • Microorganism recognition • Activation of innate immunity • Regulation of innate immune function at the maternal-fetal interface 	Nr	Nr	Yes	[124]
TLR-4	<ul style="list-style-type: none"> • Microorganism recognition • Activation of innate immunity • Cooperates with CD14 	Nr	Nr	Yes	[108,124,125]

835 CC and CXC: chemokines; CD: cluster of differentiation; CR3: complement receptor 32;
836 HIV: human immunodeficiency virus; HLA: human leukocyte antigen; ICAM: intercellular
837 adhesion molecule; LPS: lipopolysaccharide; Nr: not reported; ROI: reactive oxygen
838 intermediates; SDF-1: stromal-derived-factor-1; TLR: toll-like receptor.

Graphical abstract

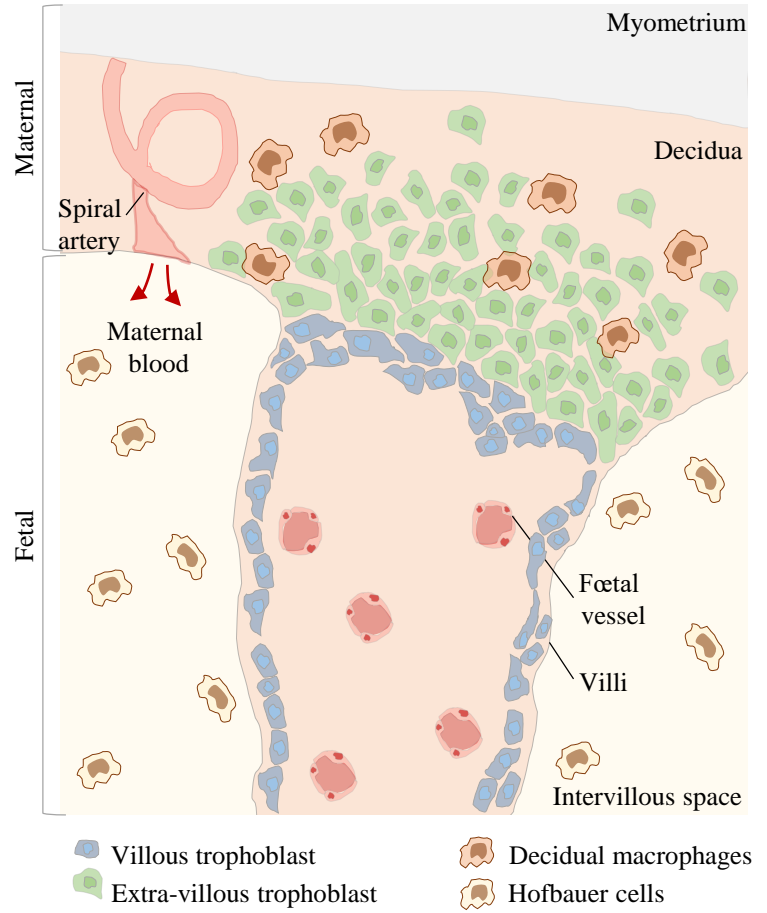
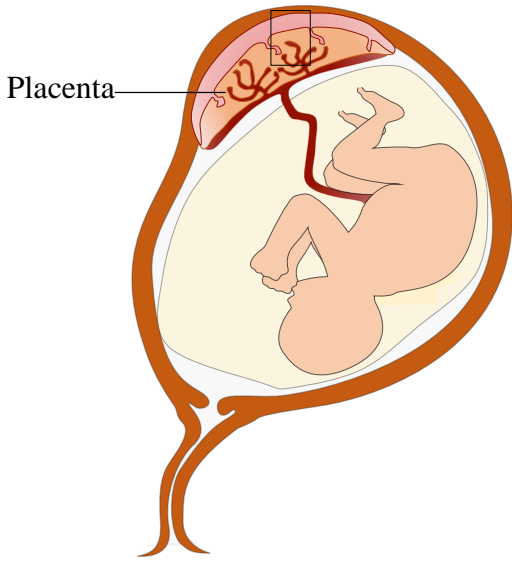


Figure 1

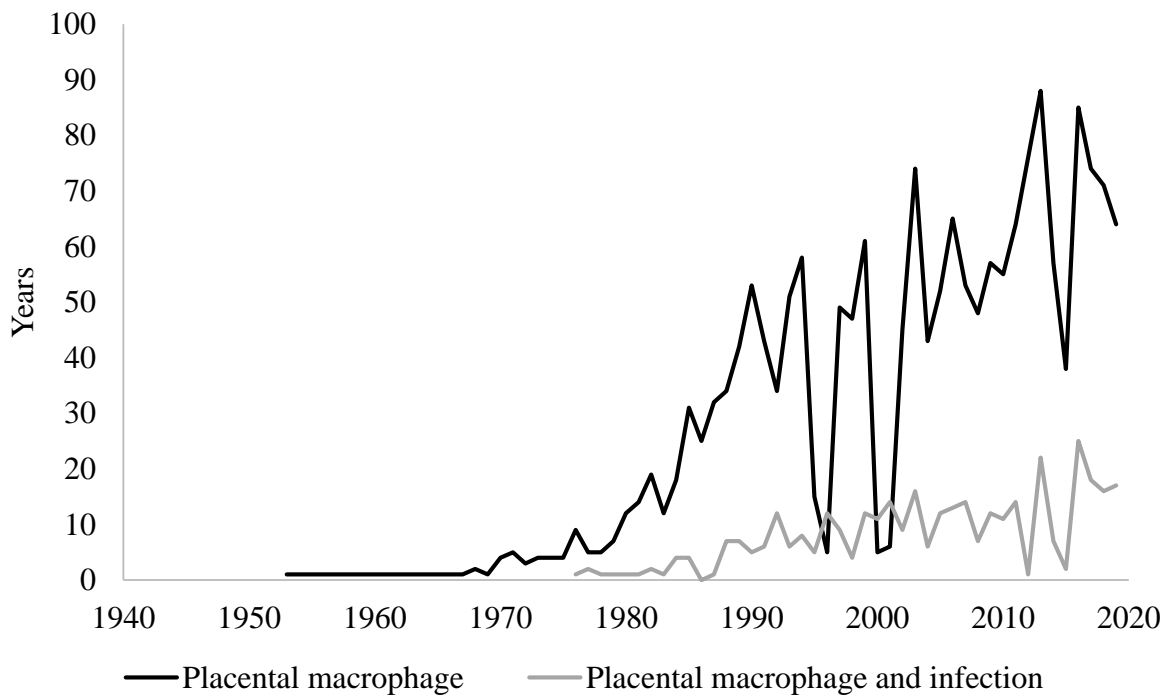
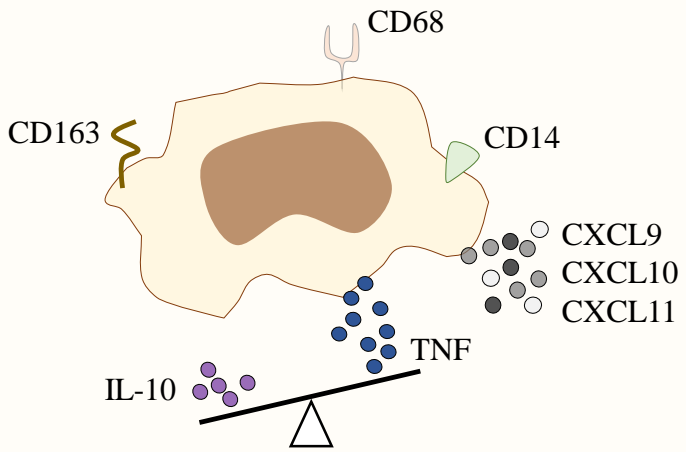


Figure 2

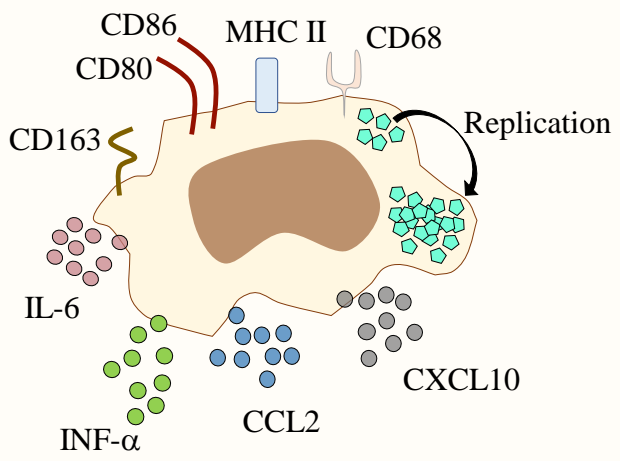
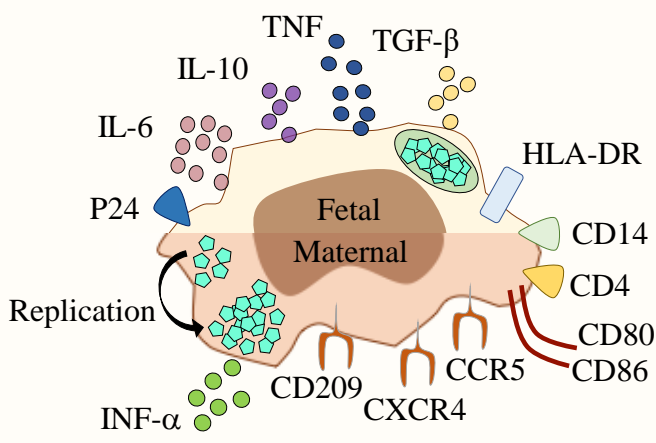
Chorioamniotitis



a. Bacterial infection

HIV virus

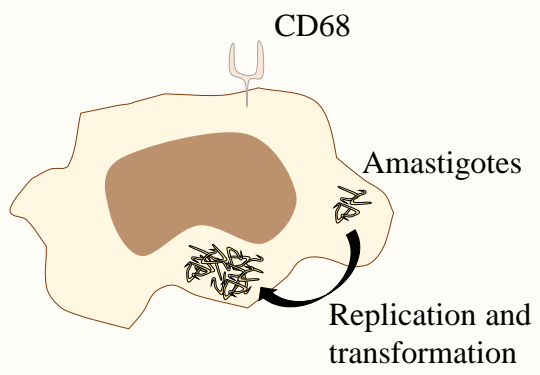
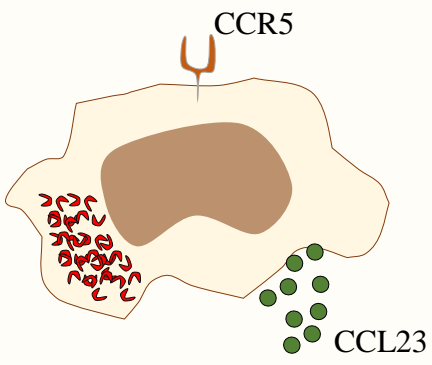
ZIKA virus



b. Viral infection

Plasmodium falciparum

Tryposoma cruzi



c. Parasitic infection