Editorial

Missing link in human fetal immunity: fetal dendritic cells orchestrate prenatal T cell immune suppression

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Developing fetus during gestation encounters variable immune stimulators, including semi-alloantigen from maternal cells, ingested amniotic fluid, food antigens, and microbes. Likewise, the expression of different histocompatibility molecules between mother and fetus can coexist for months without mutual rejection. In fetal immune system, how antigen-presenting cells (APC) interacting with T cells in response to foreign or self-antigen results in mutual tolerance remains unclear. Previous reports by Michaelsson *et al.* and Takahata *et al.* discovered there were a large population of regulatory T (Treg) cells in fetal lymphoid organs and core blood (1,2), which plays an essential role in immune suppression and is gradually declined after birth. Interestingly, Mold *et al.* further showed maternal alloantigen promotes the fetal Treg differentiation in uterus (3), indicating there may be other unknown important factors induced by APC-antigen interaction and favoring Treg cells differentiation during gestation. A recent paper published in *Nature* by McGovern *et al.* (4) characterized the different subsets of APC and further identified arginase-2 producing fetal dendritic cells (DC) function as a regulator to promote the suppressive prenatal T cells to control the maternal-fetal immune balance and response. Their findings bridge the gap between innate and adaptive immune cells in human fetus and broaden our understanding of the homeostatic immune-suppressive responses during gestation.

McGovern *et al.* (4) identified the different subsets of APC from 72 fetuses of 12–16 weeks estimated gestational age (EGA) and 24 fetuses of 17–22-week EGA. By using flow cytometry, they characterized the fetal APC: $CD14^+$ monocytes/macrophages, plasmacytoid dendritic cells (pDC), conventional dendritic cells 1 (cDC1), and cDC2 within fetal spleen, skin, thymus, and lung by 13 weeks EGA. Likewise, the comparable gene profiling of DC subset-specific transcription factors or similar antigen expression were observed in fetal DC and adult DC, except for low level of CD141, FcεR1, and CLA in fetal DC. McGovern *et al.* performed the first in-depth systemic analysis of the human fetal DC during gestation, and also compared them with adult DC using combination of flow cytometry and transcriptomes to demonstrate fetal DC were phenotypically similar to adult DC.

To investigate the functions and heterogeneity of the fetal tissue DC populations, McGovern *et al.* characterized the surface antigen expression profiles of fetal cDC from different tissues within single donors, and compared them with adult cDC using CyTOF and One-SENSE analysis. They found fetal cDC1 and cDC2 showed great heterogeneity between tissues, especially in lung, at the single-cell level and conserved tissue-specific cDC phenotypes between adults and fetuses. In particular, gut cDC expresses increased chemokine receptor CCR7 and the

activation markers CD80 and CD86, when compared with cDC in other tissues. As CCR7 is known to mediate DC migration into lymph node in adults, they further analyzed the migration ability of fetal gut cDC by identifying migratory (HLA-DR^{hi}CD11c$^{lo/int}$) and resident (HLA-DR^{int}CD11c^{hi}) DC. They found while there were very few migratory DC in mesenteric lymph nodes (MLN) at 14–15-week EGA, the number of migratory DC began to increase from 16- to 17-week EGA. Additionally, migratory HLA-DR^{+} cells in lymphatic vessels of 17–22-week EGA fetal skin were observed by immunohistochemistry, indicating fetal cDC can migrate via lymphatic vessels *in vivo*. Likewise, they demonstrated the migration ability of fetal DC using *ex vivo* skin explants. Based on their results, the authors suggest that fetal skin and gut DC have the capacity to migrate through lymphatic vessels to lymph nodes from 16 weeks EGA. On the other hand, McGovern *et al.* further investigate whether fetal cDC, which could be functionally similar to adult DC, were able to respond Toll-like receptor (TLR) stimulation and to activate T cells *in vitro*. Splenic cDC2 from 17 to 22 week EGA fetuses and adult samples were sorted out and stimulated with a panel of TLR agonists. Both adult and fetal cells secreted similar amounts of the pro-inflammatory cytokines GM-CSF, IL-6, IL-8, and MIP-1β and induced comparable proliferation of adult splenic T cells in a mixed lymphocyte reaction. Thus, fetal cDC are capable of both sensing pathogens and stimulating T cells as well as their migratory ability, indicates that they have the potential to initiate an immune response upon the stimulation by microbe-derived products around 17 weeks EGA.

Notably, the fetal immune environment is prone to be immune tolerant by producing abundant Treg cells (1,2). To understand whether and how fetal DC lead to the tolerogenic T cell responses, McGovern *et al.* analyzed T cell phenotype in mixed lymphocyte reaction by co-culturing allogeneic adult T cells with fetal or adult spleen cDC2. Interestingly, compared to adult cDC2, fetal cDC2 induced significantly higher frequencies of CD4^{+}CD25^{+}FOXP3^{+}CD127^{-}CTLA4^{+} Treg cells, which were functionally immunosuppressive. Likewise, the authors found the significantly reduced pro-inflammatory cytokines but increased Th2-polarizing cytokine IL-4 in the co-culture system of allogeneic T cells along with fetal cDC2 or cDC1, but not adult cDC2.

To explore how T cells are differentially regulated between fetal DC and adult DC, and tend to differentiate into Treg cells specifically interacting with fetal DC, the authors explored over 3,000 differentially expressed genes and identified critical pathways related to inducible nitric oxide synthase/tumor-necrosis factor-α (iNOS/TNF-α) axis by ingenuity pathway analysis (IPA). Interestingly, the authors found the higher expression of arginase-2 only in fetal DC, but not in adult DC among several differentially expressed genes involved in immune suppression/inflammation. Arginases are known as immunoregulatory enzymes catabolizing the L-arginine, which converts to L-ornithine or urea, to restrict the production of pro-inflammatory cytokine TNF-α (5-7). Moreover, L-arginine generally regulates oxidative phosphorylation during naïve T cell activation, promoting memory T cell development, and anti-tumor function (8). Dunand-Sauthier *et al.* showed that repression of arginase-2 expression is critical for the ability of DCs to drive T cell activation (9). However, the detailed function of arginase in DC is still unclear. McGovern *et al.* found T cells did not produce TNF-α in co-culture with fetal DC compared with adult DC. Furthermore, the authors neutralized arginase activity in fetal DC cultures by adding excess L-arginine or arginase inhibitors (ABH and BEC) to restore TNF-α production, confirming the role of arginase-2 in fetal cDC-mediated suppression. Importantly, arginase-2 activity in fetal DC only impacts T cell TNF-α production but no other pro-inflammatory cytokines (GM-CSF, IFNγ, IL-17A and IL-1β) or Treg numbers as well as inhibitory cytokines (IL-13, IL-10). It suggests fetal DC utilize other unknown mechanisms, which may be independent from regulating TNF-α production, to induce Treg cells or mediate T cell producing other cytokines. In summary, the authors indicated fetal DC expressing arginase-2 are critical to repress T cell TNF-α production and then further promote immune suppression in response to allogeneic antigens in the absence of TLR stimulation. However, the precise underlying mechanism of how arginase-2 is differentially regulated between fetal and adult DC, and the specifically effects on only TNF-α production by T cells remain to be addressed.

Elevated production of TNF-α has been reported in pregnancy complications such as recurrent miscarriage (10), gestational diabetes (11), and ulcerative colitis (12). Herein, McGovern *et al.* provide a clue to show the human fetal DC functionally regulate early immune response by suppressing TNF-α production in T cells through arginase-2 activity. Their studies will shed light on the therapeutic development by targeting fetal DC or manipulating arginase-2 activity to regulate immune tolerance. However, more studies will need to determine the underlying mechanisms of

regulating arginase-2 differentially expression between fetal and adult DC. Likewise, under the allogenic condition, how TLR stimulation can overcome immune suppression induced by arginase-2-expressing fetal DC is also need to be determined. In addition to neonate $CD71^+$ erythroid cells and fetal DC, increased arginase activity also has been reported in myeloid-derived suppressor cells (MDSC) in tumor microenvironment of many cancer types (7,13). On the other hand, increasing cellular L-arginine level in T cells could promote its anti-tumor activity by shifting the metabolic status from glycolysis to oxidative phosphorylation (8). Further investigation of the upstream mechanisms of controlling metabolism and immune regulatory function of arginases will not only advance our knowledge of fetal immune system, but also benefit the field of cancer immunology.

Briefly, the novel findings by McGovern *et al.* (4) unravel a previously unknown mechanism of immunological tolerance mediated by fetal cDC during gestation. Together with previous reports on fetal natural killer cells (14) and Treg cells (1-3), their findings on the function of fetal DC highlight that how fetal immune cells work together to maintain tolerance as well as fighting against pathogens in human early immune development. As more and more new immune cell subsets have been identified in fetal immune system, their studies will provide valuable insights into the development of immune tolerance and pathogenesis of insufficiently immune-tolerant disorders, including Rh disease, pre-eclampsia, recurrent miscarriage, gestational diabetes etc. Importantly, their impressive findings may offer the new therapeutic strategies of these diseases to improve human health.

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