Establishment of tissue-resident immune populations in the fetus

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Abstract
The immune system establishes during the prenatal period from distinct waves of stem and progenitor cells and continuously adapts to the needs and challenges of early postnatal and adult life. Fetal immune development not only lays the foundation for postnatal immunity but establishes functional populations of tissue-resident immune cells that are instrumental for fetal immune responses amidst organ growth and maturation. This review aims to discuss current knowledge about the development and function of tissue-resident immune populations during fetal life, focusing on the brain, lung, and gastrointestinal tract as sites with distinct developmental trajectories. While recent progress using system-level approaches has shed light on the fetal immune landscape, further work is required to describe precise roles of prenatal immune populations and their migration and adaptation to respective organ environments. Defining points of prenatal susceptibility to environmental challenges will support the search for potential therapeutic targets to positively impact postnatal health.

Keywords Fetal immunity · Prenatal development · Embryogenesis · Immune ontogeny

Introduction
The development of the immune system during the prenatal period is layered in time and space to meet developmental needs and prepare the human fetus for postnatal life [1]. The identification of fetal immune cell populations specific to their tissue environment at a certain fetal age suggests that the immune system serves roles for organ growth and maturation [2–5]. Furthermore, strong evidence describes the persistence and self-maintenance of fetal-derived immune cell populations in most adult tissues, contributing to the resident immune compartments independent of adult long-term hematopoietic stem cells (HSC) [6, 7]. This exemplifies the potential for lasting impact of the prenatal period on postnatal immunity. Tissue residency is conventionally assigned to an immune population that possesses self-renewal capacity, expresses a tissue-specific transcriptional program, e.g., homing receptors, and undergoes little to no exchange with the circulating pool of immune cells [8, 9]. During embryogenesis, the spatiotemporal seeding of the immune system in the various organ systems can be considered the establishment of immune tissue residency. We here review the formation of tissue-resident immunity in the human fetus, supported by evidence from animal models, focusing on recent insights in prenatal gut, lung, and brain development.

Establishment of the fetal immune system in time and space
The immune system develops in spatiotemporally highly coordinated waves of hematopoiesis [1, 10], described for mouse myeloid lineages as primitive, transient definitive, and definitive waves [11]. In humans, early hematopoietic cells (primitive wave) are detected in the extraembryonic yolk sac (YS) around 4 postconception weeks (PCW1).

1 PCW describes the fetal age since fertilization, which occurs about 2 weeks later than the start of the last menstrual cycle, which, in turn, is used to estimate gestational age (EGA) in weeks. Throughout this
Primitive HSC-like and erythro-myeloid progenitors (EMPs) give rise to premacrophages, mast cells, natural killer (NK), and innate lymphoid cell (ILC) progenitors, while megakaryocytes and erythroid cells enable oxygen supply to the growing fetus [12–14]. Concomitantly, definitive HSC and multipotent progenitors (MPP) that are capable to give rise to all mature blood and immune cells for the life of the individual are generated in the intraembryonic hemogenic endothelium in the aorta-gonad-mesonephros (AGM) region [15–17] and other hemogenic regions, including the umbilical cord and placenta [18]. In human fetuses after 6 PCW,YS- and AGM-derived macrophages and mast cells can be detected among fetal peripheral tissues such as skin, brain, and kidney; some of them constitute lifelong self-maintained populations that are independent from repopulation by bone marrow (BM)–derived precursors, as shown in mice, while others such as in the gut will be gradually replaced by circulating precursors derived from definitive HSC [11, 12, 14, 15, 19]. Between 6–9 PCW, both YS- and AGM-derived progenitors and definitive HSC with long-term repopulation capacity will seed the fetal liver to commence definitive hematopoiesis with long-term reconstitution potential [20, 21]. The fetal liver is the major hematopoietic organ during fetal development, contributing during all developmental stages and supporting active erythro-myeloid hematopoiesis and HSC expansion [12, 22]. After establishment of the hematopoietic fetal liver, the fetal BM will be seeded by fetal liver–derived HSC at 11–12 PCW, establishing it as the niche for lifelong hematopoiesis after birth, including the quiescent state of adult HSC [23]. Interestingly, osteoclasts, stromal cells essential for hematopoietic niche homeostasis, are EMP-derived cells [24]. In contrast to YS- and AGM-derived macrophages and mast cells, differentiation of the neutrophil lineage, dendritic cells (DC), and monocytes are considered dependent on the fetal BM niche in humans [23, 25] and mice [26]. B cell lineage expansion is a major feature of second trimester fetal BM hematopoiesis [23]. T cell differentiation and maturation on the other hand occur mainly in the fetal thymus and start with the onset of fetal liver hematopoiesis (6–9 PCW) [27].

**Tissue-resident immune ontogeny through the lens of fetal macrophage development**

The establishment of tissue compartmentalization and lifelong self-sustained immune cell populations originating from embryonic precursors is best described for macrophages in developing mouse tissues [11, 13], which is accompanied by limited but readily increasing human evidence (reviewed in [28]). A nowadays outdated concept hypothesized that tissue-resident macrophages arise from blood monocytes differentiating in the BM, known as the “mononuclear phagocyte system” [29]. Methodological achievements like fate-mapping experiments revealed that certain cell types in certain tissues originate from different developmental pools of precursor cells of early and late embryonic, neonatal, and adult stages. The complex composition of immune cells of different origins is termed “layered immune system,” where certain cell types have distinct origins ranging from entirely or partly fetal- to adult-derived precursors. This concept is for instance apparent in the establishment of tissue-resident macrophages, mast cells, γδ T cells, and ILCs [7, 14, 30–32].

In addition to the primitive and definitive waves of hematopoiesis, another wave of “transient definitive hematopoiesis” from multipotent progenitors (EMPs and lymphoid–myeloid progenitors (LMP)) gives rise to early lymphoid populations and tissue-resident macrophages via a monocytic precursor in mice [33]. Importantly, this wave is still independent of long-term HSC and includes YS EMPs, which seed the fetal liver, where they develop into multiple myeloid lineages including fetal monocytes until mouse embryonic day E16.5 [34]. These monocytes seed virtually all embryonic tissues except the brain after mouse midgestation and adapt their transcriptional program to their niche to become specialized tissue-resident macrophages [33]. Tissue-resident macrophages are to varying levels, self-maintained in postnatal tissues, independently of definitive HSC and replenishment by blood monocytes in steady-state conditions [35, 36]. Prominent examples of these macrophages of strict embryonic origin that are independent of circulating macrophages include brain microglia [37], epidermal Langerhans cells [38], and alveolar macrophages [39]. Other populations can be gradually replaced by adult HSC–derived monocytes, including liver Kupffer cells, splenic, and intestinal macrophages [36, 40, 41].

In an attempt to explain the layered nature of tissue-resident macrophage populations across tissues and ages of an individual, Guilliams and Scott [42] proposed a niche model, hypothesizing that during organogenesis, tissue niches are created (e.g., in the brain) and become available for a limited number of premacrophages from the YS (first primitive wave), which in turn, upon engraftment, receive signals to adopt a tissue-specific phenotype. With continued development, more tissue niches become available for the second transient-definitive wave of embryonic precursors (fetal liver–derived monocytes) until the niche is full. Accordingly, the contribution of definitive HSC-derived monocytes to neonatal tissue composition would be attributable to continued organ maturation after birth. Replacement only occurs when spots in the niche become available. Differences in niche availability for replacement with circulating precursors

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Footnote 1 (continued)

review, we report PCW and EGA verbatim from the source reports to avoid introducing inaccuracies.
i.e., liver, spleen, and intestine available vs brain, skin, and lung being unavailable) might stem from absence or presence of self-renewal-promoting cues, respectively, which are likely to be highly tissue- and/or precursor-specific [42, 43].

During embryogenesis, tissue-resident macrophages contribute to differentiation, maturation, and remodeling of fetal organs, as described in detail for the brain below. Epidermal Langerhans cells are first observed in human fetal skin at 4–5 PCW [44]. In adult skin, they exhibit a specialized phenotype which includes the capacity to repopulate and present antigen, amidst supporting barrier function and repair, and contributing to extracellular matrix remodeling [32, 44–46]. While their developmental function remains incompletely understood, fetal Langerhans cells present a mature phenotype by 16 PCW [47, 48]. Prenatal skin macrophages have been suggested to support angiogenesis and chemotaxis [48].

In the fetal liver, fetal Kupffer cells are considered to adopt similar functions as their adult counterparts, coordinating erythropoiesis and iron recycling [49, 50], responding to bacterial compounds by secreting bona fide tissue-resident macrophage cytokines TNFα, IL-6, and IL-1β in early gestation humans [51, 52], and showing high proliferative capacity, as well as peroxidase activity in mice [53]. The tissue-resident macrophages of embryonic origin of the spleen, red pulp macrophages, are potent iron recyclers and removers of senescent erythrocytes from the neonatal circulation in mice [54, 55], a role they may assume during embryogenesis.

**Fetal tissue-resident lymphoid cells**

Fetal lymphoid cells partially derive from the wave of transient definitive hematopoiesis prior to definitive hematopoiesis and include NK cells [56], likely lymphoid tissue inducer cells (LTi) [30, 57], as well as marginal zone and B-1 B cells [58], and thymus-derived fetal γδ T cells [32, 59], where, for the latter two, a transient HSC precursor has been described in mice that disappears with adulthood [60]. Similar to myeloid cells, fetal lymphoid cells possess functions that support prenatal development. B-1 cells, considered part of the innate immune system, function in a T cell–independent manner by spontaneously secreting antibodies with limited specificity in peripheral tissues [61, 62], conferring the fetus with unspecific yet immediate immune response capacity. Fetal EMP-derived NK cells are highly potent cytotoxic cells, yet hyporesponsive to HLA* neg target cells compared to their adult HSC-derived counterparts [3, 56]. The early developmental origin of human ILC lineages has recently been mapped across fetal tissues during early gestation (8–12 PCW), establishing their varying proportions in and proliferative (i.e., differentiating) states per organ [63]. In a fate-mapping model in mice, prenatal ILC were gradually replaced postnatally, suggesting potential specific roles in their various prenatal tissue sites [30], which will require further investigation. Thymus-derived lineages of fetal T cells derive from fetus-exclusive HSC [64] and appear in the periphery with the start of the second trimester to seed empty niches in lymphoid and mucosal tissues [65–67], reviewed in [68]. In humans, T cells of all lineages are established in utero after gestational week 14 [69–71], possessing innate-like [72], protective [5, 73, 74], and tolerogenic [65, 66, 75] immune response capacity. This is in stark contrast to mice, who only develop T cells after birth [76]. Of note, circulating fetal T cells in the cord blood at term primarily show a naïve phenotype and an impaired response towards alloantigens [77], while T cells in the early fetal intestine possess an effector memory phenotype with clonal diversity [5, 66, 74]. This human prenatal T cell landscape adequately exemplifies the compartmentalization of fetal immunity across tissues: systemic, circulating immune cells do not necessarily reflect tissue-resident phenotypes and functions of self-sustained immune cells that contribute to local organogenesis and immunity later in life.

We display current seminal evidence for the human fetal immune landscape and their functional attributes in Fig. 1, and summarize human and mouse studies of fetal immune subsets across tissues in Table 1. Overall, at least in mice, the contribution of definitive hematopoiesis in fetal liver, and later fetal BM, to prenatal tissue-resident immunity has been suggested to be smaller than the contribution from EMP and LMP, which are giving rise to the majority of cell lineages supporting fetal organ development. As proposed by Hoeffel and Ginhoux [33], the stemness of BM-HSC might be preserved until fetal progenitors are fully consumed and have established tissue residency. Furthermore, as proposed by many, including [6], fetal stem and progenitor cells that sense maternal perturbations (infection/inflammation/microbiome/metabolic state) might give rise to progenitors with altered persistence, differentiation potential, and cellular output. Such impact on progenitor populations might amplify into deviations in long-term immune homeostasis and immunity later in life. Consequently, improving fetal and neonatal health will depend on a thorough understanding of prenatal-specific immunity in a spatiotemporal manner.

**Development and function of resident immunity in the fetus**

**Mucosal immune populations in the fetal gut**

As the largest barrier organ in the human body, the intestine has to coordinate nutritional demands and immune symbiosis with the gut microbiome [78]. Especially after birth, the mucosal intestine gets bombarded by environmental, nutritional, and microbial exposure [79]. As a result, the intestine needs to balance innocuous responses to these exposures,
while at the same time provide protection against potential pathogenic exposure. Unfortunately, differences in intestinal development between humans and animal models — mice are born with an immature gastrointestinal mucosa [79] — highlight the hurdles and difficulties of studying human intestinal immune development. However, recent technological advances have made it possible to study the development of the mucosal intestine in precious human fetal tissue. Several studies have emphasized that the human fetal intestine contains a distinct tissue-specific immune composition and signature [80] that consists of antigen presenting cells (APC), ILC subsets, T cells, γδ T cells, and B cells which can already be observed in human fetal intestine at 6 to 23 weeks of gestation [59, 63, 67, 78, 80–82]. A recent scRNAseq study performed in intestinal tissue from 17 human embryos, ranging from 8 to 22 weeks post conception, suggest that intestinal immune cells are rare prior to the first trimester [78]. However, an enrichment of myeloid cells could be observed before 10 PCW, whereas an influx of T cells, NK cells, ILC1, and ILC3 were observed at 12

Fig. 1 Tissue-resident immune populations and functional features in human fetuses. While still incomplete, the current landscape of innate and adaptive immune populations residing in developing tissues during the first and second trimester indicates their role in organogenesis while providing protective/reactive and tolerogenic immunity. Representative seminal evidence is shown. Tissue-resident macrophages adopt specialized phenotypes supporting their niche development, including microglia in the central nervous system [2], Langerhans cells (LC) in skin [44], Kupffer cells in the liver [12], stromal macrophages (MΦ) in the bone marrow [23], and potentially red pulp [55] and alveolar macrophages (AM) [108, 117]. Similarly, innate lymphoid cells (ILC), bona fide tissue-resident cells, are distributed across tissues displaying site-specific phenotypes with as yet incompletely characterized function during fetal life [63]. Lung NK cells possess potent antibody (Ab)- and cytokine-induced cytotoxicity, yet are biased towards tolerating HLA<sup>αβ</sup> cells [3]. In the skin, mature mast cells are sensitized towards allergens via IgE [186], and differentiation of erythroid progenitors might supplement fetal liver erythropoiesis [12]. Innate-like B1 B cells are prominent in the fetal liver and bone marrow, concomitant with naïve and memory B-2 B cells [61, 62], while B cell clonality in the gut is primarily private, and not shared between individuals [82]. B cell lineage expansion occurs in the second trimester bone marrow [23]. Spleen dendritic cells (DC) have antigen-presentation capacity, supporting tolerogenic T cell responses [110]. T cells have an innate-like, fast-response phenotype (invariant γδ T cells) in the thymus [59, 229], skin [73], and intestine [59], however, are strongly biased towards mediating (maternal) tolerance [66, 71, 75], yet show TCR diversity [67, 82] and effector memory [5, 67, 82] in the mucosal surface of the gut. Cord blood CD71<sup>+</sup> erythrocytes (not shown) are perinatal immunosuppressors, potentially derived from fetal liver erythroid precursors [12, 244, 245].
Table 1 Immune populations resident in human and mouse fetal tissues. Color-coding of table mirrors tissue highlighted in Fig. 1. Information regarding non-human models is indicated in gray, E12.5, embryonic day 12.5; YS, yolk sac; FL, fetal liver; EMP, erythro-myeloid progenitor; LC, innate lymphoid cell; DC, dendritic cell; pDC, plasmacytoid DC; cDC, conventional DC; Treg, regulatory T cell; DN, double negative; DP, double positive; EGA, estimated gestational age; GI, gastrointestinal tract; PCW, postconception week; LTi, lymphoid tissue inducer; MAIT cell, mucosal-associated invariant T cell; mMΦ, pvMΦ, cMΦ, subdural meninges, perivascular space, and choroid plexus macrophages; P, postnatal day; iNKT cell, invariant natural killer T cell; KIR, killer immunoglobulin-like receptor; wks, weeks

| Organ | Species | Gestational age | Immune cell | Phenotype/Function/Ontogenic process | Reference |
|-------|---------|-----------------|-------------|-------------------------------------|-----------|
| Skin  | Human   | 6-12 wks EGA, 18-30 wks EGA | Langerhans cell | CD1α+, CD207+, HLA-DR−, OKT-6−, and ATPasea Erythroid progenitors can contribute to erythropoiesis and supplement fetal liver erythropoiesis | [4, 44, 48, 246] |
| Skin  | Human   | 7-12 PCW | Megakaryocyte-erythroid-mast cell progenitor (MEMP), Mast cell, Megakaryocytes and mid/late erythroid cells | CD45+CD206+CD209+, Support angiogenesis and leukocyte seeding | [4, 12, 48, 233] |
| Skin  | Human   | 7-24 wks EGA | Macrophage, Monocyte, Neutrophil-myeloid progenitor, Monocyte-DC | CD45+CD11c+, CD11c+ | [4, 12, 48, 233] |
| Skin  | Human   | 7-23 wks EGA | DC (pDC, cDC1, cDC2) | HLA-DR+/CD1c+, CD11c+ | [4, 12, 48, 233] |
| Skin  | Human   | 7-12 PCW, 18-24 wks EGA | Mast cell | CD45+CD117+, Mature phenotype, IgE bound | [12, 48, 73, 217, 233] |
| Skin  | Human   | 7-12 PCW | Early lymphoid/T precursor | T cell | [12] |
| Skin  | Human   | 17-30 wks EGA | T cell | CD8 memory T cell, IFNγ production | [4, 73, 233, 246] |
| Skin  | Human   | 17-22 wks EGA | CD45+CD206+CD209+, Support angiogenesis and leukocyte seeding | [73] |
| Skin  | Human   | 18-24 wks EGA | Treg | CD3+FoxP3+, Treg accumulation coincides with hair follicle development | [4, 233] |
| Skin  | Human   | 7-12 PCW | ILC1, ILC2, ILC3, ILC precursor | IL7R+, RORC+ and KIT+ | [12, 48, 63] |
| Skin  | Human   | 7-12 PCW | NK cell | Higher expression of GZMM and GZMK compared to adult | [12, 48] |
| Skin  | Human   | 7-12 PCW, 23 wks EGA | Immature B cell, (Pre pro) B cell | CD19+HLA-DRint-CD24+ | [4, 12] |
| Mouse | E12.5-17.5 | YS- and FL-derived Langerhans cells | CD11b+F4/80+CSF-1R+CX3CR1+ | [38] |
| Mouse | E12-18 | EMP-derived Monocyte | CD11bhiF4/80loCD64+Ly6C−/+ | [33] |
| Mouse | E9.5, E12.5 | Macrophage | CD45+CD11b+F4/80aLy6C0−, CX3CR1hi | [33, 247] |
| Mouse | E14.5-16.5 | YS-derived Mast Cell | c-Kit/Avidin+, Fetal-specific, Replaced postnatally by adult Mast Cells | [14] |
| Mouse | E17.5 | ILC2 | Ly56+IL-7Ra+Thyl+ST2+ | [30] |
| Kidney | Human | 7-16 PCW | Macrophage, DC | Anti-inflammatory gene signatures | [248] |
| Kidney | Human | 9-16 PCW | Monocyte, T cell, NK cell | Reduced cytotoxic gene signatures | [248] |
| Kidney | Human | 12-16 PCW | B cell | No evidence of class-switching | [248] |
| Kidney | Human | 7-12 PCW | (Pre pro) B cell, ILC precursor, Early lymphoid/T precursor, NK, Neutrophil-myeloid progenitor, pDC, DC1, DC2, Monocyte-DC, Monocyte, Macrophage, megakaryocyte-erythroid-mast cell progenitor (MEMP), Mast cell, Megakaryocytes | Single-cell transcriptome map, Lack of erythroid cells | [12] |
| Mouse | E12-18 | Monocyte | CD11bhiF4/80loCD64+Ly6C−/+ | [33] |
| Mouse | E11-18 | Macrophages | Promote tubular cell proliferation, branching, nephron formation; CD45+CD11b+F4/80aLy6C0− | [33, 249, 250] |
| Organ          | Stage  | Cell Type                                                                 | Characteristics                                                                                       | References |
|---------------|--------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------|
| Spleen        | Human  | NK cell                                                                  | Various differentiation stages present (CD56, CD16, NKG2A), KIR+ CD56 or NKG2A, or CD16+ hyporesponsive cytotoxicity against HLA-A* target cells, strong cytokine-mediated cytotoxicity response | [3, 251]  |
|               | Human  | CD5+ B cell                                                              | Unconventional phenotype, unsupportive of Ig production                                              | [252]      |
|               | Human  | ILC1, ILC2, ILC3                                                         | ILC3 dominant population                                                                            | [63]       |
|               | Human  | DC                                                                       | cDC1, cDC2. Responsive to TLR stimulation, Induce adult T cell proliferation, Arg-2+ DC regulate fetal T cell TNFα production | [110]      |
|               | Human  | iNKT cell                                                                | CD3+ TCR Vα23+ CD1d-PBS57 tetramer-, immature and less differentiated phenotype (CD4+CD8*), high proliferative capacity, and hyporesponsive IFNγ response | [98]       |
|               | Human  | NK cells                                                                 | Various differentiation stages present (CD56, CD16, NKG2A), KIR+                                    | [3]        |
|               | Human  | Memory B-2 and innate-like B-1 B cells                                   | IgM and IgD expression                                                                               | [62]       |
|               | Human  | SP, DP, DN T cells, γδ T cells, ILC3, NK cells, T naive, Macrophages, DC1, DC2 | Potentially tissue-resident GNG4+ CD8αα+ T(I) colocalize with DC1, and non-activated DC in the perimedullary region; activated DC and Treg enriched in the center of the medulla, Additional fetal thymus-specific unconventional T cell subsets | [253]      |
|               | Human  | ILC1, ILC2, ILC3                                                         | High proportion of putative ILC1                                                                  | [63, 253]  |
|               | Human  | Invariant γδ T cells                                                     | Programmed effector function, Generated independently of functional TCR expression; compared to gut γδ T cells: distinct, nonoverlapping TCRDV2R | [59, 229]  |
|               | Human  | CD14+ monocytes/macrophages, pDC, cDC1 and cDC2                         | /                                                                                                     | [110]      |
|               | Mouse  | DN, DP thymocytes                                                        | Thymus homeostasis                                                                                   | [254]      |
|               | Mouse  | Conventional T cells, non-conventional T cells, myeloid                  | /                                                                                                     | [255]      |
| Liver         | Human  | Memory B-2 and innate-like B-1 B cells                                   | IgM and IgD expression                                                                               | [62]       |
|               | Human  | NK cells                                                                 | Various differentiation stages present (CD56, CD16, NKG2A), KIR+, hyporesponsive cytotoxicity against HLA-A* target cells, Strong cytokine-mediated cytotoxicity response | [3, 251]  |
|               | Human  | NK cells                                                                 | Cytoplasmic CD3 delta, epsilon*, Lower cytotoxicity than cord blood or adult NK cells                 | [118]      |
|               | Human  | ILC1, ILC2, ILC3                                                         | Lymphoid precursor (IL-3RA*) derived                                                                | [63]       |
| Gut           | Human  | T cell                                                                   | Extrathymic T cell differentiation                                                                 | [88]       |

* Throughout the text, various cell types and stages are described with specific characteristics and references for further reading.
| Human | 12-27 wks EGA | CD4+ T cell | Memory phenotype (CD45RA-CCR7+), Clonal expansion (compartmentalization), TNFα+ Intestinal tissue damage by too high concentrations of TNFα+ CD4 T cells, Involvement in preterm necrotizing enterocolitis |
|-------|---------------|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Human | 8-23 wks EGA | CD8+ T cell | Memory phenotype, Impaired cytotoxicity, Tolerance against forein antigen, Increased GI viral susceptibility at birth |
| Human | 6-9 wks EGA | NK cell | |
| Human | 8-23 wks EGA | MAIT cell | CD3+CD161hiTCR Vα7.2+ PLZF+, mature phenotype, innate-like antimicrobial responses |
| Human | 16-23 wks EGA | NKT cell | CD3+TCR Vα23+ CD1d tetramer+ (loaded with a-GalCer analog PBS57), mature phenotype and robust IFNγ responses |
| Human | 16-22 wks EGA | Treg | CD4+FoxP3+CD25+, Detected in mesenteric lymph node, Support tolerance towards alloantigens |
| Human | 6-22 PCW | LTi | Recruit immune cells to site of developing intestinal immunity |
| Human | 8-23 wks EGA, 8-12 PCW | ILC1, ILC2, ILC3 | |
| Human | 8-23 wks EGA | NK cell | |
| Human | 8-23 wks EGA | NK cell | Various differentiation stages present (CD56, CD16, NKG2A), KIR+, Detected in mesenteric lymph node, no cytotoxic response against HLA-ε target cells |
| Human | 8-23 wks EGA | Immature B cell, Transitional B cell | Support lymphoid follicle and Peyer’s Patch development |
| Mouse | E12.5 | Macrophage | CD11b+ F4/80+ Ly6c+ |
| Mouse | E12.18 | Monocyte | CD11bhiF4/80aCD64+Ly6c+ |
| Mouse | E17.5 | ILC2 | Lin-IL-7Ra+Thy1+ ST2+ |
| Human | 8-16 PCW | Alveolar macrophages | |
| Human | 8-12 PCW | ILC2, ILC3 | ILC3: Immunity against in utero infection |
| Human | 8-23 wks EGA | NK cell | Various differentiation stages present (CD56, CD16, NKG2A), KIR+, hyporesponsive cytotoxicity against HLA-ε target cells, strong antibody-and cytokine-mediated responses |
| Human | 12-22 wks EGA | CD14+ monocytes/macrophages, pDC, cDC1 and cDC2 | |
| Human | 18-23 wks EGA | MAIT cell | Vα7.2+ CD161hi CD8+ |
| Human | 14-23 wks GA | T cells | Memory CD4 and CD8 T cells, cytotoxic granzyme B+Thet CD8 T cells, PD1+Ki67+ Tregs, and CD161+Vα7.2-CD4+TCRαβ |
| Human | 16-23 wks EGA | NKT cell | CD3+TCR Vα23+ CD1d-PBS57 tetramer+ |
| Mouse | E13-18 | Alveolar macrophages | Maintaining physiological surfactant levels, lung morphogenesis |
| Mouse | E19 | ILC2 | M2 polarization of AM, maintenance of lung homeostasis, epithelial cell plasticity, barrier surveillance |
| Human | 6-18 wks EGA | Microglia | Activated, Transcriptionally heterogeneous, Undergoing maturation, Phagocytosis, CNS (immune) surveillance |
| Human | 6-24 wks EGA | Astrocytes | Cytokine production (IL-1β, IL-6, TNFα) |
PCW [78], coinciding with the development of gut-associated lymphatic tissue (GALT) [79, 83–85]. The basic intestinal immune landscape — proportions of major innate and adaptive immune cells — is established prior to the second trimester and is stable into infancy [82]. However, diversity within the major immune cell populations can be observed, with an enrichment of CD11c+ APC, ILC, and CD4+ T cells, and reduced plasma cells in the fetus compared to infant [82]. Interestingly, in the adult, maintenance of intestinal mucosal immunity occurs both through migration of circulating BM-derived cells and by differentiation from tissue-resident progenitor cells that were seeded during fetal development [86]. For instance, macrophages are replenished by circulating monocytes [41], while ILC subsets and their progenitors reside in the tissue itself [63, 81, 87]. Also T cell progenitors reside in the intestine itself, as intestinal T cell differentiation is independent of the thymus [59, 88]. In humans, GALT, including lamina propria, mesenteric lymph nodes (mLN), and Peyer’s patches (PP), begins to develop 11–12 PCW, and at gestational week 19 the fetal intestines reach full structural maturity [79, 83–85, 89].

Several non-immune cells such as mesenchymal and epithelial cells are important for development of intestinal immunity [57, 78, 89–91]. It has been shown that interactions between mesenchymal lymphoid tissue organizing (mLTo), endothelial LTo (eLTo), and LT cells — which belong to the ILC family — are critical for recruiting immune cells to the site of the developing intestinal immunity [57, 78, 89–91]. In addition, epithelial cells in the fetal intestine will produce chemerin to attract macrophages from the circulation into the fetal gut mucosa [92], while after birth IL-8 and TGFβ secreted by epithelial cells and mast cells will attract macrophages to the intestinal mucosa [93].

The general hypothesis that the fetal immune system is naive and will only mature after birth has been challenged by the observation that a relatively mature adaptive immune system is present in the fetal gut [82]. For instance, clonally expanded CD4+ T cells with a memory phenotype (Tm) [5, 67, 74, 82, 88, 94, 95] show no overlap with regards to clonality in blood, and are present in the fetal intestine at 13–23 weeks of gestation [5, 67, 88, 94], highlighting compartmentalization of the fetal immune system. T cell receptor repertoire diversification and clonal distribution of intestinal T cells starts in utero and continues after birth [82]. These fetal CD4+ Tm cells can be found in colocalization with APC in the fetal intestine and are able to produce pro-inflammatory cytokines upon stimulation [5, 67, 74]. In particular, intestinal TNFα+ CD4+ Tm cells are able to support intestinal stem cell growth and epithelial development [5]. Importantly, a too high concentration of TNFα-producing CD4+ Tm cells mediates intestinal tissue damage, which is in line with the observation of increased frequencies of TNFα+ CD4+ Tm cells in the intestine of necrotizing enterocolitis (NEC)–affected preterm infants [5]. Overall, these data showed that TNFα-producing CD4+ Tm cells are involved in tissue generation in the fetus, while preterm birth-induced activation can induce intestinal inflammation and damage in premature infants. CD8+ T cells with a
Memory phenotype [95, 96] can also be detected in the fetal intestine, with proportions increasing after birth. However, fetal and infant intestinal CD8+ T cells showed reduced functional capacity compared to adult intestinal CD8+ T cells [96], which is in contrast with results observed in mice [97]. This impaired cytotoxic CD8+ T cell immunity suggests a tolerance support towards foreign antigens after birth, while at the same time it might contribute to the increased gastrointestinal viral susceptibility observed during early life. The expression of CD69 and CD103 on both CD4 and CD8 Tm cells suggests that these intestinal T cells are of the tissue-resident memory (TRM) phenotype [82]. Also γδ T cells [59], invariant NK T cells [98], and mucosal-associated invariant T (MAIT) cells with a mature phenotype and innate-like antimicrobial responses are present in human fetal intestine [99]. The presence of these TRM T cells suggests in utero exposure to foreign antigens, potentially mediated through swallowing of amniotic fluid by the fetus as early as 11 weeks of gestation (EGA) [100, 101]. Mishra et al. detected a low but consistent microbial presence in human fetal organs, including the gut, and with live fetal-isolated microbial strains capable of inducing memory T cell activation and proliferation in vitro [95]. Even though this study suggests that fetal microbiota are capable of educating fetal intestinal T cells, the presence of microbiota in utero is still very controversial [102–104], predominantly due to the lack of appropriate controls and methodological limitations. Nevertheless, it remains imperative to elucidate which agents are responsible for in utero maturation of intestinal T cells.

B cells, on the other hand, have a relatively immature phenotype in the fetal gut, and maturation will occur after birth [82, 90]. In the fetal intestine, an enrichment for transitional B cells can be observed, a subset that has recently migrated from the BM and/or liver, while an enrichment of IgM+ plasma cells can be observed in the intestine of infants [82]. The in utero function of B cells is likely to support the development of lymphoid follicles and PP, as observed in mice [105]. After birth, the expansion of plasma cells will likely shape the selection of a healthy and beneficial intestinal microbiome.

Mucosal immune populations in the fetal lung

Lung-resident immune cells are key to mount immunity towards airborne pathogens to which the airways and interstitium are permanently exposed [106]. Mature DC and alveolar macrophages (AM) are among the first cells to encounter invading microbes [106]. Although the fetus is not exposed to airborne pathogens and the lung continues to mature postnatally into the first years of life [107], immune cells and precursors already seed the fetal lung, establishing immunity to upcoming lifelong challenges. A distinct immune cell repertoire can be detected in the human fetal lung as early as 8 weeks post conception [3, 63, 74, 95, 98, 99, 108–110], coinciding with the start of the pseudoglandular stage of lung development (i.e., differentiation of epithelial cells, formation of conduction airway and terminal bronchioles, formation of pulmonary blood vessels) [107].

AM are the most abundant immune cell type in the adult lung, maintaining lung homeostasis through clearance of debris, invading pathogens, and pulmonary surfactant (reviewed in [111–113]). Macrophages scattered in the fetal lung have been detected around 13–17 PCW in humans [108, 110], and at E13.5 in mice [114]. Currently, little is known about the origin and phenotype of human fetal AM. In mice, however, lung development occurs in parallel with seeding of fetal liver-monocyte derived AM, a self-replenishing population whose maturation is dependent on GM-CSF [39, 115] and maintained until adulthood [36]. The role of fetal liver-derived macrophages in the establishment of AM in the murine fetus was confirmed in a fate-mapping approach [33, 34, 116]. Different reservoirs of fetal monocytes, i.e., BM-derived monocytes, YS-derived macrophages, and fetal-liver monocytes, were tested for their ability to serve as AM precursors. Fetal liver-derived macrophages showed superior GM-CSF responsiveness based on their proliferation-associated gene expression yielding in higher proliferative capacity in vitro [116], showed upregulation of bona fide macrophage differentiation markers such as CD64 and MerTK upon seeding of future resident tissue in vivo, and outcompeted YS macrophages and BM monocytes in colonizing an empty AM niche [33]. In addition, using humanized mouse models, it has been confirmed that human fetal-liver AM precursors are able to seed the lung, giving rise to AM [117].

Next to macrophages, also DC and NK cells will be one of the first immune cells to encounter invading pathogens in the newborn and adult lung. Although lung-resident DC are well characterized in the adult lung, information on DC in the developing fetal lung is limited. However, gene array and flow cytometry analyses have revealed insights into the presence of human fetal lung DC at gestational week 12–22 [110], including plasmacytoid DC (pDC), conventional (c) DC1, and cDC2, showing tissue-specific phenotypes. Data from human fetal lungs obtained at gestational week 15–22 showed that NK cells were present in the mesenchyme of the developing lung tissue [3]. NK cell differentiation and killer immunoglobulin-like receptors (KIR) acquisition starts early, likely before 15 weeks of gestation in the developing fetal lung, with fetal lung NK cells being the most differentiated in comparison to fetal liver, BM, lymph node, and spleen NK cells [3]. This suggests that NK cell differentiation occurs within the lung itself. While fetal lung NK cells are less differentiated compared to circulating adult NK cells, their high expression of multiple KIR and intracellular expression of perforin and granzyme B suggests that
they may be functional [3]. Indeed, in agreement with fetal liver NK cells [118], fetal lung NK cells show degranulation and cytotoxic activity against HLA^neg^ target cells, albeit to a lower extent than their adult peripheral counterparts [3]. In contrast, fetal lung NK cells were highly responsive to cytokine stimulation and antibody-dependent killing of target cells [3]. Interestingly, upon IL-12 stimulation, the percentage of fetal lung NK cells that express IFNγ are higher than adult peripheral NK cells [3]. In conclusion, although fetal lung NK cells are hypo-responsive to cells lacking HLA class I, they possess a strong cytokine- and antibody-mediated immune response capacity, suggesting a balance between fetal-maternal tolerance while still maintaining the ability to respond to infection in utero.

Characterizing ILC populations across human fetal tissues revealed a transcriptomic map of diverse subpopulations with site-specific expression profiles in 8–12 PCW fetuses [63]. ILC1, ILC2, and ILC3 subsets can be found in the fetal lung, with ILC3 being the predominant ILC subset [63]. During murine fetal growth, ILC are involved in the development of secondary lymphoid organs (spleen, lymph nodes, and PP) [119–121], while in non-lymphoid tissues, such as the intestine and lung, mature ILC are considered to establish immunity during colonization and after birth (reviewed in [122, 123]). Increasing frequencies of a CD103+ expressing subset of ILC3, indicating intraepithelial origin, have been identified in the human fetal lung with increasing gestational age (8–20 weeks EGA) [109]. At 20 weeks EGA, these CD103+ ILC3 will make up 15% of ILC3 in the fetal lung [109]. These cells can also be detected in the amniotic fluid at 8–20 weeks EGA, likely through migration from the fetal lung or fetal intestine, where they are believed to mount immunity against in utero infections [109]. Results from lineage tracing and parabiosis experiments in mice have shown that mature ILC2, identified by markers such as Lin^neg^ IL7Ra^+^Thy1^+^ST2^+, are present in the lung at E17.5 [30]. An extensive proliferation of ILC2 occurs in the murine lung at the time of birth, which is linked to the first breath [124]. This first breath leads to a mechanical stimulus that induces IL-33 secretion by type 2 alveolar epithelial cells, which is able to activate a variety of cells in the lung such as regulatory T cells (Treg), DC, mast cells, NK cells, AM, and ILC2 [124]. Due to the activation by IL-33, ILC2 of newborn mice start to secrete IL-13, which in turn drives AM polarization towards an M2 phenotype [124]. Two months after birth, only 5–10% of tissue-resident ILC2 are embryonically derived, suggesting a gradual exchange of the tissue-resident pool by circulating ILC [30].

Recent reports show that adaptive immune cells present in the second trimester human fetal lung (13–23 weeks EGA) include memory CD4 and CD8 T cells, cytotoxic granzyme B+/Tbet+ CD8 T cells, PD1+ Ki67+ Tregs, and CD161+ Vα7.2–CD4+ TCR-αβ+ T cells [74, 95]. Furthermore, the second trimester human lung harbors a population of innate-like Vα7.2+CD161+ CD8+ MAIT cells, with IFNγ and IL-22-producing capacity [99], and invariant NKT cells (CD1d-PBS57 tetramer+ CD3+ TCRαβ+) [98]. Beyond their detection and phenotype-based functional implications, the role of T cells for prenatal lung development and immunity remains to be investigated.

Although not immune cells per se, clinical studies in humans suggest that mesenchymal stromal cells (MSC) possess immune-modulatory properties making them a potential target for cell therapy for idiopathic pulmonary fibrosis (IPF) [125] and acute respiratory distress syndrome (ARDS) [126]. Fetal lung-resident MSCs show lung-specific properties that are distinct from BM-derived and adult lung-resident MSC, and play a role during lung development [127]. They produce higher amounts of macrophage migration inhibitory factor (MIF) when compared to adult lung-resident MSC, a chemokine which hinders random macrophage migration and supports lung development by promoting growth of pulmonary arterial smooth muscle cells [128]. Moreover, MIF is expressed tenfold higher in newborns compared to children and adults, underpinning its involvement in lung development [128, 129].

### Parenchymal and border-associated immune populations in the fetal central nervous system

Neurodevelopment of the human central nervous system (CNS) follows spatially and temporally highly orchestrated patterns (reviewed in [130]). Knowledge about the development of tissue-resident immunity in the brain during the fetal period remains incomplete. Even in the adult CNS, steady-state immune surveillance of brain surfaces was only recently characterized more comprehensively [131–134]. In the parenchyma, homeostatic tissue residency is dominated by microglia, the primary brain macrophage population, while central and systemic inflammation generates a small population of resident T cells [135–137]. Immune and non-immune roles of microglia in brain development have been extensively described in physiological and pathological conditions ([138], reviewed in [139, 140]).

Microglia colonize the brain early in development. Their origin has been revealed in studies in rodents, showing that microglia are derived from primitive and YS EMP–derived precursors who establish themselves in the neuroectoderm by E9.5 [37, 141–143]. Rodent infiltrated microglia locate around subcortical regions (hippocampus) and corpus callosum on E13.5, then expand and migrate into distant brain regions for final residency, proliferating beyond birth following a precisely timed transcriptional program [144]. From rodent studies, it is known that their numbers contract in postnatal week 3 and subsequently stabilize to adult levels after week 4 [145, 146]. Microglial colonization coincides
with rodent brain maturation, and so does their morphology. Developmental, immature microglia are amoeboid (large and round) in shape, resembling activated adult microglia, and are dramatically different from the thin, ramified morphology of adult microglia at steady state, a morphology they assume in parallel with increasing maturation of individual brain regions after birth [147]. In humans, microglia are spotted in close mesenchymal vicinity to neural tissue by 4.5 weeks gestation, and in the neural tissue 1 week later, responding to chemokine signals [148–152]. Recently, human fetal microglia have been transcriptionally characterized on the single-cell level ranging from 9 to 18 weeks EGA, displaying tremendous heterogeneity, and undergoing dynamic processes of maturation to acquire a homeostatic profile, with overlapping and distinct features compared to adult microglia [2].

Microglia are macrophages and, as such, actively engaged in phagocytosis of cellular debris and opsonized synapses, apoptotic clearance, and induction of apoptosis [153–155]. In addition, microglia support a variety of non-immune developmental processes of the macaque and rodent fetal brain including neurogenesis [156] and angiogenesis [157]. In mouse late gestation and early neonatal periods, they contribute to complement-mediated synaptic pruning [158], synaptogenesis [159], survival of neurons [160], oligodendrogenesis, and myelination [161]. This variety of microglia functions depends on time and localization. As one type among tissue-resident macrophages derived from the first primitive and YS EMP–derived premacrophages, microglia are distinct from their counterparts residing in peritoneum, liver, or lung, due to the specific microenvironment in the CNS that primes their functional capacity [34, 43, 162]. Importantly, coinciding with maturation of the blood–brain-barrier (BBB) on E13 in mice [163], the brain niche is considered inaccessible for further precursor seeding after E14.5, thus rendering the microglial population derived from fetal origin, and requiring in situ repopulation capacity for the remainder of the individual’s lifespan [42]. In human embryos, the BBB is considered mature around gestational week 8 [163]. Investigating developmental spatiotemporal patterning of human microglia and their progenitors is crucial in understanding both developmental and mature microglia diversity.

The developing brain parenchymal niche is furthermore colonized by astrocytes, a neural stem cell-derived, yet highly immunocompetent cell type. Their interaction with microglia and other infiltrating immune cell subsets makes them an important component of brain immunity, as they respond to and secrete inflammatory mediators (reviewed in [164]). For example, during the human second trimester, astrocytes produce TNFα and IL-6 upon IL-1β stimulation, a cytokine produced by LPS-responsive fetal microglia [165]. This promotes synaptic transmission and affects synaptic scaling [166]. Human astrocytes start transforming from glial cells after 12 weeks EGA [167–169]. Similar to microglia, astrocytes have phagocytic activity and engage in synaptic pruning [170], while simultaneously promoting microglial pruning during postnatal development [171].

Conventional immune cell subsets are found at very low frequencies in the unchallenged developing brain parenchyma [172–174]. In the adult brain in steady state, the majority of tissue-resident immune cells are non-parenchymal immune subsets residing in the organ border such as the dura mater, subdural meninges, and choroid plexus, and on the abluminal side of the BBB, to surveille and influence mature CNS function [131–133, 138, 175]. These brain-border-associated immune subsets in the choroid plexus include both adaptive and innate immune cells and show a phenotype distinct from microglia [138] and circulating immune cells, indicating their selective enrichment [134]. The choroid plexus is an epithelial bilayer that forms the blood-cerebrospinal fluid (CSF) barrier (BCSFB), that, in addition to immune cells, hosts mesenchymal, and neuronal cells. Its role for establishment of the fetal brain immune landscape across time and space remains scarcely described, while its involvement in mouse brain immune surveillance and embryonic neuroinflammation has been documented [176, 177].

A number of recent studies are starting to build a narrative of parenchymal and brain border-associated immune cell presence establishing in utero. The fetal immune composition in the choroid plexus on E16.5 in mice resembles both the adult and aging brain, with regard to gene expression patterns in B and T cells, macrophages, monocytes, basophils, DC, neutrophils, and mast cells, while unique embryonic features were identified as well [178]. For example, border-associated macrophages in the embryonic choroid plexus express CD206 and are MHC class IIlow, compared to their adult CD206low and MHC class IIhigh (i.e., CD74) counterparts. They are also enriched for the expression of a set of markers (e.g., Lyve1) assigned to adult subdural-specific macrophages [162, 178]. Perivascular, meningeal, and choroid plexus non-parenchymal macrophages, previously assumed to be short-lived and continuously replaced by adult BM-derived circulating cells, were determined to share their embryonic origin with YS-derived parenchymal microglia (wave of transient definitive hematopoiesis) [142], indicating that these precursors are present during fetal brain development. Bulloch et al. describe another myeloid subset, CD11c+ DC, in the choroid plexus, but also in the murine brain parenchyma on E16.5, co-localizing with microglia. In adult mice, these same cells responded to injury with microglia-like morphology [172]. At the same fetal age, Tanabe and Yamashita isolated T and B cells from the mouse brain, finding abundant innate-like B-1...
cells expressing high levels of IgM [174]. These cells localize in the choroid plexus and meninges and, rarely, in the cortical parenchyma on postnatal day 1. They followed CXCR5-dependent recruitment in response to CXCL13 secreted from the choroid plexus, and promoted the proliferation of oligodendrocyte precursor cells (OPC) in vitro. This B-1 population was highly transient, reaching its peak frequency 1 day after birth, and disappearing by postnatal day 10. A small but functionally significant CD4+ T cell population with a brain-resident phenotype is found in the adult human and mouse brain at steady state, with a subset localizing in non-vascular, non-meningeal, parenchymal spaces [173]. Of note, these brain-resident CD4+ T cells, although rare in general, were particularly frequent in the fetal mouse brain right before delivery, when they were supporting the early-life transition of microglia from a fetal to mature transcriptional program, ultimately enabling proper synaptic pruning [173]. Anecdotal evidence for the involvement of non-microglial immune cells in organogenesis describes the estradiol-dependent involvement of mast cells in the development of sexual differentiation in the preoptic area in the rat [179].

**Evidence for immune memory in the fetus**

To complete the porous picture on local fetal immunity in humans with the generally better described system-level perspective, we will highlight evidence for fetal priming of immune function in humans and rodents, based on the mechanisms of innate trained immunity and adaptive antigen-specific memory.

The developing, circulating fetal immune system senses the maternal circulating environment at the fetal-maternal interface. The fetus is exposed to maternal antigen [66], maternal-derived pathogen-associated molecular patterns (PAMPs), DNA and other products from the mother’s commensal microbiota [180–183], maternal antibodies (including passive immunity) [184–186], cytokines [180], and to vertical transfer of pathogens or their products, i.e., transmission of infection [187, 188], as well as vertical transfer of intact maternal cells (220). These maternal microchimeric cells seed across fetal organs to become part of the tissue-resident population with as yet incompletely described consequences for the fetus and neonate [189, 190]. These exposures may be categorized as inherent maternal support and education, and therefore be considered beneficial for fetal immune development. However, the fetus sensing maternal (immune) perturbations, as described in the concept of the developmental origins of health and disease, or “Barker hypothesis,” may have lifelong detrimental consequences for offspring’s immune health (reviewed in [6, 7]), as highlighted in Box 1 for prenatal immune activation of tissue-resident immune populations.

The fetal innate immune system might be trained by these transplacental exposures, leading to persistent transcriptional and epigenetic changes in innate cells and their capacity to respond to secondary challenges unrelated to the primary trigger/pathogen, a concept termed “trained immunity” in adult immune responses [222]. For instance, in utero exposure to hepatitis B virus (HBV) leads to a more mature monocyte phenotype and function in cord blood of uninfected neonates, most likely mediated by changes in cytokine environment, and affects T cell polarization, indicative of the concomitant effect on the adaptive arm [223]. Similar observations of altered immune capacity were made for placental malaria [224] and human immunodeficiency virus (HIV) [225]. In mice, the BM-lung immune axis was trained following maternal microbial exposure in utero, leading to protection from inflammatory airway disease via enhanced survival and proliferation of the lung DC population which was programmed in its BM-resident precursor [226]. Whether pathogen-nonspecific immunity in uninfected fetuses and neonates resulting from maternal inflammation/infection exists and is inherently beneficial for offspring’s health warrants further research [227, 228].

Adaptive fetal immune memory in the periphery is observed after gestational week 14, following thymic emigration and seeding of peripheral organs which equips the human fetus with the complete repertoire of T cell subsets [69–71]. The fetal environment prioritizes unique phenotypes of T cells, including a strong bias towards immune tolerance and the preferential differentiation of naive T cells into Tregs [65]. Thymic [229] and circulating [72] γδ T cells with fetus-specific phenotypes serve fast-acting functions, in addition to innate-like features of CD4+ and CD8+ T cells [230, 231], which, in mouse CD8+ T cells, are retained until adulthood [97]. Despite a relative sparsity in foreign antigen load, the fetal immune system recognizes transferred non-inherited maternal antigens by inducing alloantigen-specific Tregs [66, 232] and shows the potential to establish resident CD4 and CD8 memory (with unknown specificity) in the gut and skin in utero [5, 74, 96, 233]. Fetal CD8+ T cell immunity is functional in its antigen recognition, even if less potent (i.e., decreased cytotoxicity) compared to adult cells [231]. Pathogen-specific CD8+ T cell responses are detectable in cord blood, including to cytomegalovirus (CMV) [234], HIV [235], malaria [236], and HBV [237]. Even in the absence of the pathogen itself, the fetal T cell compartment senses foreign antigens, as maternal influenza vaccination is associated with potent antigen-specific T cells in cord blood [238].

While the mechanisms of priming beneficial vs. detrimental trained and antigen-specific memory remain to be
Evidence for postnatal consequences resulting from prenatal disturbances of resident immune populations are emerging for gut and lung, and have been extensively described for the brain. In the gut, transient prenatal maternal infection at E10.5 caused an increase in intestinal Th17 cells in the adult offspring that, while enhancing protection against gut infection, also increased susceptibility to colitis [180]. In addition, fetal exposure to chorioamnionitis has been associated with dysregulation of fetal gut immunity, intestinal inflammation, and the development of necrotizing enterocolitis weeks after birth [191, 192]. While the exposure of the lung to infections during the neonatal and adult phase is known to lead to chronic lung diseases, less is known about the consequences of inflammatory exposure on fetal lung immune development. In utero, the fetal lung is constantly exposed to the amniotic fluid and pregnancy complications like chorioamnionitis can lead to an inflammatory milieu within the amniotic fluid, resulting in increased leukocyte infiltration, surfactant production, decreased alveolarization (reviewed in [193, 194]), maturation of monocytes to alveolar macrophages, and both the induction as well as the paralysis of inflammatory responses in the fetal lung [195]. In the brain, an association exists between immune activation during embryogenesis, and neurodevelopmental disorders later in life, such as autism spectrum disorder, schizophrenia, and obsessive compulsive disorder [196–198]. Maternal stress/anxiety, nutrition, or infection (e.g., maternal immune activation (MIA)) can program the developing neural structures with long-term sequelae for behavior, cognition, and brain immunity [199–202]. For instance, early-life viral infection is considered to be associated with the adult onset of schizophrenia [197, 203, 204]. Aberrant microglia priming during development as a mechanistic link between immune activation and developmental disorders has been reviewed in [139, 196].

Briefly, mediators of prenatal immune activation and impaired neurodevelopment could be the vertical transmission of an infection, maternal antibodies that react with fetal neural tissue [205], microbiome alterations [206], or the transfer of an inflammatory milieu of maternal cytokines, PAMPS, or viral particles that in turn activate the fetal immune system itself [6, 207]. While glial-derived cytokines are critically contributing to normal brain development, elevated levels of systemic and central IL-1β, IL-6, and TNFα have been shown in experimental models to affect neural development and impair learning and memory, as well as behavior in rodents [208–211], via altered microglial and astrocyte functions, including microglial activation [139, 165, 212]. Increased permeability of the BBB and BCSFB in response to inflammation allows for infiltration of circulating and resident immune cells, and other immune mediators such as cytokines and antibodies into the brain parenchyma [177, 213–215].

In the adult mouse brain, microglia and border-associated macrophage populations show a highly reactive state in response to a neuroinflammatory microenvironment [138], which is supported by parenchymal infiltration of a non-resident BM-derived monocyte population to the site of brain injury [216]. In addition, CNS tissue-resident T cells establish memory after local and systemic infection [135, 137], and can sense microbiome alterations and antibiotic treatment in the periphery [173].

In the perinatal human brain, neuroinflammation and brain injury are common in infants born prematurely (reviewed in [217, 218]). Astrocytes and microglia secrete cyto- and chemokines causing leukocyte infiltration [139]. In humans and mice, accumulated γδ T cells have been found to fuel fetal brain inflammation via IFNγ and non-canonical (i.e., not IL-17) signals [219–221]. Peripheral microbial composition (i.e., expanded proportion of *Klebsiella* in the gut) correlates with inflammation and is predictive of the severity of brain injury in extremely preterm infants [220], emphasizing a gut-immune-brain axis with likely prenatal origin that links neuro- with systemic development.

The dynamic perinatal period is susceptible to external influence. Deviations in programming of fetal immune precursors can have lifelong consequences for the health of the entire organism. This presents opportunities for interventions to support healthy developmental trajectories. Recent technical advances allow the in-depth, high-throughput assessment of a much smaller sample volume to generate high-dimensional maps of spatiotemporal dynamics of organ development in humans. Furthermore, to spur our understanding of human development, human gestational samples, complemented by stem cell-derived organoid models [239–243], instead of rodent, sheep, or non-human primate models with limited overlap in their gestational physiology, are needed to reveal functional overlap and separation of systemic vs. compartmentalized tissue-resident immunity, and identify windows of susceptibility and therapeutic opportunity.

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**Declarations**

**Conflict of interest** The authors declare no competing interests.

**References**

1. Park J-E, Jardine L, Gottgens B, Teichmann SA, Hanifia M (2020) Prenatal development of human immunity. Science 368(6491):600–603
2. Kracht L, Borggrevin M, Eskandar S, Brouwer N, de Sousa C, Lopes SM et al (2020) Human fetal microglia acquire homeostatic immune-sensing properties early in development. Science 369(6503):530–537
3. Ivarsson MA, Loh L, Marquetard N, Kekäläinen E, Berglin L et al (2013) Differentiation and functional regulation of human fetal NK cells. J Clin Invest 123(9):3889–3901
4. Dhariwala MO, Karthikeyan D, Vasquez KS, Farhat S, Weckel A et al (2020) Developing human skin contains lymphocytes demonstrating a memory signature. Cell Rep Med. 1(8):100132
5. Schreurs RRCE, Baumdick ME, Sangeibel AF, Kaufmann M, Mokry M et al (2019) Human fetal TFN-α-cytokine-producing CD4+ effector memory T cells promote intestinal development and mediate inflammation early in life. Immunity 50(2):462–476. e8
6. Apostol AC, Jensen KDC, Beaudin AE (2020) Training the fetal immune system through maternal inflammation-a layered hygiene hypothesis. Front Immunol 11:123
7. Mass E, Gentek R (2021) Fetal-derived immune cells at the roots of lifelong pathophysiology. Front Cell Dev Biol 9:648313
8. Masopust D, Soerens AG (2019) Tissue-resident T cells and other resident leukocytes. Annu Rev Immunol 37:521–546
9. Chou C, Li MO (2018) Tissue-resident lymphocytes across innate and adaptive lineages. Front Immunol 9:2104
10. Hossain Z, Reza AHMM, Qasem WA, Friel JK, Omri A (2022) Development of the immune system in the human embryo. Pediatr Res. https://doi.org/10.1038/s41390-022-01940-0
11. Hoefl G, Ginhoux F (2018) Fetal monocytes and the origins of tissue-resident macrophages. Cell Immunol 303:5–15
12. Popescu D-M, Botting RA, Stephenson E, Green K, Webb S et al (2019) Decoding human fetal liver haematopoiesis. Nature 574(7778):365–371
13. Mass E, Ballesteros I, Farlik M, Halbritter F, Günther P et al (2016) Specification of tissue-resident macrophages during organogenesis. Science 353(6304):aaaf4238
14. Gentek R, Ghigo C, Hoefl G, Bulle MJ, Msallam R et al (2018) Hemogenic endothelial fate mapping reveals dual developmental origin of mast cells. Immunity 48(6):1160-1171.e5
15. Julien E, El Omar R, Tavian M (2016) Origin of the hematopoietic system in the human embryo. FEBS Lett 590(22):3987–4001
16. Zhu Y, Wang T, Gu J, Huang K, Zhang T et al (2020) Characterization and generation of human definitive multipotent hematopoietic stem/progenitor cells. Cell Discov 6(1):89
17. Zeng Y, He J, Bai Z, Li Z, Gong Y et al (2019) Tracing the first hematopoietic stem cell generation in human embryonic stem cells by single-cell RNA sequencing. Cell Res 29(11):881–894
18. Gekas C, Rhodes KE, Van Handel B, Chhabra A, Ueno M, Mikkola HKA (2010) Hematopoietic stem cell development in the placenta. Int J Dev Biol 54(6–7):1089–1098
19. Bian Z, Gong Y, Huang T, Lee CZW, Bian L et al (2020) Deciphering human macrophage development at single-cell resolution. Nature 582(7813):571–576
20. Ema H, Nakauchi H (2000) Expansion of hematopoietic stem cells in the developing liver of a mouse embryo. Blood 95(7):2284–2288
21. Gekas C, Dieterlen-Liévre F, Orkin SH, Mikkola HKA (2005) The placenta is a niche for hematopoietic stem cells. Dev Cell 8(3):365–375
22. Martin MA, Bhatia M (2005) Analysis of the human fetal liver hematopoietic microenvironment. Stem Cells Dev 14(5):493–504
23. Jardine L, Webb S, Goh I, Quiroga Londoño M, Reynolds G et al (2021) Blood and immune development in human fetal bone marrow and Down syndrome. Nature 598(7880):327–331
24. Jacome-Galarza CE, Percin GL, Muller JT, Mass E, Lazarov T et al (2019) Developmental origin, functional maintenance and genetic rescue of osteoclasts. Nature 568(7753):541–545
25. Slayton WB, Li Y, Calhoun DA, Juul SE, Itturraspe J et al (1998) The first-appearance of neutrophils in the human fetal bone marrow cavity. Early Hum Dev 53(2):129–144
26. Fogg DK, Sibon C, Miled C, Jung S, Autourpier P et al (2006) A clonogenic bone marrow progenitor specific for macrophages and dendritic cells. Science 311(5757):83–87
27. Haddad R, Guimio SC, Ginet G, Avcin D, Baggetta N et al (2006) Dynamics of thymus-colonizing cells during human development. Immunity 24(2):217–230
28. Miah M, Goh I, Hanifia M (2021) Prenatal development and function of human mononuclear phagocytes. Front Cell Dev Biol. 9:64937
29. van Furth R, Cohn ZA, Hirsch JG, Humphrey JH, Spector WG, Langevoort HL (1972) The mononuclear phagocyte system: a new classification of macrophages, monocytes, and their precursor cells. Bull World Health Organ 46(6):845–852
30. Schneider C, Lee J, Koga S, Ricardo-Gonzalez RR, Nursbaum JC et al (2019) Tissue-resident group 2 innate lymphoid cells differentiate by layered ontogeny and in situ perinatal priming. Immunity 50(6):1425-1438.e5
31. Simic M, Manosavala I, Spinelli L, Gentek R, Shayan RR et al (2020) Distinct waves from the hemogenic endothelium give rise to layered lymphoid tissue inducer cell ontogeny. Cell Reports. 32(6):108004
32. Gentek R, Ghigo C, Hoefl G, Jorquera A, Msallam R et al (2018) Epidermal y8 T cells originate from yolk sac hematopoiesis and clonally self-renew in the adult. J Exp Med 215(12):2994–3008
33. Hoefl G, Chen J, Lavin Y, Low D, Almeida FF et al (2015) C-Myb(+ ) erythro-myeloid progenitor-derived fetal monocytes give rise to adult tissue-resident macrophages. Immunity 42(4):665–678
34. Gomez Perdiguero E, Klapproth K, Schulz C, Busch K, Azzoni E et al (2015) Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. Nature 518(7540):547–551
35. Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB et al (2013) Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. Immunity 38(4):792–804
36. Yona S, Kim K-W, Wolf Y, Mildner A, Varol D et al (2013) Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. Immunity 38(1):79–91
37. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P et al (2010) Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 330(6005):841–845
38. Hoefl G, Wang Y, Greter M, See P, Teo P et al (2012) Adult Langerhans cells derive predominantly from embryonic fetal
liver monocytes with a minor contribution of yolk sac-derived macrophages. J Exp Med 209(6):1167–1181

39. Guillas M, De Kleer I, Henri S, Post S, Vanhouthe L et al (2013) Alveolar macrophages develop from fetal monocytes that differentiate into long-lived cells in the first week of life via GM-CSF. J Exp Med 210(10):1977–1992

40. Bain CC, Hawley CA, Garner H, Scott CL, Schriddle A et al (2016) Long-lived self-renewing bone marrow-derived macrophages displace embryo-derived cells to inhabit adult serous cavities. Nat Commun 7:11852

41. Bain CC, Bravo-Blas A, Scott CL, Perdiguerro EG, Geissmann F et al (2014) Constant replenishment from circulating monocytes maintains the macrophage pool in the intestine of adult mice. Nat Immunol 15(10):929–937

42. Guillas M, Scott CL (2017) Does niche competition determine the origin of tissue-resident macrophages? Nat Rev Immunol 17(7):451–460

43. Lavin Y, Winter D, Blecher-Gonen R, David E, Keren-Shaul H et al (2014) Tissue-resident macrophage enhancer landscapes are shaped by the local microenvironment. Cell 159(6):1312–1326

44. Foster CA, Holbrook KA, Farr AG (1986) Ontogeny of Langerhans cells in human embryonic and fetal skin: expression of HLA-DR and OKT-6 determinants. J Invest Dermatol 86(3):240–243

45. Seneschal J, Clark RA, Gehad A, Baecher-Allan CM, Kupper TS (2012) Human epidermal Langerhan cells maintain immune homeostasis in skin by activating skin resident regulatory T cells. J Invest Dermatol 130(5):1345–1354

46. Furilo L, Briotet I, Journaux A, Billard H, Péguet-Navarro J (2010) Human langerhans cells are more efficient than CD14(-) CD1c(+) dermal dendritic cells at priming naive CD4(+) T cells. J Immunol 185(4):350–364

47. Fujita M, Furuikawa F, Horiguchi Y, Ueda M, Kashihara-Sawami M, Imamura S (1991) Regional development of Langerhans cells and formation of Birbeck granules in human embryonic and fetal skin. J Invest Dermatol 97(1):65–72

48. Reynolds G, Vech P, Fletcher J, Poyner EFM, Stephenson E et al (2021) Developmental cell programs are co-opted in inflammatory skin disease. Science 371(6527):eaba6500

49. Palis J (2016) Interaction of the macrophage and primitive erythroid lineages in the mammalian embryo. Front Immunol 7:669

50. Li W, Wang Y, Zhao H, Zhang H, Xu Y et al (2019) Identification and transcriptome analysis of erythroblastoid island macrophages. Blood 134(5):480–491

51. Kutteh WH, Rainey WE, Carr BR (1991) Glucocorticoids inhibit lipopolysaccharide-induced production of tumor necrosis factor-alpha by human fetal Kupffer cells. J Clin Endocrinol Metab 73(2):296–301

52. Kutteh WH, Rainey WE, Carr BR (1991) Regulation of interleukin-6 production in human fetal Kupffer cells. Scand J Immunol 33(5):607–613

53. Naito M, Hasegawa G, Takahashi K (1997) Development, differentiation, and maturation of Kupffer cells. Microsc Res Tech 39(4):350–364

54. Okreglicka K, Iten I, Pohlmeier L, Onder L, Feng Q et al (2021) PPARγ is essential for the development of bone marrow erythroid island macrophages and splenic red pulp macrophages. J Exp Med. 218(5):e20191314

55. Kurotaki D, Uede T, Tamura T (2015) Functions and development of red pulp macrophages. Microbiol Immunol 59(2):55–62

56. Dege C, Fegan KH, Creamer JP, Berrien-Elliott MM, Luff SA et al (2020) Potently cytotoxic natural killer cells initially emerge from erythro-myeloid progenitors during mammalian development. Dev Cell 53(2):229-239.e7

57. van de Pavert SA (2021) Lymphoid tissue inducer (LTI) cell ontogeny and functioning in embryo and adult. Biomed J 44(2):123–132

58. Yoshimoto M, Montecino-Rodriguez E, Ferkowicz MJ, Portayre P, Shelley WC et al (2011) Embryonic day 9 yolk sac and intra-embryonic hemogenic endothelium independently generate a B-1 and marginal zone progenitor lacking B-2 potential. Proc Natl Acad Sci U S A 108(4):1468–1473

59. McVay LD, Jaswal SS, Kennedy C, Hayday A, Carding SR (1998) The generation of human gammadelta T cell repertoires during fetal development. J Immunol 160(12):5851–5860

60. Beaudin AE, Boyer SW, Perez-Cunningham J, Hernandez GE, Derderian SC et al (2016) A transient developmental hematopoietic stem cell gives rise to innate-like B and T cells. Cell Stem Cell 19(6):768–783

61. Dorshkind K, Montecino-Rodriguez E (2007) Fetal B-cell lymphopoiesis and the emergence of B-1-cell potential. Nat Rev Immunol 7(3):213–219

62. Bueno C, van Roos J, Muñoz-López A, Sanjuan-Pla A, Juan M et al (2016) Immunophenotypic analysis and quantification of B-1 and B-2 B cells during human fetal hematopoietic development. Leukemia 30(7):1603–1606

63. Liu C, Gong Y, Zhang H, Yang H, Zeng Y et al (2021) Delineating spatiotemporal and hierarchical development of human fetal innate lymphoid cells. Cell Res 31(10):1106–1122

64. Mold JE, Venkatasubramanyam S, Burt TD, Michaelsson J, Rivera JM et al (2010) Fetal and adult hematopoietic stem cells give rise to distinct T cell lineages in humans. Science 330(6011):1695–1699

65. Ng MSF, Roth TL, Mendoza VF, Marson A, Burt TD (2019) Helios enhances the preferential differentiation of fetal human CD4+ naïve T cells into regulatory T cells. Sci Immunol 4(41):eaa95947

66. Mold JE, Michaelsson J, Burt TD, Muench MO, Beckerman KP et al (2008) Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. Science 322(5907):1562–1565

67. Li N, van Unen V, Abdealaal T, Guo N, Kasatskaya SA et al (2019) Memory CD4+ T cells are generated in the human fetal intestine. Nat Immunol 20(3):301–312

68. Rackaityte E, Halkias J (2020) Mechanisms of fetal T cell tolerance and immune regulation. Front Immunol 11:588

69. Haynes BF, Martin ME, Kay HH, Kurtzberg J (1988) Early events in human T cell ontogeny. Phenotypic characterization and immunohistologic localization of T cell precursors in early human fetal tissues. J Exp Med. 168(3):1061–80

70. Cупedo T, Nagasawa M, Weijer K, Blom B, Spits H (2005) Development and activation of regulatory T cells in the human fetus. Eur J Immunol 35(2):383–390

71. Michaelsson J, Mold JE, McCune JM, Nixon DF (2006) Regulation of T cell responses in fetal T cells responses in the developing human fetus. J Immunol 176(10):5741–5748

72. Dimova T, Brouwer M, Gosselin F, Tassignon J, Leo O et al (2015) Effector γδV9Vδ2 T cells dominate the human fetal γδ T-cell repertoire. Proc Natl Acad Sci U S A 112(6):E556–E565

73. Reitermaier K, Krausgruber T, Fortelny N, Ayub T, Vieyra-Garcia PA et al (2021) αβγδ T cells play a vital role in fetal human skin development and immunity. J Exp Med. 218(4):e20201189

74. Halkias J, Rackaityte E, Hillman SL, Aran D, Mendoza VF et al (2019) CD161 contributes to prenatal immune suppression of IFNγ-producing PLZF+ T cells. J Clin Invest 129(9):3562–3577

75. Darrasse-Jéze G, Marodon G, Salomon BL, Catala M, Klatzmann D (2005) Ontogeny of CD4+CD25+ regulatory/suppressor T cells in human fetuses. Blood 105(12):4715–4721
76. Mold JE, McCune JM (2012) Immunological tolerance during fetal development: from mouse to man. Adv Immunol 115:73–111
77. Chen L, Cohen AC, Lewis DB (2006) Impaired allogeneic activation and T-helper 1 differentiation of human cord blood naive CD4 T cells. Biol Blood Marrow Transplant 12(2):160–171
78. Fawcett-Corbett D, Antanaviciute A, Parikh K, Jagielowicz M, Gerós AS et al (2021) Spatiotemporal analysis of human intestinal development at single-cell resolution. Cell 184(3):810-826.e23
79. Torow N, Marsland BJ, Horner MW, Collwitzer ES (2017) Neonatal mucosal immunology. Mucosal Immunol 10(1):5–17
80. Li N, van Unen V, Guo N, Abdelaal T, Somarakis A et al (2019) Early-life compartmentalization of immune cells in human fetal tissues revealed by high-dimensional mass cytometry. Front Immunol 10:1932
81. Li N, van Unen V, Höllt T, Thompson A, van Bergen J et al (2018) Mass cytometry reveals innate lymphoid cell differentiation pathways in the human fetal intestine. J Exp Med 215(5):1383–1396
82. Stras SF, Werner L, Tootahker JM, Olaloye OO, Oldham AL et al (2019) Maturation of the human intestinal immune system occurs early in fetal development. Dev Cell 51(3):357-373.e5
83. Blümner P, Pfefferle PI, Renz H (2007) Development of mucosal immune function in the intrauterine and early postnatal environment. Curr Opin Gastroenterol 23(6):655–660
84. O’Connell A, Rivers A, Slayton W (2021) The development of the human immune system. In: De Alarcón P, Werner E, Christensen R, Sola-Visner M (eds) Neonatal hematology: pathogenesis, diagnosis, and management of hematologic problems. Cambridge University Press, Cambridge, pp 25–42. https://doi.org/10.1017/9781108773584.005
85. MacDonald TT, Spencer J (1994) Ontogeny of the gut-associated lymphoid system in man. Acta Paediatr Suppl 83(395):3–5
86. Ginhoux F, Guilliams M (2016) Tissue-resident macrophage ontogeny and homeostasis. Immunity 44(3):439–449
87. Dogra P, Rancan C, Ma W, Toth M, Senda T et al (2020) Tissue determinants of human NK cell development, function, and residence. Cell 180(4):749-763.e13
88. Howie D, Spencer J, DeLord D, Pitulakis C, Wathen NC et al (1998) Extrathymic T cell differentiation in the human intestine early in life. J Immunol 161(1):5862–5872
89. Elmentainte R, Kumasaka N, Roberts K, Fleming A, Dann E et al (2021) Cells of the human intestinal tract mapped across space and time. Nature 597(7875):250–255
90. James KR, Elmentainte R, Teichmann SA, Hold GL (2022) Redefining intestinal immunity with single-cell transcriptomics. Mucosal Immunol 30:1–11. https://doi.org/10.1038/s41385-021-00470-y
91. Krishnamurthy AT, Turley SJ (2020) Lymph node stromal cells: cartographers of the immune system. Nat Immunol 21(4):369–380
92. Maheshwari A, Kurundkar AR, Shaik SS, Kelly DR, Hartman Y et al (2009) Epithelial cells in fetal intestine produce chemerin to recruit macrophages. Am J Physiol Gastrointest Liver Physiol 297(1):G1–10
93. Smythies LE, Maheshwari A, Clemens R, Eckhoff D, Novak L et al (2006) Mucosal IL-8 and TGF-beta recruit blood monocytes: evidence for cross-talk between the lamina propria stroma and myeloid cells. J Leukoc Biol 80(3):492–499
94. Bunders MJ, van der Loos CM, Klarenbeek PL, van Hamme JL, Boer K et al (2012) Memory CD4(+)CCR5(+) T cells are abundantly present in the gut of newborn infants to facilitate mother-to-child transmission of HIV-1. Blood 120(22):4383–4390
95. Mishra A, Lai GC, Yao LJ, Aung TT, Shental N et al (2021) Microbial exposure during early human development primes fetal immune cells. Cell 184(13):3394-3409.e20
96. Schreurs RER, Sagebiel AF, Steinert FL, Highton AJ, Klarenbeek PL et al (2021) Intestinal CD8+ T cell responses are abundantly induced early in human development but show impaired cytotoxic effector capacities. Mucosal Immunol 14(3):605–614
97. Smith NL, Patel RK, Reynolds A, Grenier JK, Wang J et al (2018) Developmental origin governs CD8+ T Cell fate decisions during infection. Cell 174(1):117-130.e14
98. Loh L, Ivarsson MA, Michaëlsson J, Sandberg JK, Nixon DF (2014) Invariant natural killer T cells developing in the human fetus accumulate and mature in the small intestine. Mucosal Immunol 7(5):1233–1243
99. Leeansyah E, Loh L, Nixon DF, Sandberg JK (2014) Acquisition of innate-like microbial reactivity in mucosal tissues during human fetal MAIT-cell development. Nat Commun 5:3143
100. Grassi R, Farina R, Floriani I, Amadio F, Romano S (2005) Assessment of fetal swallowing with gray-scale and color Doppler sonography. AJR Am J Roentgenol 185(5):1322–1327
101. Diamant NE (1985) Development of esophageal function. Am Rev Respir Dis 131(5):S29–32
102. Kennedy KM, Bellissimo CJ, Breznik JA, Barrett J, Braun T et al (2021) Over-coming fetal microbial exposure. Cell 184(24):5839–5841
103. Mishra A, Yao LJ, Wasser M, Khyriem C, Malleret B et al (2021) Reply to Over-coming fetal microbial exposure. Cell 184(24):5842–5844
104. Walter J, Horner MW (2021) A philosophical perspective on the prenatal in utero microbiome debate. Microbiome 9(1):5
105. Shen P, Fillatreau S (2015) Antibody-independent functions of B cells: a focus on cytokines. Nat Rev Immunol 15(7):441–451
106. Hartl D, Tirovanziam R, Laval J, Greene CM, Habel D et al (2018) Innate immunity of the lung: from basic mechanisms to translational medicine. J Innate Immun 10(5–6):487–501
107. Joshi S, Kotecha S (2007) Lung growth and development. Early Hum Dev 83(12):789–794
108. Dame JB, Christensen RD, Juul SE (1999) The distribution of granulocyte-macrophage colony-stimulating factor and its receptor in the developing human fetus. Pediatr Res 46(4):358–366
109. Marquardt N, Ivarsson MA, Sundström E, Åkesson E, Martini E et al (2016) Fetal CD103 + IL-17–producing group 3 innate lymphoid cells represent the dominant lymphocyte subset in human amniotic fluid. J Immunol 197(8):3069–75
110. McGovern N, Shin A, Low G, Low D, Duan K et al (2017) Human fetal dendritic cells promote prenatal T-cell immune suppression through arginase-2. Nature 546(7660):662–666
111. Trapnell BC, Nakata K, Bonella F, Campo I, Griese M et al (2019) Pulmonary alveolar proteinosis. Nat Rev Dis Primers 5(1):16
112. Hou F, Xiao K, Tang L, Xie L (2021) Diversity of macrophages in lung homeostasis and diseases. Front Immunol. 12:753940
113. Balhara J, Gounni AS (2012) The alveolar macrophages in asthma: a double-edged sword. Mucosal Immunol 5(6):605–609
114. Lakhdar O, Yamamura A, Hernandez GE, Anderson KK, Lund SJ et al (2019) Differential immune activation in fetal macrophage populations. Sci Rep 9(1):7677
115. Schneider C, Nobs SP, Kurrer M, Rehruer H, Thiele C, Kopf M (2014) Induction of the nuclear receptor PPAR-y by the cytokine GM-CSF is critical for the differentiation of fetal monocytes into alveolar macrophages. Nat Immunol 15(1):1026–1037
116. van de Laar L, Saelens W, De Prijck S, Martens L, Scott CL et al (2016) Yolk sac macrophages, fetal liver, and adult macrocytes can colonize an empty niche and develop into functional tissue-resident macrophages. Immunity 44(4):755–768
117. Evren E, Ringqvist E, Doisne J-M, Thaller A, Sleiers N et al (2022) CD11b+ fetal precursors migrate to the perinatal lung and give rise to human alveolar macrophages. J Experiment Med 219(2):e20210987

118. Phillips JH, Horii T, Nagler A, Bhat N, Spits H, Lanier LL (1992) Ontogeny of human natural killer (NK) cells: fetal NK cells mediate cytolytic function and express cytotoxic CD3 epsilon, delta proteins. J Exp Med 175(4):1055–1066

119. Tan JKH, Watanabe T (2014) Murine spleen tissue regeneration from neonatal spleen capsule requires lymphotoxin priming of stromal cells. JI 193(3):1194–1203

120. Eberl G, Marmon S, Sunshine M-J, Rennert PD, Choi Y, Littman DR (2004) An essential function for the nuclear receptor RORγt in the generation of fetal lymphoid tissue inducer cells. Nat Immunol 5(1):64–73

121. Yoshida H, Honda K, Shinkura R, Adachi S, Nishikawa S et al (1999) IL-7 receptor α+ CD3– cells in the embryonic intestine induces the organizing center of Peyer’s patches. Int Immunol 11(5):643–655

122. Arts D, Spits H (2015) The biology of innate lymphoid cells. Nature 517(7534):293–301

123. Yu JC, Khodadadi H, Malik A, Davidson B, da Salles É, SL, et al (2018) Innate immunity of neonates and infants. Front Immunol 9:1759

124. Saluzzo S, Gorki A-D, Rana BMJ, Martins R, Scanlon S et al (2017) First-breath-induced type 2 pathways shape the lung immune environment. Cell Rep 18(8):1893–1905

125. Tzouvelekis A, Paspalaris V, Koliakos G, Ntolios P, Bouros E et al (2013) A prospective, non-randomized, no placebo-controlled, phase Ib clinical trial to study the safety of the adipose derived stromal cells-stromal vascular fraction in idiopathic pulmonary fibrosis. J Transl Med 11(1):171

126. Simonson OE, Mougiakakos D, Heldring N, Bassi G, Johansson HJ et al (2015) In vivo effects of mesenchymal stromal cells in two patients with severe acute respiratory distress syndrome. Stem Cells Transl Med 4(10):1199–1213

127. Rolandsson Enes S, Andersson Sjoland A, Skog I, Hansson L, Larsson H et al (2016) MSC from fetal and adult lungs possess lung-specific properties compared to bone marrow-derived MSC. Sci Rep 6(1):29160

128. Kevil KA, Bhandari V, Kettunen M, Leng L, Fan J et al (2008) A role for macrophage migration inhibitory factor in the neonatal respiratory distress syndrome. J Immunol 181(1):601–608

129. Perveen S, Ayasolla K, Zagloul N, Patel H, Ochani K et al (2019) MIF inhibition enhances pulmonary angiogenesis and lung development in congenital diaphragmatic hernia. Pediatr Res 85(5):711–718

130. Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N (2016) The cellular and molecular landscapes of the developing human central nervous system. Nature 530(7585):472–479

131. Rustenjoven J, Drieu A, Mamuladze T, de Lima KA, Dykstra T et al (2021) Functional characterization of the dural sinuses as a neuroimmune interface. Cell 184(4):1000–1016.e27

132. Croese T, Castellani G, Schwartz M (2021) Immune cell compartmentalization for brain surveillance and protection. Nat Immunol 22(9):1083–1092

133. Cugurra A, Mamuladze T, Rustenjoven J, Dykstra T, Beroshvili G et al (2021) Skull and vertebral bone marrow are myeloid cell reservoirs for the meninges and CNS parenchyma. Science 373(6553):eabc7844

134. Korin B, Ben-Shaanan TL, Schiller M, Dubovik T, Azulay-Debby H et al (2017) High-dimensional, single-cell characterization of the brain’s immune compartment. Nat Neurosci 20(9):1300–1309

135. Wakim LM, Woodward-Davis A, Bevan MJ (2010) Memory T cells persisting within the brain after local infection show functional adaptations to their tissue of residence. Proc Natl Acad Sci U S A 107(42):17872–17879

136. Korn T, Kallies A (2017) T cell responses in the central nervous system. Nat Rev Immunol 17(3):179–194

137. Urban SL, Jensen JJ, Shan Q, Pewe LL, Xue H-H et al (2020) Peripherally induced brain tissue-resident memory CD8+ T cells mediate protection against CNS infection. Nat Immunol 21(8):938–949

138. Mrdjen D, Pavlovic A, Hartmann FJ, Schreiner B, Utz SG et al (2018) High-dimensional single-cell mapping of central nervous system immune cells reveals distinct myeloid subsets in health, aging, and disease. Immunity 48(2):380–395.e6

139. Bilbo SD, Schwarz JM (2009) Early-life programming of later-life brain and behavior: a critical role for the immune system. Front Behav Neurosci 3:14

140. Reemts K, Noctor SC, Lu cassen PJ, Hol EM (2016) The Indispensable Roles of Microglia and Astrocytes during Brain Development. Front Hum Neurosci 10:566

141. Kierdorf K, Erny D, Goldmann T, Sander V, Schulz C et al (2013) Microglia emerge from erythromyeloid precursors via Pu.1- and Irf8-dependent pathways. Nat Neurosci. 16(3):273–80

142. Goldmann T, Wieghof er H, Jordão MJC, Prutek F, Hagemeiner N et al (2016) Origin, fate and dynamics of macrophages at central nervous system interfaces. Nat Immunol 17(7):797–805

143. Wang CC, Wu CH, Shieh JY, Wen CY (2002) Microglial distribution and apoptosis in fetal rat brain. Brain Res Dev Brain Res 139(2):337–342

144. Matcovitch-Natan O, Winter DR, Giladi A, Vargas Agui lar S, Spinrad A et al (2016) Microglia development follows a stepwise program to regulate brain homeostasis. Science. 353(6301):aad8670

145. Kim I, Mlsna LM, Yoon S, Le B, Yu S et al (2015) A postnatal peak in microglial development in the mouse hippocampus is correlated with heightened sensitivity to seizure triggers. Brain Behav. 5(12):e00403

146. Nikodemova M, Kimyon RS, De I, Small AL, Collier LS, Watters JJ (2015) Microglial numbers attain adult levels after undergoing a rapid decrease in cell number in the third postnatal week. J Neuroimmunol 278:280–288

147. Cuadros MA, Navascués J (1998) The origin and differentiation of microglial cells during development. Prog Neurobiol 56(2):173–189

148. Andjelkovic AV, Nikolic B, Pachter JS, Zecevic N (1998) Macrophages/microglial cells in human central nervous system during development: an immunohistochemical study. Brain Res 814(1–2):13–25

149. Monier A, Evrard P, Gressens P, Verney C (2006) Distribution and differentiation of microglia in the human encephalon during the first two trimesters of gestation. J Comp Neurol 499(4):565–582

150. Monier A, Adle-Biassette H, Delezio A-L, Evrard P, Gressens P, Verney C (2007) Entry and distribution of microglial cells in human embryonic and fetal cerebral cortex. J Neuropathol Exp Neurol 66(5):372–382

151. Male D, Rezaie P (2001) Colonisation of the human central nervous system by microglia: the roles of chemokines and vascular adhesion molecules. Prog Brain Res 132:81–93

152. Menassa DA, Gomez-Nicola D (2018) Microglial dynamics during human brain development. Front Immunol 9:1014

153. Marín-Teija VL, Dusart I, Colín C, Gerva i A, van Rooijen N, Mallat M (2004) Microglia promote the death of developing Purkinje cells. Neuron 41(4):535–547

154. Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR et al (2012) Microglia sculpt postnatal neural circuits
in an activity and complement-dependent manner. Neuron 74(4):691–705

155. Galloway DA, Philips AEM, Owen DRJ, Moore CS (2019) Phagocytosis in the brain: homeostasis and disease. Front Immunol 10:790

156. Cunningham CL, Martínez-Cerdeño V, Noctor SC (2013) Microglia regulate the number of neural precursor cells in the developing cerebral cortex. J Neurosci 33(10):4216–4233

157. Fantin A, Vieira JM, Gestri G, Denti L, Schwarz Q et al (2010) Tissue macrophages act as cellular chaperones for vascular anastomosis downstream of VEGF-mediated endothelial tip cell induction. Blood 116(5):829–840

158. Stevens B, Allen NJ, Vazquez LE, Howell GR, Christopherson KS et al (2007) The classical complement cascade mediates CNS synapse elimination. Cell 131(6):1164–1178

159. Miyamoto A, Wake H, Ishikawa AW, Eto K, Shibata K et al (2016) Microglia contact induces synapse formation in developing somatosensory cortex. Nat Commun 7:12540

160. Ueno M, Fujita Y, Tanaka T, Nakamura Y, Kikuta J et al (2013) Layer V cortical neurons require microglial support for survival during postnatal development. Nat Neurosci 16(5):543–551

161. Shigemoto-Mogami Y, Hoshikawa K, Goldman JE, Sekino Y, Sato K (2014) Microglia enhance neurogenesis and oligodendrogenesis in the postnatal subventricular zone. J Neurosci 34(6):2231–2243

162. Van Hove H, Martens L, Scheyltjens I, De Vlaminck K, Pombo Antunes AR et al (2019) A single-cell atlas of mouse brain macrophages reveals unique transcriptional identities shaped by ontogeny and tissue environment. Nat Neurosci 22(6):1021–1035

163. Ek CI, Dziegielewksa KM, Habgood MD, Saunders NR (2012) Barriers in the developing brain and Neurotoxicology. Neurotoxicology 33(3):586–604

164. Priego N, Valiente M (2019) The potential of astrocytes as immune modulators in brain tumors. Front Immunol 10:1314

165. Lee SC, Liu W, Dickson DW, Brosnan CF, Berman JW (1993) Cytokine production by human fetal microglia and astrocytes. Differential induction by lipopolysaccharide and IL-1 beta. J Immunol. 150(7):2659–67

166. Stellwagen D, Malenka RC (2006) Synaptic scaling mediated by glial TNF-alpha. Nature 440(7087):1054–1059

167. Holst CB, Broschner CB, Vitting-Seerup K, Møllgård K (2019) Astrogligenesis in human fetal brain: complex spatiotemporal immunoreactivity patterns of GFAP, S100, AQP4 and YKL-40. J Anat 235(3):590–615

168. Kadhim HJ, Gadisseux JF, Evrard P (1988) Topographical and cytological evolution of the glial phase during prenatal development of the human brain: histochemical and electron microscopic study. J Neuropathol Exp Neurol 47(2):166–188

169. Marín-Padilla M (1995) Prenatal development of fibrous (white matter), protoplasmic (gray matter), and layer I astrocytes in the human cerebral cortex: a Golgi study. J Comp Neurol 357(4):554–572

170. Chung W-S, Clarke LE, Wang GX, Stafford BK, Sher A et al (2013) Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways. Nature 504(7480):394–400

171. Vainchtein ID, Chin G, Cho FS, Kelley KW, Miller JG et al (2018) Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. Science 359(6381):1269–1273

172. Bulloch K, Miller MM, Gal-Toth J, Milner TA, Gottfried-Bla-tmore A et al (2008) CD11c/EYFP transgene illuminates a discrete network of dendritic cells within the embryonic, neonatal, adult, and injured mouse brain. J Comp Neurol 508(5):687–710

173. Pascueto E, Burton OT, Roca CP, Lagou V, Rajan WD et al (2020) Microglia require CD4 T cells to complete the fetal-to-adult transition. Cell 182(3):625-640.e24

174. Tanabe S, Yamashita T (2018) B-1a lymphocytes promote oligodendrogenesis during brain development. Nat Neurosci 21(4):506–516

175. Ziv Y, Ron N, Butovsky O, Landa G, Sudai E et al (2006) Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. Nat Neurosci 9(2):268–275

176. Cui J, Xu H, Lehtinen MK (2021) Macrophages on the margin: choroid plexus immune responses. Trends Neurosci 44(11):864–875

177. Cui J, Shiple FB, Shannon ML, Alturkistani O, Dani N et al (2020) Inflammation of the embryonic choroid plexus barrier following maternal immune activation. Dev Cell 55(5):617-628.e6

178. Dani N, Herbst RH, McCabe C, Green GS, Kaiser K et al (2021) A cellular and spatial map of the choroid plexus across brain ventricles and ages. Cell 184(11):3056-3074.e21

179. Lenz KM, Pickett LA, Wright CL, Davis KI, McCarthy MM (2018) Mast cells in the developing brain determine adult sex behavior. J Neurosci 38(37):8044–8059

180. Lim AI, McFadden T, Link VM, Han S-J, Karlsson R-M et al (2021) Prenatal maternal infection promotes tissue-specific immunity and inflammation in offspring. Science. 373(6558):eabf3002

181. Nyangahu DD, Jaspan HB (2019) Influence of maternal microbiota during pregnancy on infant immunity. Clin Exp Immunol 198(1):47–56

182. Stinson LF, Boyce MC, Payne MS, Keelan JA (2019) The not-so-sterile womb: evidence that the human fetus is exposed to bacteria prior to birth. Front Microbiol 10:1124

183. Dimova T, Terzieva A, Djerev L, Dimitrova V, Nikolov A et al (2017) Mother-to-newborn transmission of mycobacterial L-forms and V82 T-cell response in placentobiome of BCG-vaccinated pregnant women. Sci Rep 7(1):17366

184. Jennenwein MF, Goldfarb I, Dolatshahi S, Cosgrove C, Noelle JF et al (2019) Fc glycan-mediated regulation of placental antibody transfer. Cell 178(1):202-215.e14

185. Albrecht M, Pagenkemper M, Wiessner C, Spohn M, Lütgehetmann M et al (2021) Infant immunity against viral infections is advanced by the placental-dependent vertical transfer of maternal antibodies. Vaccine S0264-410X(20):31629–7

186. Msallam R, Balla J, Rathore APS, Kared H, Malleret B et al (2020) Fetal mast cells mediate postnatal allergic responses dependent on maternal IgE. Science 370(6519):941–950

187. Arora N, Sadovsky Y, Demodysh TS, Coyne CB (2017) Microbial vertical transmission during human pregnancy. Cell Host Microbe 21(5):561–567

188. Hoo R, Nakimuli A, Vento-Tormo R (2020) Innate immune mechanisms to protect against infection at the human deciduoplacental interface. Front Immunol 11:2070

189. Kinder JM, Stelzer IA, Arck PC, Way SS (2017) Immunological implications of pregnancy-induced microchimerism. Nat Rev Immunol 17(8):483–494

190. Stelzer IA, Urbschat C, Schepanski S, Thiele K, Triviai I et al (2021) Vertically transferred maternal immune cells promote neonatal immunity against early life infections. Nat Commun 12(1):4706

191. Juber BA, Elgin TG, Fricke EM, Gong H, Reese J, McElroy SJ (2020) A murine model of fetal exposure to maternal inflammation to study the effects of acute chorioamnionitis on newborn intestinal development. J Vis Exp (160). https://doi.org/10.3791/61464

192. Elgin TG, Fricke EM, Gong H, Reese J, Mills DA et al (2019) Fetal exposure to maternal inflammation interrupts murine intestinal development and increases susceptibility to neonatal intestinal injury. Dis Model Mech 12(10):dmm040808
193. Jackson CM, Mukherjee S, Wilburn AN, Cates C, Lewkowich IP et al (2020) Pulmonary consequences of perinatal inflammatory exposures: clinical perspective and review of basic immunological mechanisms. Front Immunol 11:1285
194. Singh AM, Sherenian MG, Kim K-Y, Erickson KA, Yang A et al (2018) Fetal cord blood and tissue immune responses to chronic placental inflammation and choorioamnionitis. Allergy Asthma Clin Immunol 14:66
195. Kramer BW, Kalliapur S, Newham J, Jobe AH (2009) Prenatal inflammation and lung development. Semin Fetal Neonatal Med 14(1):2–7
196. Bilbo SD, Block CL, Bolton JL, Hanamsagar R, Tran PK (2018) Megrocal development - maternal immune activation by environmental factors, microbialgial development, and relevance for autism spectrum disorders. Exp Neurol 299(Pt A):241–251
197. Choudhury Z, Lennox B (2021) Maternal immune activation and schizophrenia-evidence for an immune priming disorder. Front Psychiatry 12:585742
198. Jones HF, Han VX, Patel S, Gloss BS, Soler N et al (2021) Maternal autoimmune and inflammation are associated with childhood tics and obsessive-compulsive disorder: transcriptomic data show common enriched innate immune pathways. Brain Behav Immun 94:308–317
199. Rudolph MD, Graham AM, Fecko E, Miranda-Dominguez O, Rasmussen JM et al (2018) Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. Nat Neurosci 21(5):765–772
200. Ganguli S, Chavali PL (2021) Intraterine viral infections: impact of inflammation on fetal neurodevelopment. Front Neurosci 15:771557
201. Tong L, Kalish BT (2021) The impact of maternal obesity on childhood neurodevelopment. J Perinatol 41(5):928–939
202. Lautarescu A, Craig MC, Glover V (2020) Prenatal stress: effects on fetal and child brain development. Int Rev Neurobiol 150:17–40
203. Fruntes V, Limosin F (2008) Schizophrenia and viral infection during neurodevelopment: a pathogenesis model? Med Sci Monit 14(6):RA71-77
204. Selten J-P, Termonshuizen F (2017) The serological evidence for maternal influenza as risk factor for psychosis in offspring is insufficient: critical review and meta-analysis. Schizophr Res 183:2–9
205. Rathore APS, Saran WAA, Lim T, Jahan N, St John AL (2019) Maternal immunity and antibodies to dengue virus promote infection and Zika virus-induced microcephaly in fetuses. Sci Adv 5(2):eaav3208
206. Thion MS, Low D, Silvin A, Chen J, Grisel P et al (2018) Microbione influences prenatal and adult microglia in a sex-specific manner. Cell 172(3):500-516.e16
207. Meyer U, Feldon J, Schedlowski M, Yee BK (2006) Immunological stress at the maternal-fetal interface: a link between neurodevelopment and adult psychopathology. Brain Behav Immun 20(4):378–388
208. Bilbo SD, Biedenkapp JC, Der-Avakian A, Watkins LR, Rudy JW, Maier SF (2005) Neonatal infection-induced memory impairment after lipopolysaccharide in adulthood is prevented via caspase-1 inhibition. J Neurosci 25(35):8000–8009
209. Smith SEP, Li J, Garbett K, Mirmics K, Patterson PH (2007) Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci 27(40):10695–10702
210. Mirabella F, Desiato G, Mancinelli S, Fossati G, Rasile M et al (2021) Prenatal interleukin 6 elevation increases glutamatergic synapse density and disrupts hippocampal connectivity in offspring. Immunity 54(11):2611-2631.e8
211. Ratnayake U, Quinn T, Walker DW, Dickinson H (2013) Cytokines and the neurodevelopmental basis of mental illness. Front Neurosci 7:180
212. Town T, Nikolic V, Tan J (2005) The microglial “activation” continuum: from innate to adaptive responses. J Neuroinflammation 2:24
213. Saunders NR, Dziegielewska KM, Mollgard K, Haldgord MD (2018) Physiology and molecular biology of barrier mechanisms in the fetal and neonatal brain. J Physiol 596(23):5723–5756
214. Schmitt C, Strazzielle N, Gherzi-Egea J-F (2012) Brain leucocyte infiltration initiated by peripheral inflammation or experimental autoimmune encephalomyelitis occurs through pathways connected to the CSF-filled compartments of the forebrain and midbrain. J Neuroinflammation 9:187
215. Kowal C, Athanassiu A, Chen H, Diamond B (2015) Maternal antibodies and developing blood-brain barrier. Immunol Res 63(1–3):18–25
216. Werner Y, Mass E, Ashok Kumar P, Ulas T, Händler K et al (2020) Cxcr4 distinguishes HSC-derived monocytes from microglia and reveals monocyte immune responses to experimental stroke. Nat Neurosci 23(3):351–362
217. Herz J, Bendl I, Felderhoff-Müser U (2022) Perinatal immune cells and perinatal brain injury: a double-edged sword? Pediatr Res 91:392–403
218. Melo AM, Taher NA, Doherty DG, Molloy EJ (2021) The role of lymphocytes in neonatal encephalopathy. Brain Behav Immun 18:100380
219. Albertsson A-M, Zhang X, Vontell R, Bi D, Bronson RT et al (2018) γδ T cells contribute to injury in the developing brain. Am J Pathol 188(3):757–767
220. Seki D, Mayer M, Haussmann B, Pjecv P, Giordano V et al (2021) Aberrant gut-microbiota-immune-brain axis development in premature neonates with brain damage. Cell Host Microbe 29(10):1558-1572.e6
221. Lewis EL, Tulina N, Anton L, Brown AG, Porrett PM, Elozvitz MA (2021) IFNγ-producing γ/δ T cells accumulate in the fetal brain following intrauterine inflammation. Front Immunol 12:741518
222. Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M et al (2020) Defining trained immunity and its role in health and disease. Nat Rev Immunol 20(6):375–388
223. Hong M, Sandalova E, Low D, Gehring AJ, Fieni S et al (2015) Trained immunity in newborn infants of HBV-infected mothers. Nat Commun 6:6588
224. Natama HM, Moncunill G, Rovira-Vallbona E, Sanz H, Sorgho H et al (2018) Modulation of innate immune responses at birth by prenatal malaria exposure and association with malaria risk during the first year of life. BMC Med 16(1):198
225. Abu-Raya B, Kollmann TR, Marchant A, MacGillivray DM (2016) The immune system of HIV-exposed uninfected infants. Front Immunol 7:383
226. Mincham KT, Jones AC, Bodinier M, Scott NM, Launois J-F et al (2020) Transplacental innate immune training via maternal microbial exposure: role of XBPI1-ERN1 axis in dendritic cell precursor programming. Front Immunol 11:601494
227. Dauby N, Goetgebuer T, Kollmann TR, Levy J, Marchant A (2012) Uninfected but not unaffected: chronic maternal infections during pregnancy, fetal immunity, and susceptibility to postnatal infections. Lancet Infect Dis 12(4):330–340
228. Kollmann TR, Marchant A, Way SS (2020) Vaccination strategies to enhance immunity in neonates. Science 368(6491):612–615
229. Tieppo P, Papadopoulou M, Gatti D, McGovern N, Chan JKY et al (2020) The human fetal thymus generates invariant effector γδ T cells. J Exp Med. 217(3):e20190580
230. Lee YJ, Jeon YK, Kang BH, Chung DH, Park C-G et al (2010) Generation of PLZF+ CD44+ T cells via MHC class II-dependent
thymocyte-thymocyte interaction is a physiological process in humans. J Exp Med 207(1):237–246

231. Galindo-Albarrán AO, López-Portales OH, Gutiérrez-Reyna DY, Rodríguez-Jorge O, Sánchez-Villanueva JA et al (2016) CD8+ T cells from human neonates are biased toward an innate immune response. Cell Rep 17(8):2151–2160

232. Kinder JM, Jiang TT, Ertelt JM, Xin L, Strong BS et al (2015) Cross-generational reproductive fitness enforced by microchimeric maternal cells. Cell 162(3):305–315

233. Schuster C, Vaculik C, Prior M, Fiala C, Mildner M et al (2012) Phenotypic characterization of leukocytes in prenatual human dermis. J Invest Dermatol 132(11):2581–2592

234. Marchant A, Appay V, Van Der Sande M, Dulphy N, Liesnard C et al (2003) Mature CD8(+) T lymphocyte response to viral infection during fetal life. J Clin Invest 111(11):1747–1755

235. Legrand FA, Nixon DF, Loo CP, Ono E, Chapman JM et al (2006) Strong HIV-1-specific T cell responses in HIV-1-exposed uninfected infants and neonates revealed after regulatory T cell removal. PLoS One 1:e102

236. Mackroth MS, Malhotra I, Mungai P, Koech D, Muchiri E, King CL (2011) Human cord blood CD4+CD25hi regulatory T cells suppress prenatally acquired T cell responses to Plasmodium falciparum antigens. J Immunol 186(5):2780–2791

237. Pietrzak-Nguyen A, Piradashvili K, Fichter M, Pretsch L, Zepp K et al (2016) MPLA-coated hepatitis B virus surface antigen (HBsAg) nanocapsules induce vigorous T cell responses in cord blood derived human T cells. Nanomedicine 12(8):2383–2394

238. Rastogi D, Wang C, Mao X, Lendor C, Rothman PB, Miller RL (2007) Antigen-specific immune responses to influenza vaccine in utero. J Clin Invest 117(6):1637–1646

239. Hendriks D, Arregi B, Hu H, de Sousa C, Lopes S, Clevers H (2021) Establishment of human fetal hematopoietic organoids and CRISPR-Cas9-based gene knockin and knockout in organoid cultures from human liver. Nat Protoc 16(1):182–217

240. Roodsant T, Navis M, Aknouch I, Renes IB, van Elburg RM et al (2020) A human 2D primary organoid-derived epithelial monolayer model to study host-pathogen interaction in the small intestine. Front Cell Infect Microbiol 10:272

241. Pasca AM, Park J-Y, Shin H-W, Qi Q, Revah O et al (2019) Human 3D cellular model of hypoxic brain injury of prematurity. Nat Med 25(5):784–791

242. Miller AJ, Dye BR, Ferrer-Torres D, Hill DR, Overeem AW et al (2019) Generation of lung organoids from human pluripotent stem cells in vitro. Nat Protoc 14(2):518–540

243. Lewis K, Yoshimoto M, Takebe T (2021) Fetal liver hematopoiesis: from development to delivery. Stem Cell Res Ther 12(1):139

244. Elahi S, Vega-López MA, Herman-Miguel V, Ramirez-Estudillo C, Mancilla-Ramírez J et al (2020) CD71+ erythroid progenitors in human neonates exhibit immunosuppressive properties and compromise immune response against systemic infection in neonatal mice. Front Immunol 11:597433

245. Delyea C, Bozorgmehr N, Koleva P, Dunsmore G, Shahbaz S et al (2018) CD71+ erythroid suppressor cells promote feto-maternal tolerance through arginase-2 and PDL-1. J Immunol 200(12):4044–4058

246. Di Nuzzo S, Pavanello P, Masotti A, Giordano G, De Panfilis G (2009) Densities, distribution and phenotypic expression of T cells in human fetal skin. Arch Dermatol Res 301(10):753–755

247. Kotler J, Feuerstein R, Zeis P, Hagemeyer N, Paterson N et al (2019) A subset of skin macrophages contributes to the surveillance and regeneration of local nerves. Immunity 50(6):1482–1497.e7

248. Stewart BJ, Ferdinand JR, Young MD, Mitchell TJ, Loudon KW et al (2019) Spatiotemporal immune zonation of the human kidney. Science 365(6460):1461–1466

249. Rea F, Woods K, Sasmono T, Campanale N, Taylor D et al (2007) Characterisation and trophic functions of murine embryonic macrophages based upon the use of a Csf1r-EGFP transgene reporter. Dev Biol 308(1):232–246

250. Schulz C, Gomez Perdiuero E, Chorro L, Szabo-Rogers H, Cagnard N et al (2012) A lineage of myeloid cells independent of Myb and hematopoietic stem cells. Science 336(6077):86–90

251. Angelo LS, Bimler LH, Nikzad R, Aviles-Padilla K, Paust S (2019) CXCR6+ NK cells in human fetal liver and spleen possess unique phenotypic and functional capabilities. Front Immunol 10:469

252. Antin JH, Emerson SG, Martin P, Gadol N, Ault KA (1986) Leu-1+ (CD5+) B cells. A major lymphoid subpopulation in human fetal spleen: phenotypic and functional studies. J Immunol. 136(2):505–10

253. Park J-E, Botting RA, Domínguez Conde C, Popescu D-M, Lavaert M et al (2020) A cell atlas of human thymic development defines T cell repertoire formation. Science. 367(6480):eaay3224

254. Zaharie D, Moleriu RD, Mic FA (2016) Modeling the development of the post-natal mouse thymus in the absence of bone marrow progenitors. Sci Rep 6:36159

255. Kernfeld EM, Genga RMI, Neherin K, Magaléte MA, Xu P, Maehr R (2018) A single-cell transcriptomic atlas of thymus organogenesis resolves cell types and developmental maturation. Immunity 48(6):1258-1270.e6

256. Stouch AN, McCoy AM, Greer RM, Lakhdari O, Yull FE et al (2016) IL-1β and inflammasome activity link inflammation to abnormal fetal airway development. J Immunol 196(8):3411–3420

257. Dranoff G, Crawford AD, Sadelain M, Ream B, Rashid A et al (1994) Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homoeostasis. Science 264(5159):713–716

258. Nishinakamura R, Wiler R, Dirksen U, Morikawa Y, Ariai K et al (1996) The pulmonary alveolar proteinosis in granulocyte macrophage colony-stimulating factor/interleukin 3/5 beta c receptor-deficient mice is reversed by bone marrow transplantation. J Exp Med 183(6):2657–2662

259. Kim HY, Lee HJ, Chang Y-J, Pichavant M, Shore SA et al (2014) Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. Nat Med 20(1):54–61

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