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REVIEW ARTICLE

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Development of the immune system in the human embryo

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The fetal immune system is highly specialized which is to generate both tolerogenic and protective immune responses to tolerate both self- and maternal-antigens. Fetal T cells with pro-inflammatory potential are born in a tolerogenic environment and are tightly controlled by both cell-intrinsic and -extrinsic mechanisms. Fetal B-1 and B-2 B cells involved in innate and adaptive immune responses, respectively, arise in staggered waves of development from distinct progenitors. Innate immune responses are the key to the protection against infection and adaptive immunity creates memory after an initial response to a specific pathogen. This review aims to discuss the recent advances in understanding the development of immune system in fetus.

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IMPACT:

- During gestation, essential developmental changes occur to survive the neonates.
- At early stage, developmental signals and changes may be influenced due to immune deficiencies.

INTRODUCTION

Human embryo develops from a single-cell zygote to a blastocyst through successive mitotic cleavages and proceeds through gastrulation and organogenesis to raise the distinctive form of the fetus. Organogenesis starts with the development of neural tube and budding off somites from the ectodermal and mesodermal tissues. With the advancement, the initial foundation of the primordium of the developing embryo transpires from which an organ can grow. In human, organogenesis begins at 3 weeks of gestation and ends at 8 weeks of gestation (Fig. 1).[1] Following the fertilization, the zygote subsequently develops into a blastocyst and a gastrula. In blastula, cells spatially rearrange themselves which is followed by the formation of three germ layers during gastrulation, namely ectoderm, endoderm, and mesoderm. These germ layers differentiate into various types of tissues or organs during organogenesis. The central and peripheral nervous systems, epidermis, sensory organs, hair, and nails generate from the differentiated cell lineages of the ectoderm. Mesodermal cells eventually give rise to certain organs, such as the skeleton, the muscle system, connective tissue, heart, blood vessels, and urogenital system. The gastrointestinal tract, liver, pancreas, and lungs are structured from the endodermal epithelial lining. The organs e.g., liver, bone marrow, thymus, spleen, skin, kidney, intestine, and lungs play a vital role to develop the immune system in the fetus.

During the development of the human immune system, it relies on sensory inputs during its development, which contributes to minimize the damage of healthy self-structure through discarding the foreign threats.[2] Prior to the development of the hematopoietic system in the bone marrow and thymus, the first transient waves of haemopoiesis occur in the mesoderm of the yolk sac and the extraembryonic mesenchymal tissue to serve the immediate needs for the growing fetus. Granulomacrophage progenitors and the pluripotent erythroid could be distinguished in the yolk sac at 3–4 weeks of gestation period. Following the migration of these primitive cells to the liver through circulation at around 4 weeks, it could work as the major site of haemopoiesis at 5–6 weeks of gestation period. The number of nucleated cells rises from 5–10 weeks of gestation and facilitates the enlargement of the liver size. At 11–12 weeks of gestation, the thymus and spleen are developed from the liver and stem cells, while at 12–19 weeks of gestation, the erythroid and granulocytic progenitor cells incorporate 42–68%, 27–41%, and 5–30% of monocytes, neutrophils, and eosinophils, respectively.[3,4] At this stage, the developing fetus contains all the essential components that are required for the innate and adaptive immunity. To defend the invading pathogens and their toxic molecules, the adaptive immune system triggers antigen-specific activation of T cells and B cells that consequently generate long-lasting memory cells for robust recall responses. Conversely, the innate immunity, which is activated by the molecular pattern molecules, offers quick protection from the pathogens, and helps to dissipate the dying or damaged self-cells. The pattern recognition receptor (PRR)-mediated immune responses are overwhelmingly decreased throughout the gestation, until about 29 to 33 weeks.[5,6] This review focuses on the immune system that is developed in embryonic stages.

DEVELOPMENT OF THE FETAL IMMUNE SYSTEM

The yolk sac

The first wave of the human haematopoiesis is a successive event, initiates in the yolk sac and develops into a balloon-like form in

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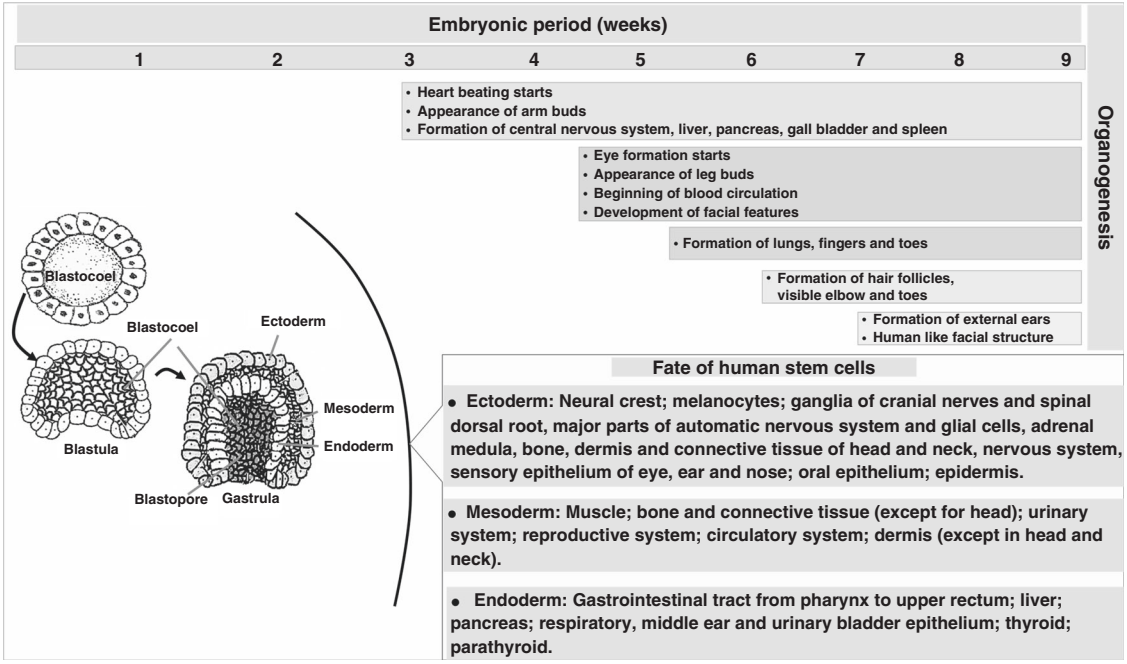

Fig. 1 Organogenesis in human embryo and fate of the stem cells. Organogenesis begins at 3 weeks of gestation and ends at 8 weeks of gestation. The cells rearrange themselves to form a hollow ball called blastula.

front of the embryo body. The mesenchymal cells of mesoderm origin differentiate into haematopoietic cells. By the 16–18 days of gestation, distinguished nascent erythrocytes are the major haematopoietic output from the yolk sac. Occasionally, as the marked onset of the blood circulation, primitive macrophages, megakaryocytes, and primitive erythroblasts are also noticeable inside the cardiac cavity, which is followed by the first appearance of the $CD45^+$ ($PTPRC^+$) cells.[7,8] Since the 4 weeks of the gestation, hematopoitic stem cell (HSC)-like progenitors, natural killer (NK) cell progenitors, erythroid cells, mast cells (MCs), and innate lymphoid cell (ILC) progenitors could be observed in the yolk sac. The MCs of connective tissue in fetal skin and kidney are closely related to the liver MCs of the fetus.[9] As the key drivers of the allergic responses, MCs bind with immunoglobulin E (IgE) through the high-affinity IgE receptors.[10] The fetal yolk sac has also been identified as one of the sources of macrophages that subsequently give rise to the macrophages in the brain, liver, lung, and epidermis.[11,12] Meanwhile, at the 6 weeks of gestation the embryonic pancreas is loaded with macrophages (Mφ).[13] The fetal NK cells then poise the infectious agents that take after their adult counterparts at assorted levels.[14] In comparison with infants, fetuses are enriched with ILCs than the NK cells.[15] For the formation of secondary lymphoid structures, the innate lymphoid tissue inducer (LTi) cells also play a crucial role.[16,17] The LTi cells recruit more LTi cells and other immune cells by networking with stromal cells.[18] As a result, the earliest development of innate lymphocytes occurs in the human embryo to assure tissue protection and remodeling.

The aorta gonad mesonephros (AGM) region

The spatiotemporal analysis revealed that intra-aortic haematopoietic clusters (IAHCs) emerge from the mesodermal precursors through the endothelial intermediates at 4 weeks of gestation and disappear by 6 week of gestation.[19,20] The formation of IAHC covers the preumbilical region of the floor of the dorsal aorta and penetrates to the vitelline artery in the human embryo. Endothelial lining of the dorsal aorta stimulates CD34 by the 3 weeks of gestation and later forms HSCs in maturity.[21] The first appearance of $CD34^+CD45^+$ cells emerge in the preumbilical region of the dorsal aorta at 4 weeks of gestation and the number reaches several hundred in the following week. Human fetal liver HSCs detect scattered angiotensin-converting enzyme $(ACE)^+$ $CD34^-$ cells underneath the dorsal aorta.[22,23] It was assumed that IAHC precursors upregulate CD34 and following the incorporation into the $CD34^+$ endothelial lining they form ACE^+ $CD34^+$ IAHCs. However, till date, the migration pathways of HSC specification in the mammalian AGM region is the least explored area that needs to be focused.[23]

The liver development

From the embryonic gut floor the rudimentary liver appears as a diverticulum and contains erythrocytes and $CD45^+$ cells, derived from the primitive yolk sac. It also holds the monocytic/macrophage lineage and the developing $CD34^+CD45^+$ cells at 3 weeks and 4 weeks of gestation, respectively.[7] In the fetal liver, some of the IAHCs and $CD34^+CD45^+$ cells take over by the AGM-derived cells, while the erythroid, myeloid, megakaryocyte, and lymphoid cell lineages produce from the decisive HSC.[24] Additionally, among the HSC-dependent macrophages, monocytes, and dendritic cells (DCs), the first production of DC was recorded in the fetal liver at 6 week of gestation during the developmental period of human embryo.[9] From the 12 weeks of gestation onward, conventional DC1, DC2, and plasmacytoid DCs are found in the tissues of different fetal organs such as skin, lung, spleen, and thymus.[25] Fetal DCs respond to Toll-like receptor ligation, and stimulate T-cell differentiation, propagation, and activation, as well as promote the production of T-cell interleukin (IL)-4, and inhibit the production of T-cell tumor necrosis factor-α (TNF-α) via arginase 2.[25] Therefore, the vital roles of DCs to maintain the tolerance of human fetus are noticeable. The first appearance of B cell lineage as precursors and mature B cells are observed in the liver of the fetus from 7 and 9 weeks of gestation, respectively.[9] Therefore, until birth the liver plays a significant role for haematopoietic differentiation and HSC proliferation.

The bone marrow development

The bone marrow (BM) development is closely associated with the invasion of cartilaginous bone by blood vessels and bone

ossification. The formation of BM randomly marks at 8 weeks of gestation, which is seeded with haematopoietic progenitors and HSCs and reliant on the vascular invasion.[26] With the growth, the BM develops as the key source of B cells that are abundantly enriched in the spleen at mid-gestation.[27] Intestinal B cells are follicular and transitional B cells form from second-trimester fetuses to infants.[15] Although the actions of the HSC in the human bone marrow are still ambiguous, it is predicted that the initial $CD34^{-}CD45^{+}$ haematopoietic cells enter the cartilaginous bone, which are colonized with $CD34^{+}CD45^{+}$ progenitors and HSCs.[28]

Spleen development

The spleen appears at 6 week of gestation, confined to the coelomic epithelium of the dorsal mesogastrium adjacent to the cranial end.[29] It generates both red and white cells in the second trimester. Spleen initiates T-cell-dependent immunity with the help of DCs. So far, the developmental process of splenic DC in fetus has not been investigated. After birth, the major DC subset comprises $CD4^{-}$ $CD8^{-}$ $CD11c^{+}$ cells that are very low represented subset in the adult spleen. During the second week of life, other DC subsets progressively appear in the spleen as $CD4^{-}$ $CD8^{+}$ and $CD4^{+}$ $CD8^{-}$ DC populations.[30] The circulating monocytes can only give rise to the mucosal DC but not to the splenic DC. The resident splenic DC could be repopulated from a bone marrow precursor that was isolated as the $CX3CR1^{+}$ $cKit^{+}$ $Mac1^{-}$. This bipotent precursor for MΦ and DC (MDP) can reconstitute the splenic DC of irradiated recipients under steady-state conditions.[25] The neonatal splenic stromal cells could provide a suitable condition for the maturation of DC into regulatory DC, which can control the immune response in the spleen and also promote the differentiation of hematopoietic stem cells into regulatory DC, a process that involves stromal-derived IL-10.[31,32]

Thymus development

The formation of the thymic epithelium starts from the third pharyngeal pouch that extends into the surrounding mesoderm in backward and lateral directions. Early lymphoid progenitors migrate into the thymus from the fetal liver at 8 weeks of gestation, where the naive T cells are developed.[33] Early thymic progenitors develop into naive T cells and migrate into other tissues.[34,35] Functional thymus and circulating T cells are produced at 10–11 weeks of gestation.[36] A regulatory T (Treg) cell is generated from the naive T cells of fetus,[37] which suppress the multiplication and secretion of cytokine from other fetal T cells.[38] Memory T cells are responded to foreign antigens, which are identified in the fetal intestine, while intestinal $CD4^{+}$ T cells can play parts in the expression of TNF-α.[39]

Lymph node development

The first lymph node begins to form from the mesenchymal cells that condensed at the base of the lymph sac at 8–11 weeks of gestation.[40] The capsule of the lymph node is formed by the marginal sinus, which is bordered by the connective tissue.[40] At 13 weeks of gestation, the mesenchyme almost fills the entire lymph sac and with the addition of capillaries, the intermediate sinuses begin to grow. The first peripheral lymph node structures are located in the cervical and retroperitoneal regions of the embryo at 8 weeks of gestation. Additionally, the peribronchial, celiac, mediastinal, axillary, inguinal, pelvic, and popliteal nodes could be detected at 9–10 weeks of gestation. Omental and mesenteric lymph nodes observe at 14 weeks of gestation.[41] Notable functions of lymph nodes are monitoring and carrying out the immune surveillance for pathogens and antigens, with boosting the immune responses through trapping them within the lymph nodes.

T lymphocyte development

The stem cells from which T cells arise in the thymus, prothymocytes are observed in the fetal liver from 7 weeks of gestation and the membrane CD3 is apparent 10 weeks of gestation.[42] Although, a higher percentage of $CD45RA^{+}$ T cells could be recognizable in the mesenteric lymph nodes of fetus, the amount of monocytes or B cells is found in very small quantity during the 18–24 weeks of gestation period. However, during that time identical numbers of T cells, B cells, and monocytes/macrophage could be observed in spleen.[43] At 12–14 weeks of the gestation period, T cells could be detected in the epithelium and lamina propria of the intestinal mucosa of fetus.[44]

Thymic development initiates at 8 weeks, while the colonization of the first T cells in the periphery and the existence of Treg cells are perceived around 12–14 weeks.[45–47] In the liver, the c/d T cells develop a $CD4^{+}$ phenotype at 20–22 weeks of gestation. The $CD3^{+}$ T cells are observed in the fetal circulation at 15–16 weeks of gestation, when they also express CD2 and CD5.[48]

The fetal intestinal functional memory T cells are able to proliferate pro-inflammatory cytokine that indicates the immune system of the fetus is not in essence immature. Pathogen-associated molecular pattern molecules (PAMPs) trigger the activation of the DCs that drive the naive T cells activation during traveling through the tissues and lymphatics.[49] The Treg cells are capable of subduing the activation, multiplication, and effector functions of wide-ranging immune cells. In the course of the second trimester of gestation, the proliferation of the Treg cells, e.g., FoxP3, CD25, and CD127 are conspicuously visible in the peripheral lymphoid organs.[50–53] Moreover, the generation of the iTreg cells depends on the levels of TGFβ and fetal T cells that are distinctive predispositions for differentiation into Treg cells.[37] In the presence of self and maternal-antigens, the prompt proliferation of the T cells is an indicator of the active immune tolerance process in the developing fetus.[54] The role of Treg cells to the perinatal immune tolerance is signified by the IPEX (immune dysregulation, polyendocrinopathy, entheropathy, X-linked) syndrome, which is consequential to the dropping of the Treg lineage-defining transcription factor FoxP3. Therefore, T cells in fetus are intently repressed by the Treg cells, an indicator of a tight control-loop of fetal immune responses.

B lymphocyte development

The generation of B-1 progenitors starts in the yolk sac and para-aortic splanchnopleura (PSp), while it is produced in the bone marrow and fetal liver at mid-gestation. At the end of the fetal life, a decreasing trend of B-1 progenitors and an upsurge of the B-2 generation production have been observed.[55,56] Matured B-1 cells could be synthesized from the PSp B-1 progenitors and the yolk sac.[57] B cells could be detected in the fetal liver and omentum at 8 weeks, and in the spleen at 13–23 weeks of gestation, while distinguished $CD5^{+}$ B cells could be perceived in the pleural cavity and the peritoneal cavity at 15 weeks of gestation.[58]

Noticeable expression of the m chain, and the surface IgM, IgD, and CD20 have been identified in the liver of fetus at 8–13 weeks of gestation.[59] Diffusely distributed B cells in the lymph nodes and spleen are detectable at 16–17 and 16–21 from weeks of gestation, respectively.[59] B cells in the peripheral circulation of the fetus appear at 12 weeks of gestation, which are found in bone marrow at 16–20 weeks of gestation. These are positive for CD19, CD20, CD21, CD22, HLA-DR, IgM, and IgD.[60] In comparison to the adult counterpart, a higher percentage of $CD5^{+}$ B cells (B-1 B cells) has been found in the fetus, which has been presumed as the first line of defense in the newborn.[61]

Immunoglobulin production

Large amount of IgG and IgM are produced by the spleen earlier at 10 weeks of gestation. Serum IgG levels started to increase from 5.5 to 22 weeks of gestation, and then dramatically increase up to the birth.[62] IgG pass from the placenta throughout gestation with a maximal upregulation from 32 weeks of gestation.[63] IgE production was detected at 11 weeks of gestation in fetal liver and lung, and by 21 weeks in the spleen.[64]

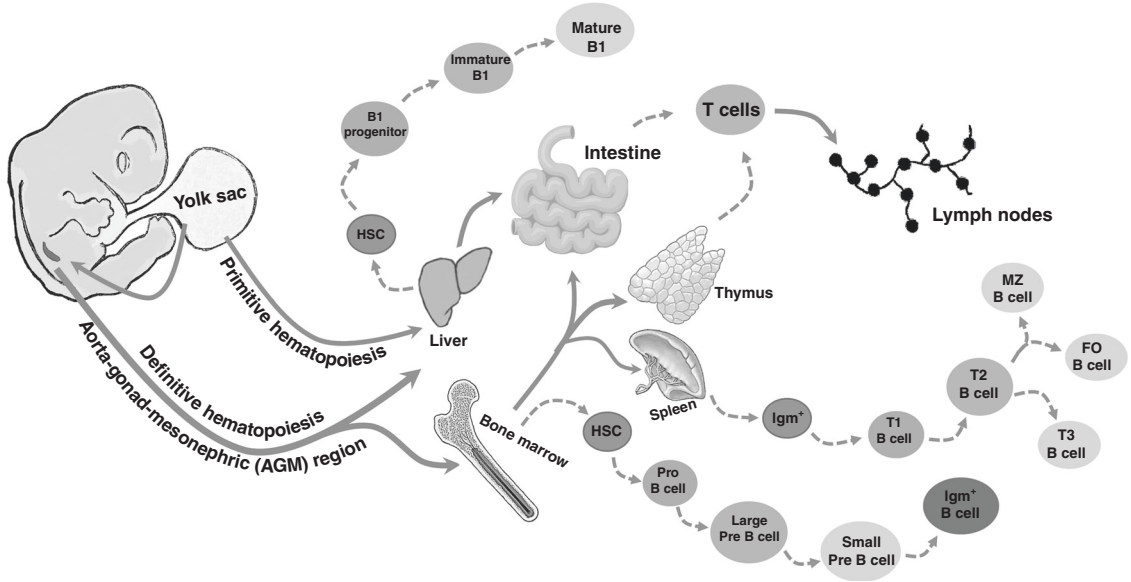

Fig. 2 Hypothesized pathway of the major immune cells production in the human embryo. Primitive hematopoiesis begins around 3rd week of gestation in the human yolk sac. Around 5th week of gestation, hematopoietic stem cells appear in the aorta-gonad-mesonephros (AGM) region and give rise to the hematopoietic progenitors that initiate definitive hematopoiesis in organs such as the liver and bone marrow. Brown arrows are indicating the migration route of hematopoietic cells and their progenitors (and precursors) among the hematopoietic organs throughout the fetal life. Broken blue arrows are indicating the synthesis of the immune cells from the vital organs.[65, 66]

The initiation of hematopoiesis from the yolk sac of human embryo, formation of the bone marrow, and all the immune cells produced from it begins at 5 weeks of gestation, which stimulate mass production of immune cells in the following weeks to boost the immune system.[65] A hypothesized route of major immune cells production from the vital organelles in a human embryo has been illustrated in Fig. 2.

CONCLUSION

The human immune system matures over several years; the adaptive immune system confers major protection while being carried by the innate immune system. During gestation, insightful developmental changes occur which is essential to survive the neonates.[67] At early stage, the challenges of the immune deficiencies with impaired responses to a pathogen may be influenced by developmental signals and changes. The stem cell transplantation, tissue engineering for immunotherapy, and regenerative medicine in the near future will upsurge the immune system development in preterm infants.

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AUTHOR CONTRIBUTIONS

Z.H. has generated the idea to write this manuscript and drafted the manuscript. A.H. M.M.R. and W.A.Q. helped in literature collection and the final drafting of the manuscript. J.K.F. and A.W.O. critically supervised and helped in manuscript finalization. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Patient consent was not required.

ADDITIONAL INFORMATION

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