How well do we understand the link between fetal hematopoiesis and susceptibility to immune dysfunction?

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Abstract

Introduction: Layered hematopoiesis generates distinct, hematopoietic stem cell (HSC)-independent progenitor waves that establish long-lived immune compartments, profoundly influencing postnatal immunity and disease susceptibility.

Areas covered: This article reviews the contribution of embryonic progenitors to resident immune populations, the impact of prenatal stressors (such as inflammation and maternal obesity) on immune programming, and the mechanisms by which fetal identity drives leukemogenesis and oncofetal reprogramming. We survey recent evidence examining how early environmental and genetic factors shape developmental hematopoietic trajectories and highlight resulting influences on postnatal disease.

Expert Opinion: While animal models provide valuable mechanistic insights in fetal hematopoiesis, translating findings to human biology remains challenging. Priorities include identifying persistent developmental signatures, employing single-cell multi-omics to track preleukemic clones, and advancing ontogeny-aware cell therapies and precision risk-stratification strategies.

Article Highlights

- Embryonic development generates HSC-independent progenitor waves that establish long-lived postnatal immune compartments
- Developmental factors shape the maturation of adult stem cell niches, leaving lasting effects on postnatal immune function and homeostasis

- Prenatal stressors induce durable changes in fetal hematopoietic progenitors, modulating susceptibility to postnatal immune and metabolic disorders
- Fetal HSPCs exhibit differential sensitivity to leukemic drivers, opening new avenues to identifying specific therapeutic vulnerabilities
- Postnatal leukemic cells can pathologically reactivate embryonic developmental programs
- Moving toward ontogeny-aware strategies requires validating experimental findings in human biology, identifying persistent developmental signatures, and advancing precision risk stratification

1. Introduction

While adult immunity was long assumed to rely exclusively on bone marrow (BM) hematopoietic stem cells (HSCs), it is now generally clear that embryonic development generates distinct, HSC-independent progenitor waves that may durably shape the postnatal immune system[1,2]. Far from serving as transient stepping stones toward adult hematopoiesis, these early progenitor waves execute distinct developmental programs that establish dedicated, long-lived immune compartments. By layering cellular identity across ontogeny, the embryo builds a structurally and functionally diverse immunological landscape long before adult-type HSCs take over blood cell production. Here, we provide a brief overview of fetal hematopoiesis and discuss how common perturbations during pregnancy, including obesity, inflammation and stress-related conditions, may alter immune development and contribute to disease susceptibility later in life. Finally, we examine how fetal-specific gene expression programs can impact childhood leukemia.

2. Long-lasting immune contributions originating from HSC-independent hematopoiesis

The long-standing HSC-centered paradigm was first challenged by findings demonstrating that adult microglia and other tissue-resident macrophages (TRMs)—such as Kupffer cells, Langerhans cells, and alveolar macrophages—originate from embryonic yolk sac-derived erythro-myeloid progenitors (EMPs) rather than HSCs [3]. A distinct developmental origin was subsequently identified within the lymphoid compartment, where B-1a cells derive from fetal Lin^- $B220^-$/lo $CD19^+$ progenitors [4] and cannot be replenished by adult long-term HSCs [5] whereas adult progenitors predominantly give rise to the B-1b compartment. More recently, genetic lineage tracing in mice confirmed the HSC-independent origin of B-1a cells [6] and showed that fetal-restricted hematopoietic stem and progenitor cells (HSPCs) exert a significant contribution to fetal lympho-myelopoiesis [7]. Other

studies showed that HSC-independent hematopoiesis originating from embryonic multipotent hematopoietic progenitors (eMPPs) can contribute to multiple lineages and persist for several months after birth [8]. Together, these discoveries establish that layered hematopoietic developmental programs contribute long-lived postnatal immune lineages before and concomitantly with adult-type HSCs.

3. Unique response of Fetal Hematopoiesis to Environmental Perturbations

To understand how developmental hematopoiesis intersects with postnatal health, it is essential to differentiate between conceptually distinct phenomena, such as the persistence of embryonic-derived immune lineages (e.g. tissue-resident macrophages and B-1a cells) into adulthood and durable programming of early progenitors by transient prenatal environmental exposures. In this context, can perturbations in fetal hematopoiesis affect immune behavior later in life with functional and pathological consequences? An emerging paradigm is that transient developmental hematopoietic programs can shape immune function long after the progenitor populations themselves have disappeared. For instance, prenatal inflammatory exposure may not only induce transient perturbations in fetal hematopoiesis; rather, it could rewire early hematopoietic programs and lead to persistent changes in postnatal immune composition or behavior. In mice, these alterations carry over even after transplantation into unmanipulated, healthy hosts, confirming that early inflammatory signals induce durable cell-intrinsic reprogramming rather than a transient response to an altered microenvironment [9]. Fetal-restricted HSPCs show immunophenotypic and temporal overlap with the developmental-restricted HSCs previously described as giving rise to innate-like B and T lymphocytes, although these populations are not necessarily identical [10]. Furthermore, the fetal HSPC compartment exhibits distinct intrinsic heterogeneity and responds to inflammatory signals in a fundamentally different manner than adult HSPCs, modulating progenitor activation and expansion to balance immediate fetal requirements against long-term immune preservation. An imbalance or shift in the proportion of B-1a and B-1b cell compartments significantly increases the risk of immune dysfunction, driving either auto-inflammatory pathology or immunodeficiency. Consequently, in addition to their essential role in sustaining embryonic and fetal hematopoiesis, developmentally restricted HSPCs may represent an important target through which early environmental signals can modulate postnatal immune function and contribute to its dysregulation, affecting conditions such as allergy, autoimmunity, or chronic inflammatory diseases. While mouse models indicate that this differential sensitivity is tied to the intrinsic properties of the

fetal hematopoietic progenitor pool, it remains to be determined whether corresponding human fetal HSPCs exhibit similar dynamics. Clarifying how these developmental imprints persist in humans could ultimately improve early clinical screening protocols and facilitate patient-specific interventions before these immune-mediated diseases fully manifest.

4. The Impact of Fetal Niche Priming and Gestational Stress on Immune Function

Beyond intrinsic programming, fetal HSPCs actively shape adult hematopoietic niches, indirectly affecting postnatal immune function. Perçin et al. recently showed that EMP-derived macrophages are indispensable for establishing a functional BM niche capable of recruiting adult HSCs during fetal development [11]. These embryonic macrophages persist in the BM and appear to regulate mesenchymal stromal cells, promoting CXCL12 expression required for HSC homing (**Figure 1A**). Therefore, the classic vision of the CXCL12-CXCR4 axis as a mechanism controlling HSC homing and retention within the BM is preceded by an earlier process in which embryonic macrophages shape a niche competent to recruit HSCs. This reliance on early macrophage signaling highlights the susceptibility of niche maturation to environmental changes during gestation. If macrophage signaling is required for the BM niche, how do relatively common physiological perturbations such as chronic sterile inflammation or excessive maternal stress during gestation impact the developing immune system? For instance, maternal obesity, which entails persistent inflammation, can reprogram fetal-derived Kupffer cells (the specialized macrophages of the liver), predisposing offspring to metabolic dysfunction-associated steatotic liver disease [12]. Macrophages are primary players in the response to inflammatory stimuli, but they do not represent the only affected cell type. Serhan *et al.* showed that prenatal stress causes fluctuations in maternal glucocorticoids which in turn dysregulate neuroimmune circuits reprogramming fetal mast cells *in utero*, driving early-life allergic conditions such as eczema [13]. Together, these findings reveal that maternal conditioning and gestational stress alters both microenvironmental niche maturation and tissue-resident cell identity, leaving lasting effects on postnatal immune function and organ homeostasis (**Figure 1B**). Other external factors, such as infections, vaccination, or pharmacological treatments, can all affect the fetus' developing immune system in complex ways that are beginning to be understood [14].

5. Developmental Identity and Oncogenic Vulnerability in Hematological Malignancies

Developmental conditioning is not limited to immune function, but intrinsic fetal vulnerabilities may also determine how HSPCs respond to oncogenic mutations. For instance, Eldeeb *et al.*

demonstrated that the leukemic fusion gene *ETV6::RUNX1* enhances self-renewal and disrupts lymphopoiesis more effectively in fetal HSCs than in their adult counterparts. When combined with prenatal inflammatory stimuli, these fetal-restricted HSPCs gain a competitive advantage over adult-type HSCs, underscoring a synergy between early mutations and inflammatory signals in establishing a preleukemic state [15]. An even more clear dependence on fetal identity is observed in *KMT2A::AFF1* infant leukemia. Ling *et al.* showed that the fetal-specific regulator *LIN28B*, expressed in fetal progenitors but absent in adult HSCs, is strictly required for *KMT2A::AFF1*-driven leukemogenesis; without *LIN28B*, the fusion gene fails to initiate malignant transformation, proving that fetal programming is a driver rather than a passive permissive state [16]. How maternal perturbations can affect fetal hematopoiesis and influence the risk of developing childhood leukemia is a largely understudied area and an interesting direction for future research.

Fetal programs can also be pathologically co-opted or re-engaged after birth, in a process often referred to as “oncofetal reprogramming”, which has been well described for solid tumors but less so for hematological cancers. Recent multi-omic studies demonstrated that high-risk juvenile myelomonocytic leukemia (JMML) HSPCs can reactivate *LIN28B*, revealing a high degree of oncofetal plasticity where malignant cells postnatally re-establish fetal developmental programs [17]. However, accumulating evidence indicates that JMML can also directly initiate *in utero*[18]. Interestingly, recent studies identified two distinct subgroups of JMML patients displaying fetal-like molecular signatures; paradoxically, the subgroup with the most pronounced *LIN28B* dysregulation exhibited less transcriptional overlap with prenatal samples [19]. Because aberrant DNA methylation in JMML is primarily a postnatal event [17], these findings suggest two distinct routes to acquiring an aberrant fetal phenotype: prenatal mutation acquisition in “vulnerable” fetal HSPCs versus postnatal oncofetal reprogramming (**Figure 1C**). Thus, clinically similar disease phenotypes can emerge from distinct cells of origin or ontogenetic windows.

These studies underscore the importance of the cell of origin and the timing of mutation acquisition in leukemogenesis. Pinning down when and in which developmental compartment a mutation occurs will be fundamental for understanding clinical heterogeneity and tailoring targeted therapies. For instance, detecting fetal oncogenic signatures in adults may allow tracking of (pre)leukemic clones, predicting and monitoring disease trajectory, and decrease the chance of recurrence, ultimately advancing human health.

6. Conclusion

We are beginning to understand that events affecting fetal hematopoiesis can influence lifelong immune function and oncogenic susceptibility; however, the precise molecular mechanisms, timing, and relevance to human disease remain incompletely defined. More specifically, fetal hematopoiesis is increasingly regarded not simply as a transient program preceding adult blood formation. Some embryonic hematopoietic lineages persist in postnatal life, and adult HSCs cannot replace all of them. Emerging evidence suggests that the same genetic alteration may have different consequences depending on the cellular context, highlighting that the pathogenic potential of a given mutation is not uniform across hematopoietic populations. Similarly, when fetal immune cells are exposed to prenatal stress signals, changes altering specific functions and contributing to postnatal immune dysregulation may persist, affecting postnatal conditions such as allergy, autoimmunity, or chronic inflammatory diseases.

Moving forward, a primary objective will be to dissect how distinct subsets within the heterogeneous fetal hematopoietic compartment respond to specific genetic and environmental perturbations, both *in utero* and during disease progression later in life. At the same time, fundamental aspects of developmental hematopoiesis including the migration/expansion dynamics and specific microenvironments of fetal HSPCs and adult HSCs remain incompletely understood. Unraveling these processes will unlock new opportunities for clinical translation. Crucially, translating these insights into human medicine will require defining which fetal molecular signatures persist into adulthood and validating whether observation in experimental models accurately reflect human biology and disease risk.

Expert Opinion

The paradigm shift toward layered hematopoiesis has fundamentally reshaped our understanding of immune regulation and leukemogenesis, demonstrating that embryonic hematopoietic progenitors, previously regarded as purely transient populations, together with fetal environmental factors exert a lasting functional influence on postnatal health. Despite these advances, critical gaps remain. Most mechanistic insights rely heavily on animal models, which do not necessarily mirror the temporal dynamics, progenitor hierarchies or molecular identities of human fetal hematopoiesis in full. Furthermore, prospectively isolating human developmentally restricted hematopoietic progenitors and tracking their functional fate *in vivo* remains both technically and ethically challenging.

To bridge this gap, the priority is to establish ontogeny-aware clinical strategies, moving from reactive “one-size-fits-all” treatments of established immune disorders and pediatric leukemias toward early risk stratification and targeted selective therapies. Achieving this requires defining the precise epigenetic mechanisms that sustain fetal-derived cellular memory into adulthood and identifying non-invasive biomarkers of prenatal immune conditioning. Key questions that are now experimentally and clinically addressable include: can exposure-specific prenatal imprints be reliably detected via epigenetic or transcriptomic profiling of accessible circulating immune cells in newborns or adults? Do these developmental signatures directly correlate with clinically meaningful immune phenotypes, such as altered vaccine responsiveness or susceptibility to autoimmune flare-ups?

In the coming years, we anticipate that the field will advance rapidly through three primary future perspectives. First, single-cell multi-omics and high-resolution spatial transcriptomics will allow researchers to map preleukemic clones and altered immune subsets back to specific developmental windows. A particularly compelling area is the intersection of maternal factors (e.g. inflammation) and developmental vulnerability in age-restricted hematological malignancies, such as juvenile myelomonocytic leukemia (JMML). Unraveling whether aberrant leukemic phenotypes stem from *in utero* initiation or postnatal oncofetal reprogramming (such as via *LIN28B* re-expression) may provide actionable clinical insight. Identifying fetal oncogenic signatures in circulating cells may thus allow clinicians to track preleukemic clones, predict disease trajectories, and reduce the risk of recurrence.

Second, developmental insights will pave the way for translational cell therapies. Acquiring a more comprehensive cellular and molecular understanding of hematopoietic ontogeny will support the *ex vivo* generation and/or expansion of autologous HSCs and fetal-restricted HSPCs for reinfusion into patients following cytotoxic therapy. Third, defining a roadmap of ontogenetic pathways could enable the selective therapeutic modulation of aberrant developmental programs without impairing healthy hematopoiesis. Ultimately, the next major frontier will be to connect fundamental principles of developmental ontogeny with measurable clinical biomarkers and human disease biology, paving the way for personalized early risk stratification and targeted therapies.

Figure 1. The impact of fetal hematopoietic ontogeny on postnatal immunity and leukemogenesis. (A) Layered hematopoiesis and BM niche priming. Embryonic hematopoiesis generates distinct, HSC-independent progenitor waves. Yolk sac-derived erythro-myeloid progenitors (EMPs) give rise to tissue-resident macrophages (TRMs), while fetal-restricted HSPCs, originating from vitelline and umbilical arteries, yield innate-like lymphoid subsets (e.g., B-1a cells). Pre-HSCs, the precursors to adult-type HSCs, originate mainly from the dorsal aorta. In the developing bone marrow, EMP-derived macrophages instruct mesenchymal stromal cells (MSCs) to express CXCL12, establishing a functional niche for adult-type HSC recruitment.

(B) Maternal perturbations and long-term immune imprinting. Gestational stressors (maternal inflammation, obesity, chronic stress) induce durable, cell-intrinsic epigenetic changes in fetal-restricted HSPCs and tissue-resident macrophages. These changes persist after birth, altering postnatal immune composition, augmenting inflammatory responses, and increasing susceptibility to allergic or metabolic disorders. MASLD: Metabolic dysfunction-Associated Steatotic Liver Disease.

(C) Developmental vulnerability and oncofetal reprogramming in pediatric hematological malignancies. Oncogenic drivers exhibit distinct cell-of-origin dependencies. The acquisition of fetal programs during leukemogenesis can occur either through *in utero* mutation acquisition within developmentally restricted HSPCs or postnatally, wherein adult leukemic cells reactivate embryonic developmental pathways (i.e. oncofetal reprogramming).

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Declaration of interest

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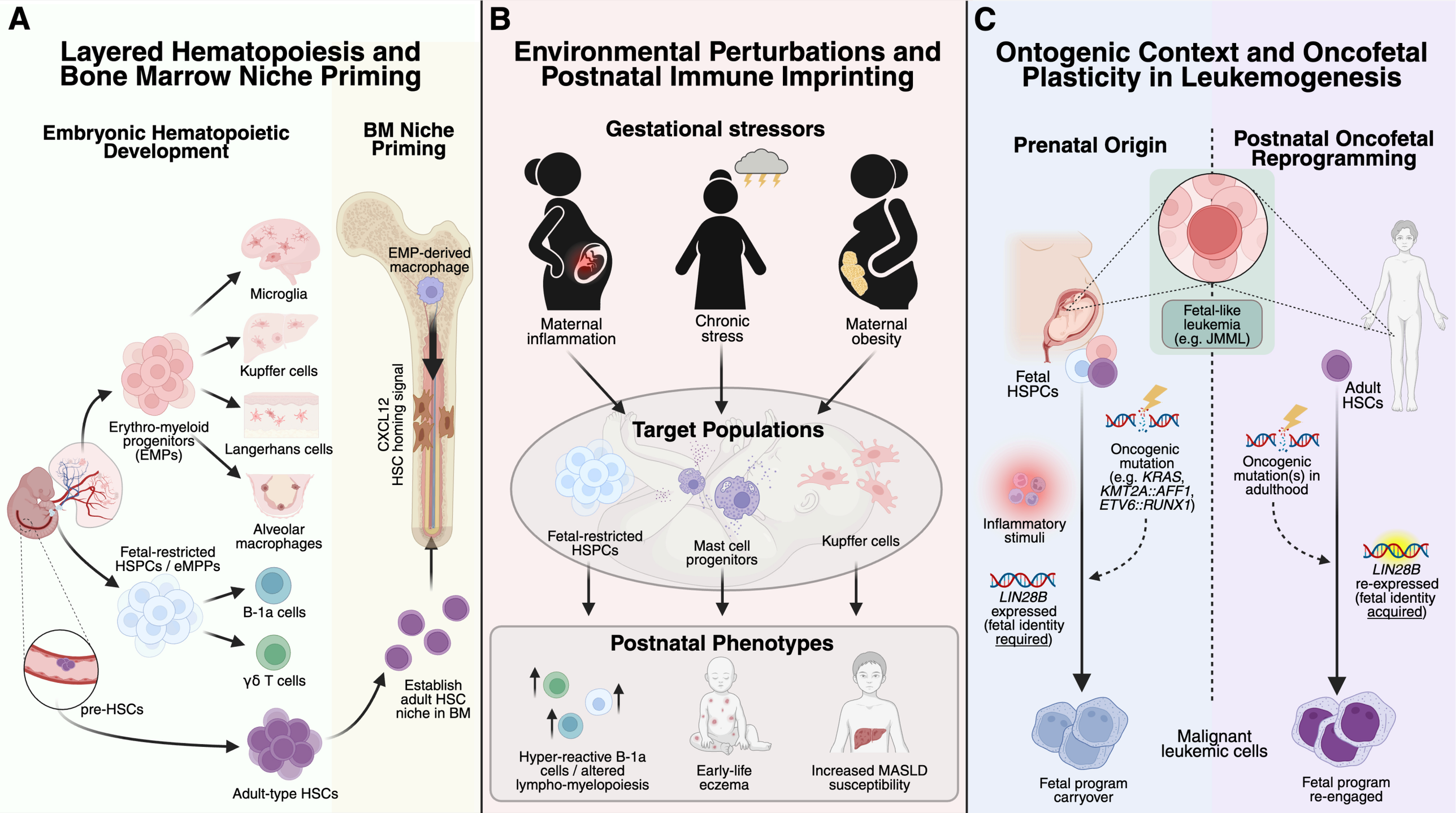
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A
Layered Hematopoiesis and Bone Marrow Niche Priming
Embryonic Hematopoietic Development
BM Niche Priming
Microglia
Kupffer cells
Erythro-myeloid progenitors (EMPs)
Langerhans cells
Alveolar macrophages
Fetal-restricted HSPCs / eMPPs
B-1a cells
γδ T cells
pre-HSCs
Adult-type HSCs
EMP-derived macrophage
CXCL12 HSC homing signal
Establish adult HSC niche in BM
B
Environmental Perturbations and Postnatal Immune Imprinting
Gestational stressors
Maternal inflammation
Chronic stress
Maternal obesity
Target Populations
Fetal-restricted HSPCs
Mast cell progenitors
Kupffer cells
Postnatal Phenotypes
Hyper-reactive B-1a cells / altered lympho-myelopoiesis
Early-life eczema
Increased MASLD susceptibility
C
Ontogenic Context and Oncofetal Plasticity in Leukemogenesis
Prenatal Origin
Postnatal Oncofetal Reprogramming
Fetal-like leukemia (e.g. JMML)
Fetal HSPCs
Adult HSCs
Oncogenic mutation (e.g. KRAS, KMT2A::AFF1, ETV6::RUNX1)
Oncogenic mutation(s) in adulthood
Inflammatory stimuli
LIN28B expressed (fetal identity required)
LIN28B re-expressed (fetal identity acquired)
Malignant leukemic cells
Fetal program carryover
Fetal program re-engaged