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Integrating Psychosocial and Molecular Insights in Labor: Single-Cell Omics of Maternal Hematology and Doula-Assisted Births

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Abstract

Psychosocial support during childbirth, particularly through doula-assisted care, has been shown to reduce maternal stress and improve obstetric outcomes, yet the underlying hematological and immunological mechanisms remain largely unexplored. Emerging single-cell technologies now enable unprecedented resolution in mapping maternal immune adaptations during labor. This review synthesizes current evidence on hematological and immune remodeling in parturition and proposes a framework for applying single-cell multi-omics to understand how doula-supported births may influence stress-related immune dynamics. By integrating insights from psychoneuroimmunology, hematology, and computational biology, we highlight potential molecular pathways linking emotional support to immune homeostasis and maternal recovery. Such interdisciplinary exploration may reveal novel biomarkers and therapeutic strategies for precision perinatal care.

Keywords

Single-Cell Transcriptomics, Maternal Immune Adaptation, Doula-Supported Birth, Hematological Regulation, Psychoneuroimmunology

1. Introduction

Childbirth is a complex physiological process involving not only mechanical and hormonal regulation but also profound hematological and immune adaptations [1]. During pregnancy, the maternal immune system undergoes finely tuned modulation to balance fetal tolerance and readiness for parturition. The transition to labor is now recognized as an immunologically active process characterized by coordinated inflammatory signaling and dynamic cellular interactions at the maternal–fetal interface [2].

Single-cell technologies have revolutionized our understanding of these processes by revealing the molecular and cellular heterogeneity within maternal blood and reproductive tissues [3]. High-resolution single-cell mapping has identified numerous previously uncharacterized immune and stromal populations that change in abundance or transcriptional state during parturition [4]. Similarly, single-cell analyses of peripheral blood have demonstrated dynamic remodeling of monocyte, T-cell, and NK-cell populations as labor approaches, reflecting systemic immune activation and hematopoietic reprogramming [5].

Parallel to these biological discoveries, psychosocial support interventions during childbirth-especially continuous presence of trained birth companions or doulas-have been shown to reduce maternal anxiety, lower cesarean delivery rates, and improve satisfaction with birth outcomes [6]. The mechanisms underlying these benefits remain poorly defined, but research in psychoneuroimmunology provides a plausible biological pathway: psychological stress during pregnancy is associated with increased levels of inflammatory cytokines (e.g., IL-6, TNF-α, CRP) and altered leukocyte function, which may influence both maternal and fetal physiology [7,8].

Despite these advances, little is known about how psychosocial support, including doula-assisted care, may influence maternal hematological and immune dynamics at the single-cell level. Understanding this connection could provide novel insights into how emotional and environmental factors shape molecular networks during labor, ultimately informing precision strategies for perinatal health. This review therefore integrates evidence from hematology, single-cell genomics, and psychoneuroimmunology to propose a framework for studying doula-supported births through the lens of single-cell hematological profiling [9,10].

2. Hematological and Immunological Changes during Labor

Labor is increasingly recognized not simply as a mechanical process of cervical dilation and uterine contraction, but as a coordinated immuno-haematological event. A number of studies indicate that maternal hematological parameters (e.g., leukocyte count, neutrophil/lymphocyte ratio, coagulation factors) shift markedly in the transition to delivery, reflecting systemic immune activation and hematopoietic adaptation.

Recent single-cell and high-dimensional analyses have begun to unveil finer details of these changes. For example, a single-cell RNA sequencing (scRNA-seq) study of peripheral blood mononuclear cells (PBMCs) from pregnant women showed that throughout gestation there is an up-regulation of interferon-stimulated genes and activation of RNA-splicing–related pathways, accompanied by shifts in immune cell subset composition [11]. This supports a model in which maternal immune architecture is progressively reprogrammed in preparation for parturition.

At the maternal–fetal interface (MFI), single-cell mass cytometry revealed 31 distinct cell populations-including 25 immune and 6 non-immune types-in term and pre-term pregnancies, and demonstrated that PD-1$^+$ CD8 T cell subsets were less abundant in term laboring versus non-laboring women, while PD-L1$^+$ non-immune stromal and extravillous trophoblast cells were decreased in pre-term laboring samples [2]. This suggests that immune-tolerance checkpoint pathways (PD-1/PD-L1) may shift during the onset of labor, altering local immune and stromal cell dynamics.

Similarly, a recent scRNA-seq analysis of human placental tissues during term labor found that maternal decidual and fetal stromal cells in chorioamniotic membranes show marked transcriptional activation of inflammatory pathways-including collagen, CXCL, TNF and IL-6 signaling-and that signatures of these changes can be detected in the maternal circulation [12]. The authors further suggest that placenta-derived single-cell signatures in maternal blood may serve as non-invasive biomarkers of labor or preterm birth risk.

Taken together, these findings frame labor as a process of systemic hematological adaptation: immune cell subsets in peripheral blood and the maternal–fetal interface undergo compositional and functional shifts; hematopoietic and stromal cells display changes in transcriptional state; and sterile inflammatory signaling pathways become amplified. These changes likely reflect the convergence of maternal preparation for delivery, fetal-maternal cross-talk, and the stress/inflammatory responses associated with parturition. In the context of this review, these hematological and immunological adaptations highlight the potential for applying single-cell technologies to study how psychosocial interventions-such as doula-supported care-might influence these cellular processes.

3. Single-Cell Technologies in Perinatal Hematology

Over the past decade, the rapid evolution of single-cell technologies has transformed hematology and immunology by providing unprecedented resolution in mapping cellular diversity and transcriptional states. In the perinatal context, these approaches have begun to reveal the complex interplay between maternal blood, immune modulation, and hematopoietic remodeling during pregnancy and labor.

3.1 Single-Cell Transcriptomics and Maternal Immune Profiling

Single-cell RNA sequencing (scRNA-seq) has uncovered distinct immune trajectories during healthy pregnancy. For instance, Pique-Regi *et al.* [13] performed single-cell transcriptional profiling of the human placenta and decidua, revealing compartment-specific enrichment of immune cells including decidual macrophages and NK-cell subsets essential for tissue remodeling and fetal tolerance. More recently, Garcia-Flores *et al*. [14] integrated single-cell transcriptomes from the chorioamniotic membranes and identified cell-type–specific activation of inflammatory and cytokine networks during spontaneous term labor.

Building upon these foundational studies, Zhou *et al*. [15] conducted peripheral blood scRNA-seq across gestational stages, reporting dynamic changes in innate and adaptive immune cell gene expression, including enhanced interferon and oxidative phosphorylation pathways preceding labor. Such data underscore the capacity of single-cell approaches to capture transient immune adaptations and hematological reprogramming across pregnancy.

3.2 Multi-Omics Integration and Hematopoietic Insights

Beyond transcriptomics, single-cell multi-omics approaches now integrate transcript, chromatin accessibility, and protein data to map hematopoietic differentiation with unprecedented detail. For example, Rubin *et al*. [16] applied single-cell ATAC-seq and RNA-seq co-assays to delineate regulatory programs of hematopoietic progenitors in humans, illustrating how transcription factor networks dynamically coordinate immune maturation-frameworks readily translatable to perinatal hematology.

Emerging work also applies single-cell proteomics (CyTOF) to maternal–fetal tissues. Liu *et al*. [2] used mass cytometry and scRNA-seq to characterize over 30 distinct immune and non-immune populations at the maternal–fetal interface, showing that PD-1$^+$ T-cell and PD-L1$^+$ stromal cell interactions shift significantly between term and preterm labor. This integration of molecular and phenotypic data provides a blueprint for examining how psychosocial or physiological stressors might alter hematological cell function at single-cell resolution.

3.3 Computational Hematology and AI-Driven Analysis

The explosion of single-cell datasets has catalyzed the rise of computational hematology-a field leveraging machine learning to extract clinically meaningful insights from high-dimensional cell data. Recent applications of artificial intelligence in pregnancy immunology have successfully predicted gestational age and preterm birth risk using single-cell gene expression signatures [17]. Similar frameworks could be extended to assess how doula-supported births modulate maternal immune state trajectories and identify cellular biomarkers linked to stress reduction or improved recovery.

Collectively, single-cell multi-omics technologies offer a transformative platform for dissecting hematological and immune dynamics in perinatal biology. These tools not only enable mechanistic mapping of maternal immune adaptation but also lay the groundwork for evaluating behavioral and psychosocial interventions through a precision hematology lens.

4. Psychosocial Support, Stress, and Hematological Regulation

Psychological and emotional stress during pregnancy and labor has long been associated with adverse obstetric and neonatal outcomes, mediated in part by neuroendocrine and immune dysregulation. Maternal stress activates the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic–adrenal–medullary (SAM) systems, leading to elevated cortisol, catecholamines, and pro-inflammatory cytokines. These neuroimmune perturbations can alter hematopoietic function, modulate leukocyte trafficking, and influence placental immune tolerance [18].

4.1 Stress-Immune Interactions in Pregnancy

Chronic psychosocial stress during gestation is linked to elevated serum interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), together reflecting systemic inflammation [7]. Recent transcriptomic analyses show that maternal stress correlates with increased expression of glucocorticoid-responsive genes and reduced type-I interferon signaling in circulating immune cells [19]. These molecular alterations mirror inflammatory signatures captured by single-cell RNA-seq studies of stressed individuals, which identify stress-responsive monocyte and T-cell subpopulations with heightened NF-κB activity and pro-inflammatory transcriptional programs [20].

In pregnancy-specific contexts, single-cell multi-omic studies have revealed that psychological stress can influence maternal immune heterogeneity. An exploratory single-cell profiling of pregnant women with high perceived stress identified an expansion of activated $CD14^{+}$ monocytes and a reduction in regulatory T-cell populations, suggesting stress-related skewing of hematopoietic differentiation [21]. These findings imply that stress management interventions may restore immune balance by modulating hematological composition.

4.2 Doula Support and Stress Mitigation

Continuous intrapartum support, especially from trained doulas, is among the most evidence-based psychosocial interventions to mitigate maternal stress. Meta-analyses demonstrate that doula-assisted care reduces cesarean delivery rates, shortens labor duration, and decreases postpartum depression symptoms [6,22]. Physiologically, such benefits may stem from attenuation of HPA-axis hyperactivation, stabilization of blood pressure, and normalization of leukocyte activity. Indeed, human studies have shown that supportive presence during childbirth reduces salivary cortisol and circulating IL-6 concentrations, indicating measurable hematological effects of emotional support [23].

4.3 Toward a Single-Cell Framework of Stress-Hematology Coupling

Integrating psychosocial science with single-cell hematology offers a novel framework for precision perinatal medicine. Single-cell multi-omic analyses of maternal blood could quantify how doula-supported births modulate stress-responsive immune pathways-such as glucocorticoid receptor signaling, oxidative phosphorylation, and cytokine regulation-at the cellular and transcriptional level. Machine-learning algorithms trained on single-cell data may further identify predictive cellular states associated with reduced stress biomarkers or improved recovery trajectories [24].

Overall, psychosocial support acts as a physiological buffer during labor, shaping immune and hematological responses through neuroendocrine–immune cross-talk. Applying single-cell technologies to this context may illuminate how emotional interventions translate into molecular adaptations, ultimately guiding integrative strategies for maternal health optimization.

5. Integrative Research Framework and Future Directions

Bridging psychosocial care with molecular hematology represents a transformative frontier for perinatal science. The convergence of single-cell technologies, AI-based analytics, and clinical psychosocial interventions such as doula-supported care provides an unprecedented opportunity to elucidate how emotional and environmental factors reshape the hematopoietic and immune landscape during labor.

5.1 Multi-Omic Integration and Systems-Level Modeling

Modern single-cell multi-omic platforms allow simultaneous profiling of gene expression, chromatin accessibility, and surface proteomes in maternal immune cells, enabling the construction of dynamic cell-state atlases across pregnancy

and childbirth. Recent studies integrating scRNA-seq and ATAC-seq revealed complex regulatory programs controlling immune tolerance and inflammation in the maternal–fetal interface [17,25]. Such frameworks can be expanded to assess how psychosocial interventions-like continuous emotional support-reshape these regulatory circuits, potentially through modulation of glucocorticoid receptor signaling or chromatin remodeling in stress-responsive hematopoietic cells.

Moreover, computational platforms such as CellChat and scVI-tools now allow prediction of intercellular communication and latent transcriptional trajectories across thousands of single cells [25,26]. Applying these models to doula-assisted versus standard labor cohorts could reveal how emotional support alters maternal cell–cell communication networks, particularly among monocytes, NK cells, and stromal populations involved in uterine remodeling and clotting.

5.2 AI-Driven Hematological Prediction and Stress Biomarkers

Artificial intelligence (AI) and machine learning (ML) algorithms, when trained on large-scale single-cell datasets, can identify predictive hematological signatures linked to maternal stress resilience. For instance, AI-assisted clustering of single-cell transcriptomes has uncovered rare progenitor and regulatory T-cell subsets critical to immune tolerance in pregnancy [27]. Integrating such models with maternal physiological and psychosocial metrics may yield interpretable biomarkers that connect emotional well-being to molecular hematology.

Single-cell proteomics and spatial transcriptomics further extend this capability by mapping localized microenvironments within the placenta and uterine tissue [28]. This enables a multilayered understanding of how stress or supportive care may spatially reprogram maternal immune niches, influencing parturition and postpartum recovery.

5.3 Translational and Ethical Implications

Future translational research should emphasize non-invasive monitoring, leveraging circulating cell-free RNA (cfRNA), extracellular vesicles, and peripheral blood single-cell profiles as biomarkers of labor readiness and psychological adaptation [29]. The integration of psychosocial, molecular, and computational domains requires rigorous ethical frameworks to ensure privacy and consent, especially when combining behavioral data with genomic information [30].

Ultimately, a single-cell–informed psychosocial hematology framework may redefine maternal health research-unifying emotional, immunological, and molecular dimensions into a cohesive model of perinatal well-being. By contextualizing doula-supported care within systems biology, future studies can move beyond correlation toward mechanism, elucidating how empathy and support translate into quantifiable biological resilience during childbirth.

6. Discussion

The integration of psychosocial support and single-cell hematology opens a new conceptual space for understanding childbirth as a multiscale biological and emotional process. Traditional obstetric paradigms have viewed labor predominantly through physiological and mechanical lenses; however, emerging single-cell studies reveal that the cellular ecosystem of pregnancy and parturition is profoundly sensitive to psychological and environmental inputs. In this context, doula-supported care represents not only a social or emotional intervention but a potential modulator of maternal hematopoiesis and immune homeostasis.

6.1 Single-Cell Insights into Labor Physiology

Recent advances in single-cell technologies have transformed our comprehension of parturition at cellular resolution. scRNA-seq and spatial transcriptomics of the placenta, decidua, and maternal peripheral blood show dynamic shifts in immune composition and inflammatory gene networks during both term and preterm labor [31,32]. Labor is characterized by the activation of neutrophil- and macrophage-driven inflammatory pathways, upregulation of chemokine genes (CXCL8, CCL2), and the emergence of stress-related transcriptional programs in hematopoietic progenitors. These findings reinforce the notion that hematological dynamics in childbirth mirror an orchestrated sterile inflammatory process rather than a simple mechanical trigger.

Moreover, the advent of single-cell epigenomic approaches such as scATAC-seq and single-cell methylome sequencing enables exploration of chromatin accessibility and DNA methylation changes across hematopoietic compartments [33]. These techniques can reveal how stress and emotional regulation may influence hematopoietic plasticity through transcriptional reprogramming-a key hypothesis for the biological embedding of psychosocial experiences during childbirth.

6.2 Psychosocial Modulation of Hematological Pathways

Maternal stress, loneliness, and fear of childbirth are associated with heightened inflammatory signaling, elevated cortisol levels, and dysregulated coagulation parameters [34]. However, continuous emotional support, such as doula care, has been shown to buffer these effects by lowering cortisol and IL-6 levels, thereby promoting hemodynamic stability and faster postpartum recovery [6,22].

Integrating these findings with single-cell immunoprofiling suggests that emotional regulation could stabilize immune cell states by suppressing hyperactivation of monocytes and cytotoxic lymphocytes, and by preserving the balance of regulatory T-cell subsets. Indeed, a 2023 single-cell study demonstrated that maternal stress exposure during pregnancy

alters the transcriptional identity of $CD14^+$ monocytes and shifts cytokine responsiveness [21]. Conversely, positive emotional environments may maintain homeostatic cell–cell communication networks via decreased NF-κB and increased IL-10 signaling pathways-hypotheses that could be empirically tested through longitudinal scRNA-seq studies of doula-supported births.

6.3 From Cell States to Clinical Translation

One of the most promising translational pathways emerging from this interdisciplinary approach is the development of stress-sensitive hematological biomarkers derived from single-cell data. These include the transcriptional activation states of immune subsets, hematopoietic progenitor bias toward inflammatory lineages, and circulating cfRNA signatures associated with emotional stress [29]. Integrating these molecular features with psychosocial metrics could produce predictive models for maternal resilience and early detection of maladaptive stress responses.

Furthermore, computational models using deep learning have begun to reconstruct gene regulatory networks underlying immune adaptation during pregnancy and labor [35]. Applying similar algorithms to datasets comparing doula-supported and unsupported births could reveal mechanistic insights into how empathy, trust, and emotional safety translate into measurable hematopoietic stability. Such work would not only redefine "biological correlates of care" but also establish evidence-based foundations for integrating psychosocial interventions into precision obstetric medicine.

6.4 Limitations and Future Directions

Despite these advances, challenges remain. Psychosocial states are multidimensional and context-dependent, making them difficult to model quantitatively in conjunction with molecular datasets. Additionally, single-cell studies in pregnancy are often limited by sample accessibility, ethical constraints, and inter-individual variability. Future research should adopt longitudinal, multi-site single-cell profiling of maternal blood and placental tissues combined with standardized psychosocial assessment tools, enabling a richer understanding of time-dependent cell-state transitions under varying emotional contexts.

Cross-disciplinary collaborations between obstetricians, computational biologists, and behavioral scientists will be essential to realize this integrative vision. Importantly, ethical considerations surrounding data privacy, informed consent, and the responsible use of genomic and behavioral data must remain central to future work [30].

7. Conclusion

Childbirth represents one of the most intricate biopsychosocial events in human physiology-an experience that synchronizes mechanical, hormonal, immunological, and emotional systems to achieve safe delivery and recovery. The emerging integration of single-cell technologies into perinatal hematology has revealed that labor is accompanied by profound cellular heterogeneity and dynamic hematopoietic reprogramming, encompassing immune activation, inflammatory modulation, and stromal–vascular adaptation.

Within this molecularly complex process, psychosocial interventions such as doula-supported care are increasingly recognized as biologically consequential. Evidence from behavioral and physiological research shows that emotional support during labor reduces maternal stress hormone release, stabilizes inflammatory responses, and improves obstetric outcomes. When considered alongside single-cell insights into maternal immune dynamics, these findings suggest that empathy, presence, and emotional safety may exert measurable effects on cellular and transcriptional states within the maternal hematological system.

Future work should move beyond descriptive associations toward mechanistic elucidation, leveraging single-cell multi-omics, spatial transcriptomics, and AI-driven integrative modeling to map how psychosocial variables reshape hematopoietic cell states in real time. Such research will not only deepen our understanding of the biological embedding of emotional support, but also pave the way for precision obstetric care-where psychosocial and molecular diagnostics jointly inform personalized strategies for maternal health.

Ultimately, this interdisciplinary synthesis-linking doula care, stress biology, and single-cell hematology-challenges traditional divisions between mind and body. It reframes birth not solely as a medical event, but as a deeply coordinated molecular dialogue between psychological experience and physiological adaptation. By embracing this holistic and data-rich paradigm, the field moves one step closer to realizing the vision of integrative, compassionate, and precision-based maternal medicine.

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