Investigating transport, mechanotransduction, and angiogenesis pathways in syncytiotrophoblast cells: A literature-based network analysis of biomarkers

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27/08/2025

1. Introduction

The human placenta is a critical organ that supports fetal development by facilitating nutrient and gas exchange, hormone production, immune regulation, and vascular remodeling. Among its components, the syncytiotrophoblast (STB) layer plays a central role as the primary interface between maternal blood and the fetus, regulating transport, mechanosensing, and angiogenesis. These processes are essential for maintaining placental homeostasis and ensuring proper fetal growth. Dysregulation in these pathways can lead to severe pregnancy complications, including preeclampsia—characterized by hypertension and impaired angiogenesis—and intrauterine growth restriction (IUGR), often associated with insufficient nutrient transport. Understanding the molecular basis of STB function requires a systems-level approach to identify key biomarkers involved in mechanotransduction, transport, and angiogenesis, as well as their interactions. Mechanosensing is particularly important because syncytiotrophoblast cells experience dynamic mechanical forces which can influence gene expression and signalling cascades related to angiogenesis and nutrient transport. In this study, we compile biomarkers reported between 2015 and 2025 from literature focusing on the STB layer, with a particular emphasis on the BeWo trophoblast cell line as a widely used in vitro model. Identified biomarkers include those related to mechanotransduction, solute transport, angiogenic signaling, and pregnancy hormones. Pathway enrichment analysis and network mapping are applied to evaluate shared functional pathways and interactions across these categories. Furthermore, protein–protein interaction (PPI) networks are constructed to highlight key hubs, cross-talk between pathways, and potential regulatory nodes. These analyses aim to provide an integrated view of STB mechanobiology, uncovering functional connections that could guide future research and therapeutic strategies for placental disorders. Specifically, the objectives of this study are to identify and classify key genes and biomarkers from the literature, perform a pathway enrichment analysis to create functionally grouped networks, and construct protein-protein interaction (PPI) networks to highlight key regulatory nodes. A central objective is to analyze the importance of mechanosensing genes relative to the other gene groups, ultimately providing a detailed molecular map of placental function.

2. Methods

a. Literature Review and Gene Categorization

This diagram outlines the methodology used for a literature review on placental physiology. The process began with a review of 45 papers published between 2015 and 2025 that focused on placental physiology, excluding those related to pathophysiology. The data collected included experimental setups, key genes and biomarkers, and results. The genes were categorized into four groups: mechanotransduction, transport, angiogenesis, and pregnancy hormones.

b. Pathway and Network Analysis

The genes were then analyzed using gProfiler for pathway enrichment, with the output providing a set of GO, KEGG, and Reactome pathway terms for each of the four groups. This was followed by a functional grouped network analysis using ClueGO, which combined the pathway terms from each group to analyze shared pathways for different types of biomarkers, with a specific focus on mechanotransduction. The number of genes expressed per pathway was graphed to assess statistical significance.

c. Protein-Protein Interaction (PPI) Network

All networks were represented as adjacency matrices to simplify the interpretation of the large number of pathways. Key clusters from the enriched pathways were selected based on their biological relevance, resulting in seven clusters. Finally, genes that appeared in three or more of the top pathway clusters were chosen to create a protein-protein interaction (PPI) network, which ultimately included 53 genes.

3. Results

a. g:Profiler Pathway Enrichment Results

These scatter plots illustrate the pathway enrichment analysis results from g:Profiler for four distinct groups of genes: mechanosensing (Fig. 1), transporter (Fig. 2), angiogenesis (Fig. 3), and pregnancy hormone-related genes (Fig. 4). Each plot categorizes the enriched pathways by their source database on the x-axis, including GO:MF (Molecular Function), GO:BP (Biological Process), GO:CC (Cellular Component), KEGG, REAC (Reactome), and WP (WikiPathways). The y-axis represents the statistical significance as the negative log10 of the adjusted p-value ($-\log10(\text{Padj})$), where a higher value signifies a more robust enrichment.

For mechanosensing genes (Fig. 1), the analysis reveals a strong enrichment in pathways related to cellular components, particularly the focal adhesion complex and extracellular matrix. The software highlighted and numbered the most significant and relevant terms, which are focused on mechanosensory transduction and cell adhesion, underscoring the key role of these genes in physical cellular interactions.

The transporter genes (Fig. 2) are significantly enriched in pathways related to membrane transport, including the transmembrane transporter complex and ion channel activity. The highlighted pathways confirm the function of these genes in facilitating the movement of substances across cellular membranes.

The plot for angiogenesis genes (Fig. 3) shows significant enrichment in terms related to blood vessel development, with prominent pathways like blood vessel morphogenesis and extracellular matrix organization. The software highlighted the most critical pathways involved in vascular formation, reinforcing the role of these genes in the development and regulation of the vascular network.

Finally, the analysis of pregnancy hormone-related genes (Fig. 4) indicates enrichment in pathways involved in hormonal signaling and regulation, such as the G-protein coupled receptor signaling pathway and ligand-activated transcription factor activity. The highlighted

terms confirm the interconnectedness of these genes with critical endocrine functions essential for pregnancy.

Across all four figures, the size of each circle is proportional to the number of genes associated with that specific pathway. These analyses collectively provide a comprehensive functional overview of each gene group and their respective biological roles within placental physiology.

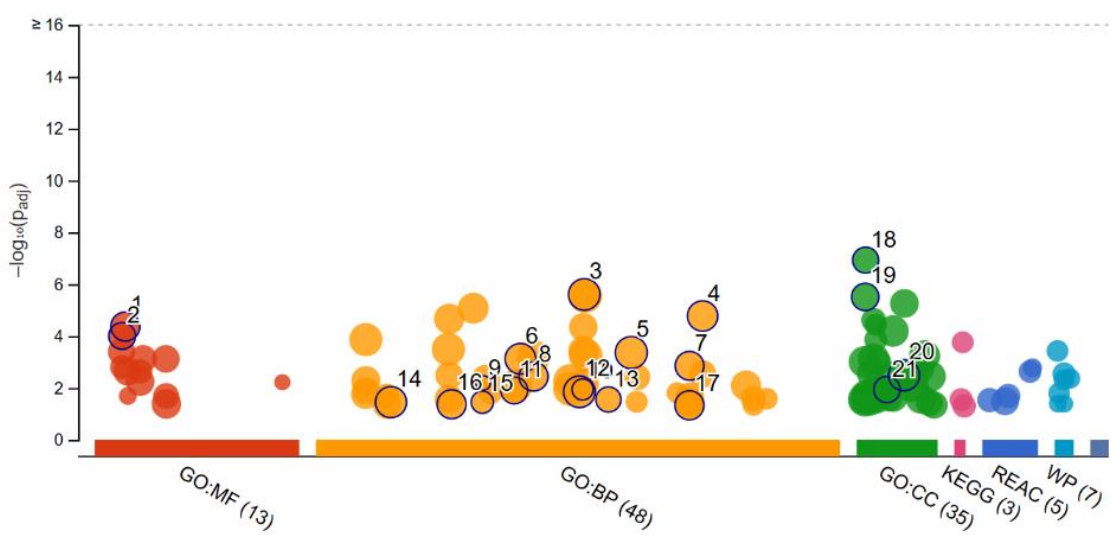


Figure 1: Scatter plot of the gene ontologies and the pathways of the input mechanosensing genes

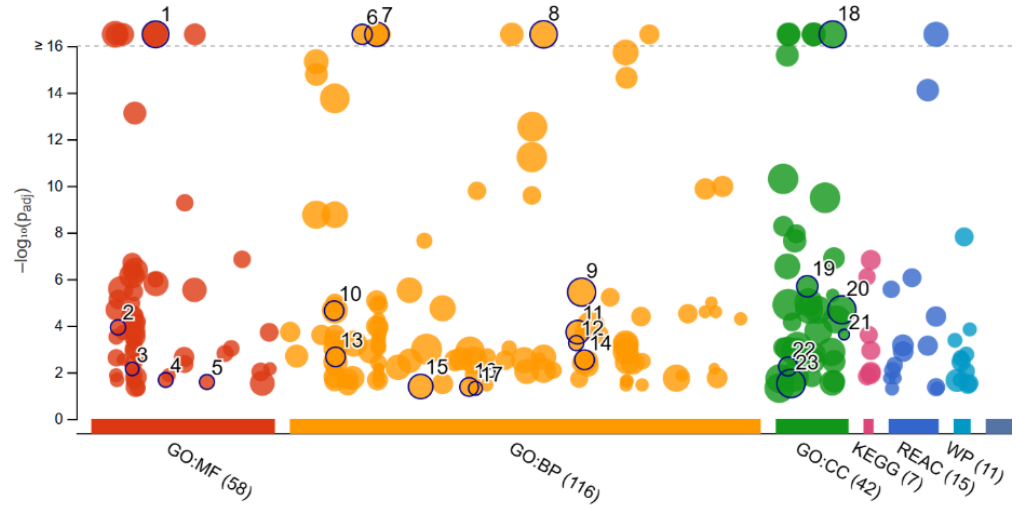


Figure 2: Scatter plot of the gene ontologies and the pathways of the input transporter genes

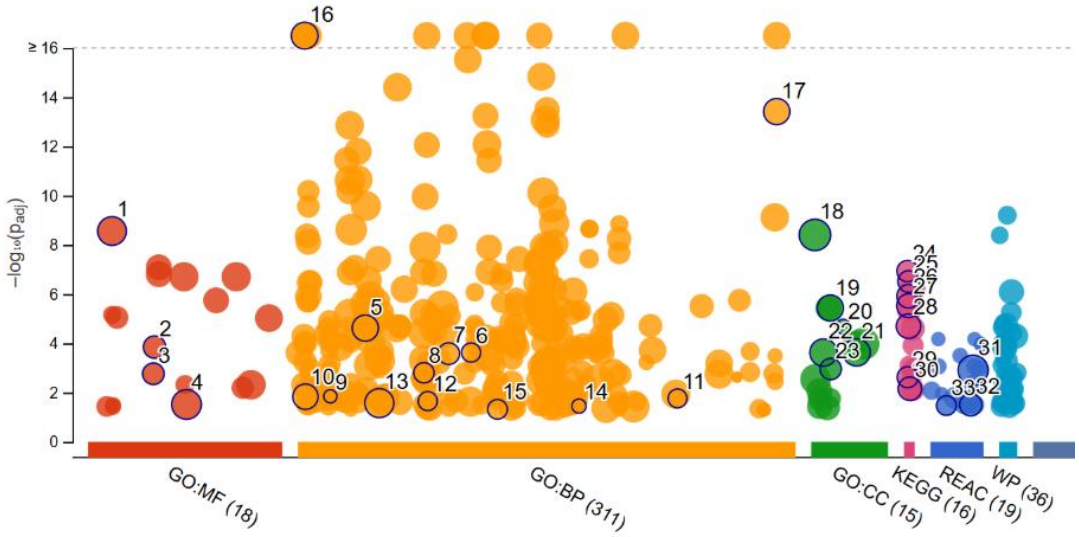


Figure 3: Scatter plot of the gene ontologies and the pathways of the input angiogenesis genes

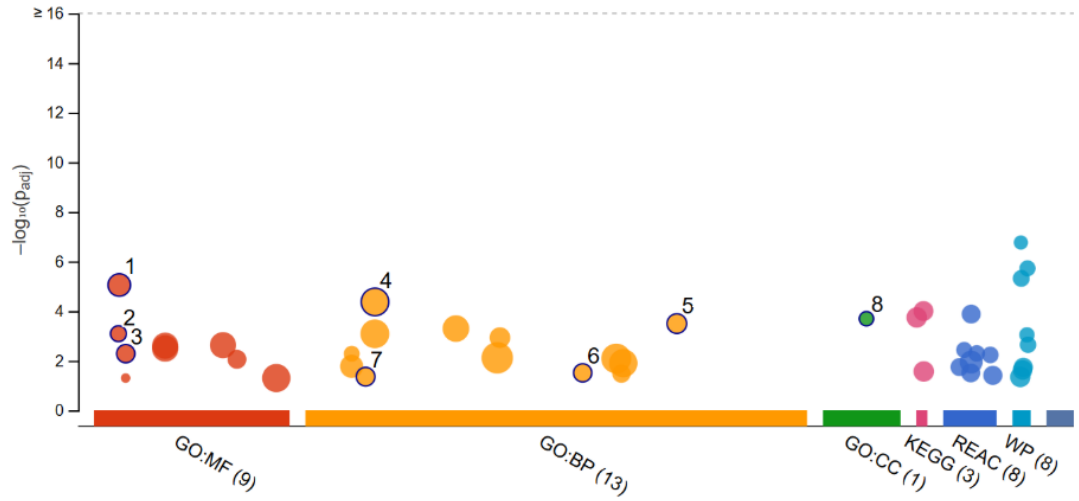


Figure 4: Scatter plot of the gene ontologies and the pathways of the input angiogenesis genes

b. Main Pathway Networks Using Cystoscope Software

The pathway enrichment analysis from the four gene groups—mechanosensing, transporter, angiogenesis, and pregnancy hormone-related—was synthesized into a functionally grouped network using Cytoscape software, specifically with the ClueGO and ClueGO Pedia apps. In this network visualization, the nodes represent the individual enriched pathways or terms, and the edges signify a connection between them based on the existence of shared genes. This

approach allowed for the identification of seven core functional clusters that represent the most significant and interconnected biological pathways.

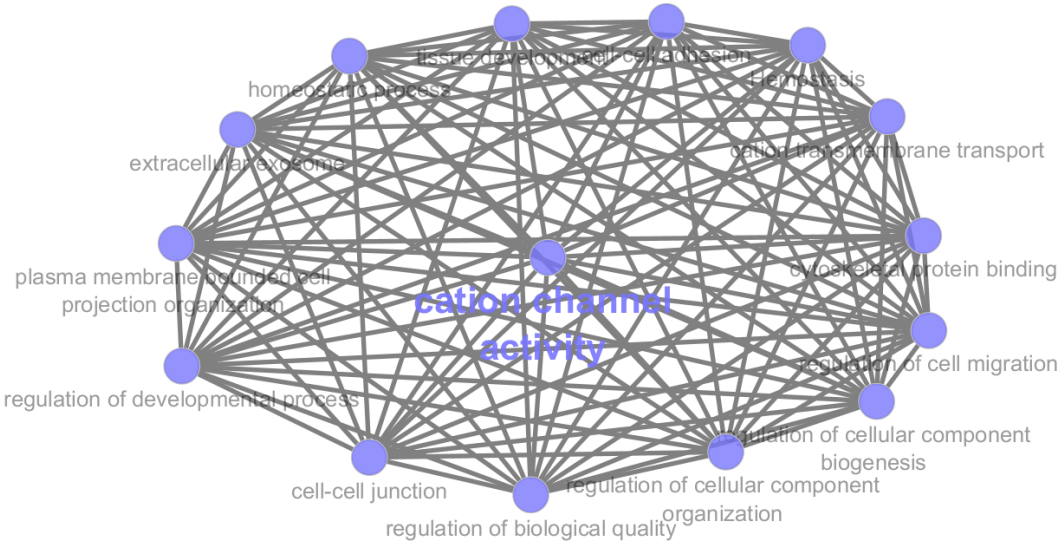


Figure 5: Regulation of Development: This cluster is related to mechanosensing pathways, highlighting a central theme that demonstrates the involvement of the studied genes in fundamental processes that govern the development of the placenta. This is a key cluster given its broad scope in ensuring proper placental formation and function.

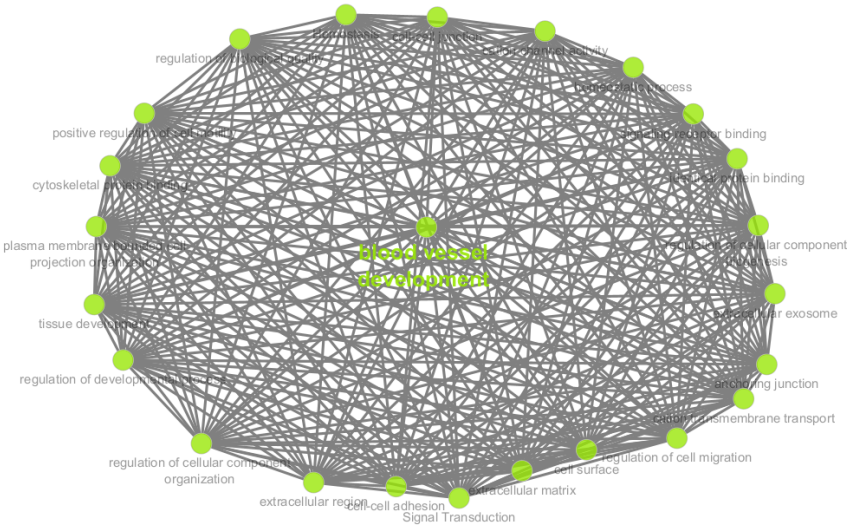


Figure 6: Cell Regulation: This cluster is related to both mechanosensing and angiogenesis pathways. It focuses on intricate cellular activities, including proliferation, differentiation, and apoptosis, all of which are essential for the rapid growth and remodeling of placental tissue.

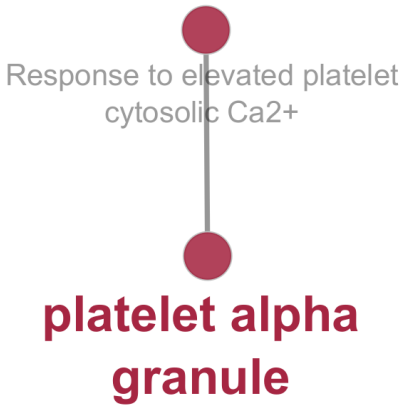


Figure 7: Platelet Alpha Granule: This cluster is also related to both mechanosensing and angiogenesis pathways. It suggests a role for the genes in processes related to hemostasis, wound healing, and growth factor storage and release, which are crucial for managing the highly vascularized environment of the placenta and for tissue repair.

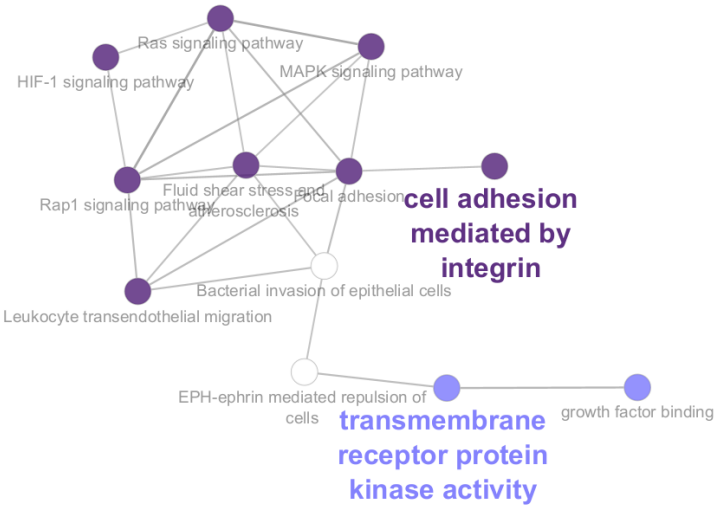


Figure 8: Ras Signaling: This cluster is related to both mechanosensing and angiogenesis pathways. As a well-known signal transduction pathway, it indicates the involvement of placental genes in regulating cell growth, survival, and differentiation, confirming their role in the complex signaling cascades that control placental development.

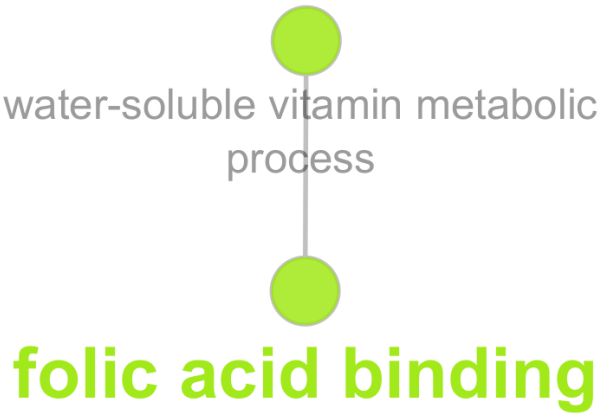


Figure 9: Folic acid Binding: This cluster is related to both mechanosensing and transporter pathways. It directly addresses the placenta's function as a transport organ, pointing to a cluster of genes involved in the uptake and binding of folic acid, a critical nutrient for fetal development.

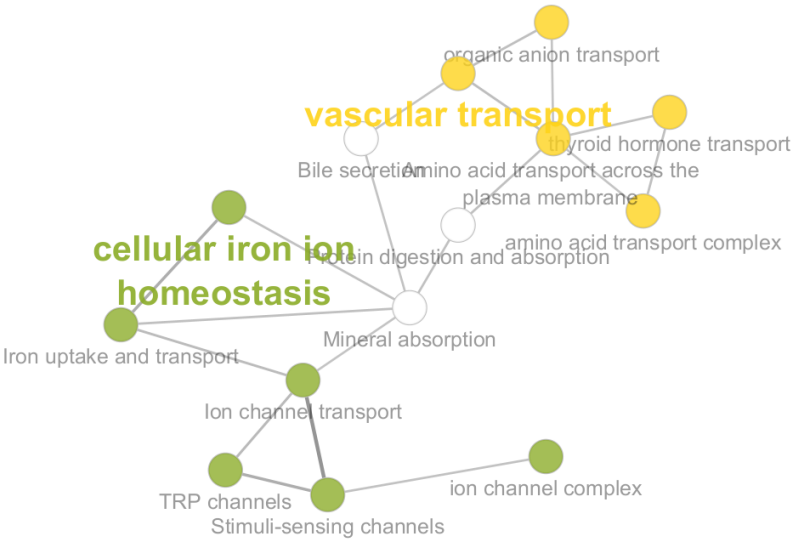


Figure 10: Vascular Transport across: This cluster is also related to both mechanosensing and transporter pathways. It specifically addresses the transport function of the placenta, with a focus on the movement of substances across the vascular barriers between maternal and fetal blood.

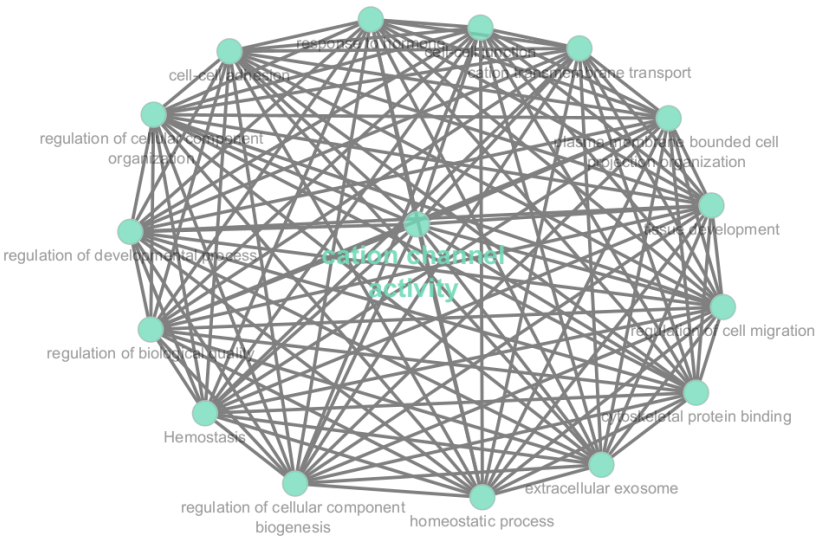


Figure 11: Regulation of Development (Mechanosensing and Hormones): This final network is related to mechanosensing and pregnancy hormone pathways. It highlights the multifaceted nature of developmental control within the placenta, with various genes contributing to different aspects of this process through hormonal signaling.

c. Joint Pathway Analyses Between Mechanosensing genes and Transport, Angiogenesis, and Pregnancy Hormones Genes

Following the functional grouped network analysis, the numerous enriched pathways were consolidated into four key, biologically relevant sets for a more focused investigation. These sets—Mechanosensing (Figure 12), Mechanosensing & Transport (Figure 13), Cell Regulation & Blood vessel development (Figure 14), and RAS signaling (Figure 15)—were chosen to represent the primary functional domains identified in the literature review. To visualize the individual pathways within each set, bar graphs were generated. In these graphs, the height of each bar corresponds to the number of genes associated with that specific pathway, meaning that a taller bar indicates a more significant and highly represented pathway within the given set. This method allows for a clear and direct comparison of the prevalence and importance of different biological processes, providing a more refined view of the most critical functions related to placental physiology.

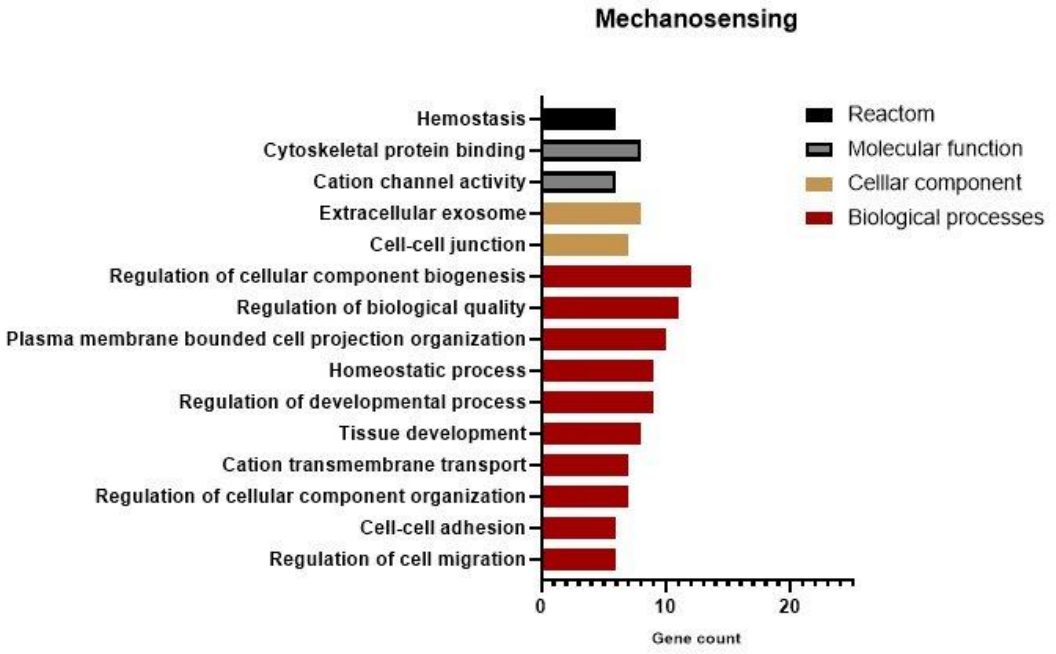


Figure 12: This bar graph shows the most significant pathways within the Mechanosensing gene set. The length of each bar indicates the number of genes associated with that pathway. Taller bars, such as "Regulation of cellular component biogenesis," "Regulation of biological quality," and "Regulation of developmental process," represent the most prominent and significant functions within this gene group.

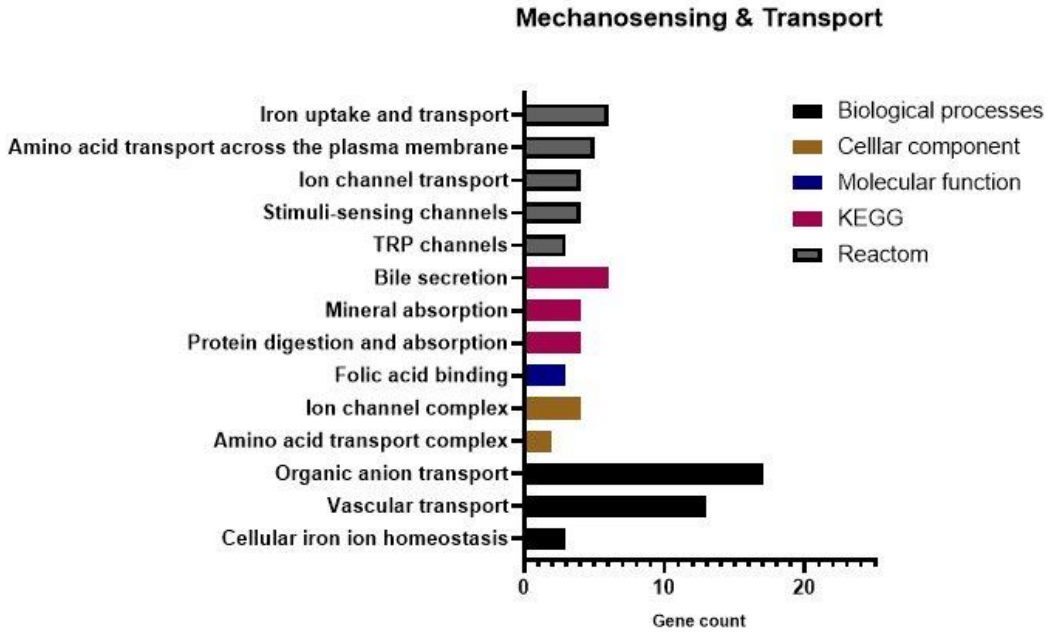


Figure 13: This figure displays the key pathways shared by the Mechanosensing and Transporter gene groups. The graph highlights crucial functions related to both physical interaction and nutrient exchange. The longest bars, corresponding to "Organic anion transport"

and "Vascular transport," confirm that transport processes are a major functional output of the genes in this combined set.

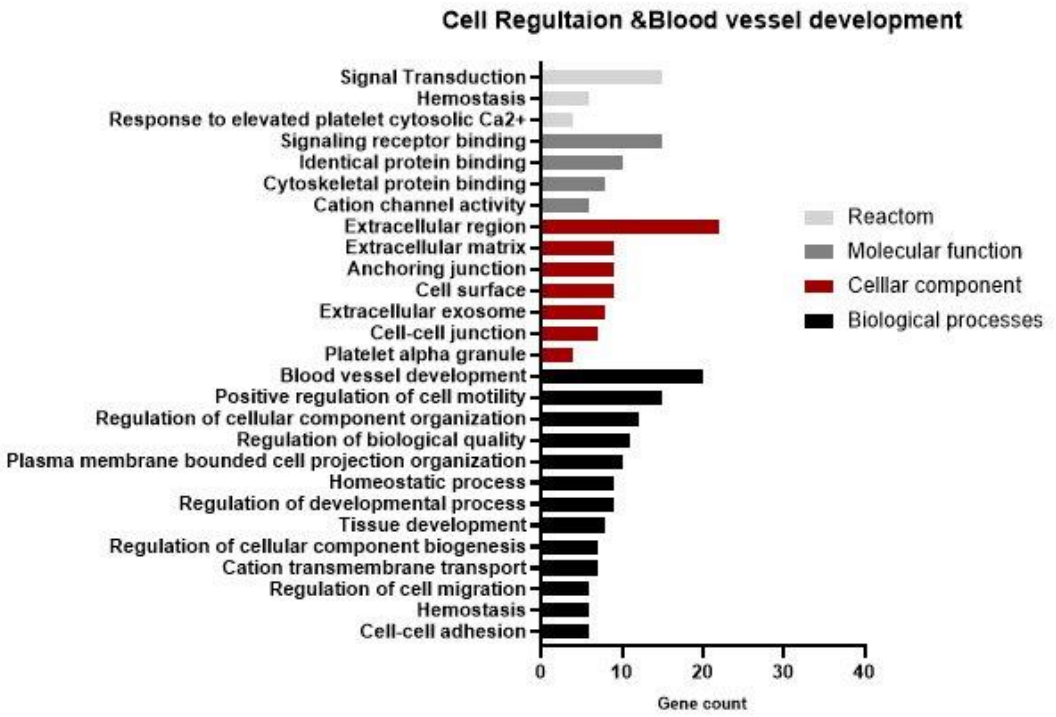


Figure 14: This bar graph illustrates the most significant pathways related to the combined Mechanosensing and Angiogenesis gene groups. The bars show high gene counts for pathways such as "Blood vessel development," "Positive regulation of cell motility," and "Regulation of biological quality," confirming the central role of these genes in coordinating both cellular behavior and the formation of the placental vasculature.

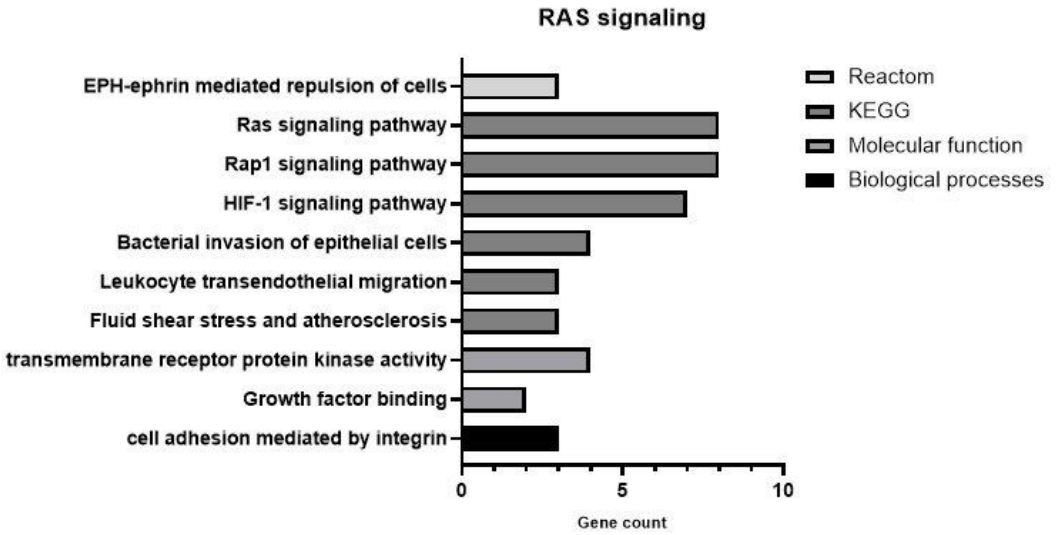


Figure 15: This figure provides a detailed view of the pathways within the RAS signaling cluster. The bar graph shows that "Ras signaling pathway," "Rap1 signaling pathway," and "HIF-1 signaling pathway" are the most highly represented functions. This indicates the strong

involvement of the genes in this cluster in regulating cell proliferation, survival, and response to hypoxia, all of which are vital for placental development.

d. Mapping Pathway Interactions

All pathways from each of the functional groupings were analysed using an adjacency matrix, with a non-zero value representing an edge (connection) between the two pathways, and the magnitude of the value representing the number of shared genes. A greater proportion of red represents a greater the number of genes shared between pathways. Dark blue represents zero genes shared. Graphs were generated using the Morpheus software. The figures below present the adjacency matrix for different clusters.

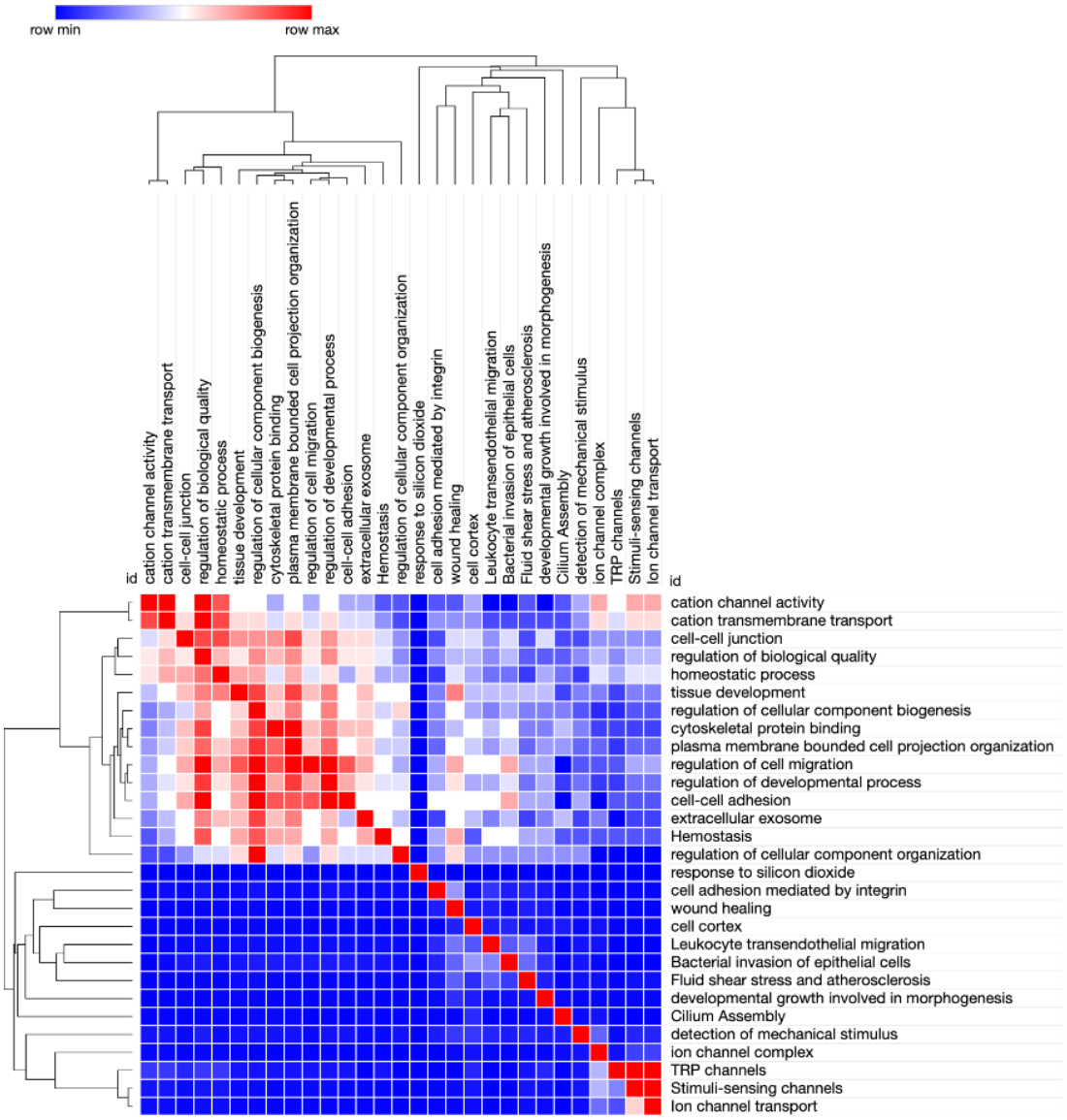


Figure 16: This adjacency matrix heatmap visualizes the interactions solely between the top pathways identified within the Mechanosensing gene group. The pattern of red and blue indicates the degree of gene sharing among these pathways. Clusters of red highlight strong functional overlaps between various

mechanosensing-related processes, such as "Cell-cell adhesion" and "Regulation of cellular component organization," emphasizing the intricate coordination of physical cues within the placenta.

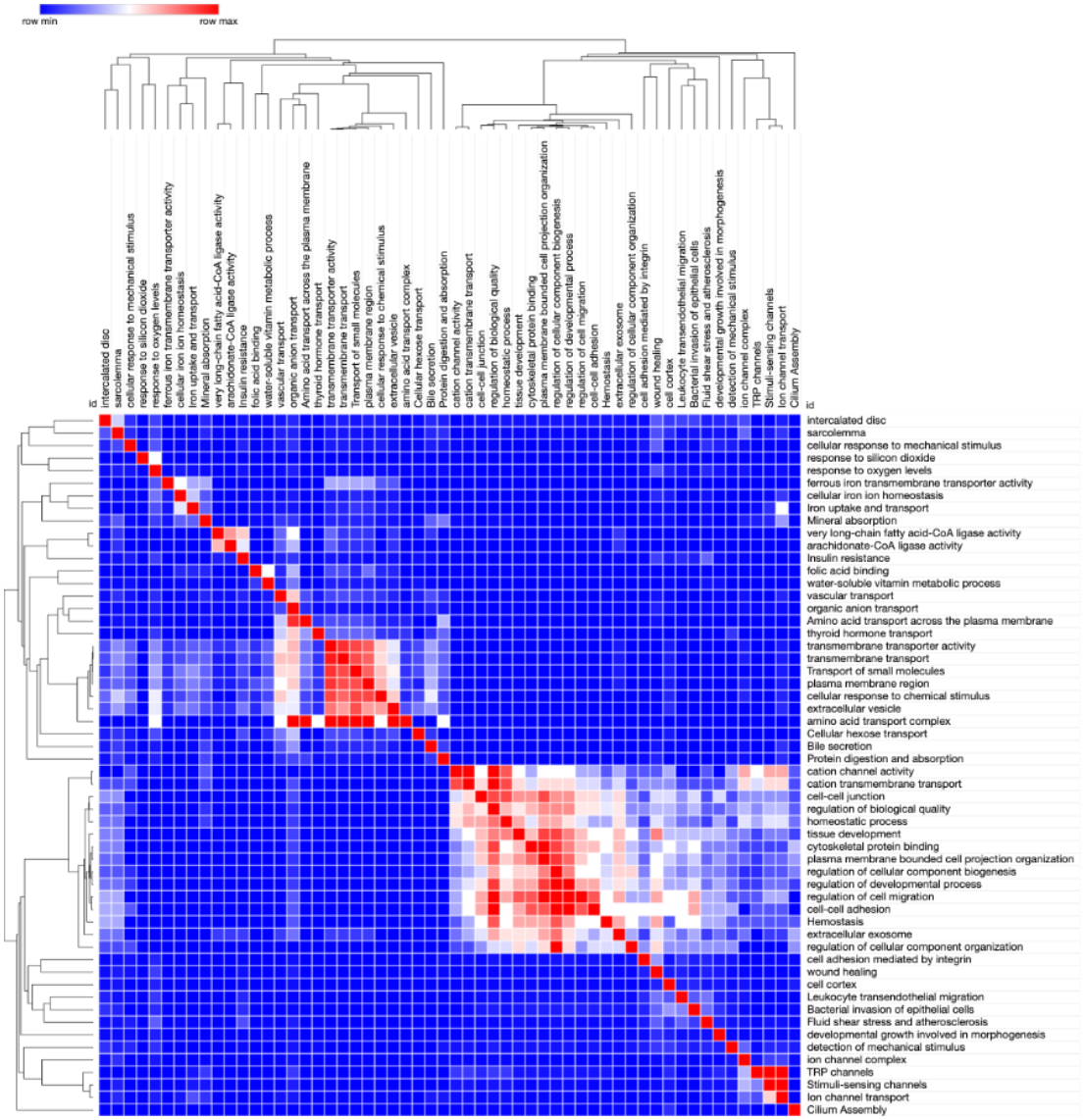


Figure 17: This heatmap shows the relationships between pathways identified in the combined Mechanosensing and Transporter gene groups. The presence of dense red clusters, particularly between pathways like "Vascular transport," "Amino acid transport across the plasma membrane," and "Folic acid binding," indicates a high number of shared genes. This visually confirms a strong functional overlap between mechanosensing and transport processes, highlighting how physical cues and cell-cell interactions are intimately linked with the transport of critical nutrients across the placenta.

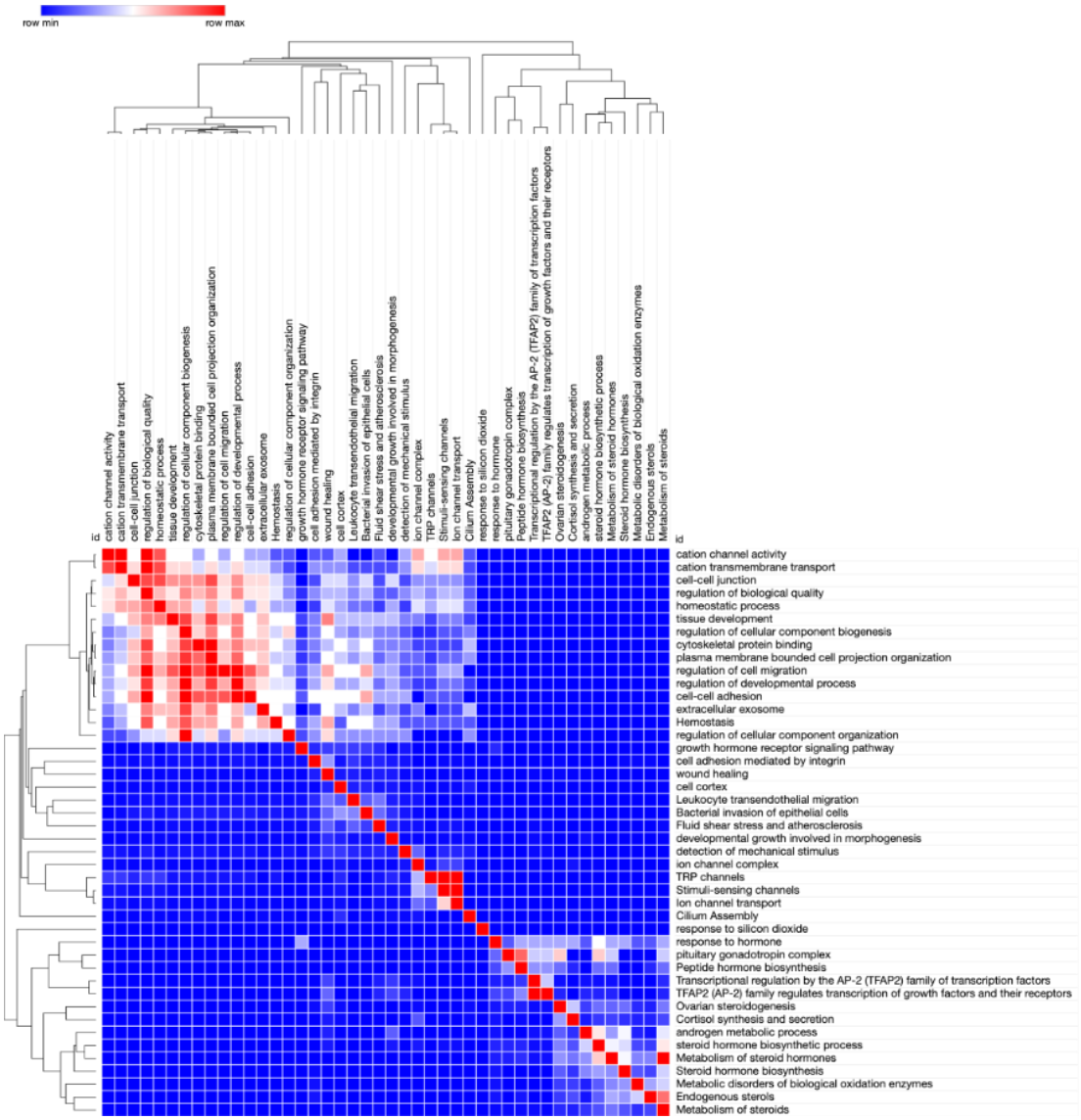


Figure 18: This adjacency matrix illustrates the interactions between pathways from the combined Mechanosensing and Pregnancy Hormone gene groups. The heatmap reveals specific clusters of gene sharing between pathways, including those related to steroid metabolism and hormone signaling. The presence of red in this matrix indicates that there is a significant functional crosstalk between genes involved in physical cellular interactions and those that regulate hormonal signaling, which is crucial for maintaining a healthy pregnancy.

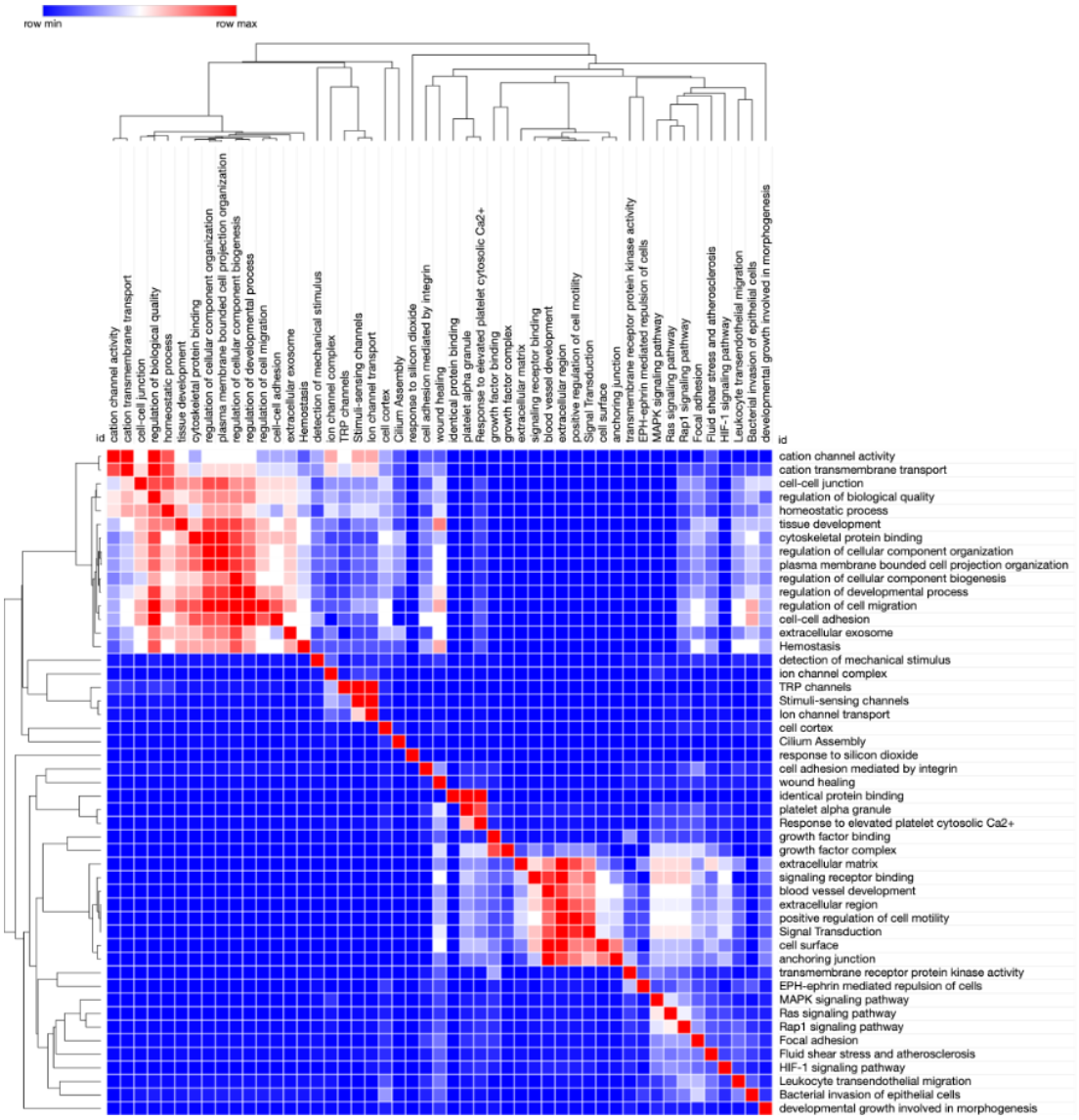


Figure 19: his heatmap displays the relationships between pathways from the combined Mechanosensing and Angiogenesis cluster. The large, interconnected red blocks demonstrate extensive gene sharing among pathways related to blood vessel development, cell motility, and various cellular regulation processes. This strong co-expression confirms the tight coordination required between cellular behavior, such as adhesion and migration, and the complex process of forming new blood vessels within the placenta, driven by mechanosensory signals.

e. Protein-Protein Interaction Network

The final step of the analysis was the construction of a protein-protein interaction (PPI) network to identify the most central and highly interconnected genes across the key functional pathways. Genes that appeared in three or more of the top seven pathway clusters were selected for this network, ensuring that only the most significant and functionally versatile genes were included. This focused approach resulted in a network of 56 proteins, providing a high-resolution view of the key molecular players and their interactions within the context of placental physiology.

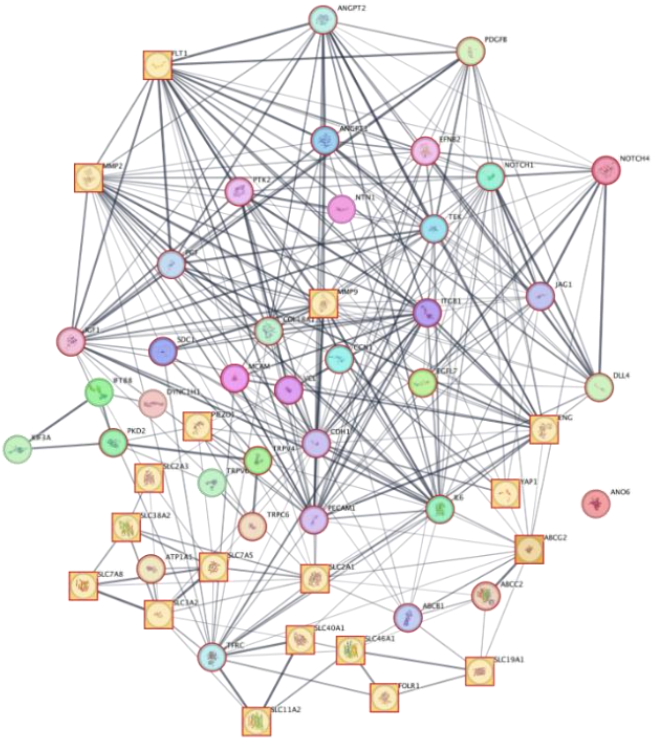


Figure 20: The above graph represents the network of 56 proteins expressed three or more times in the top seven clusters from the pathway analysis. The network visualization was completed using Cytoscape, with key genes highlighted by a square yellow outline and nearest neighbors highlighted using a red outline. This map reveals the central nodes and highly interconnected relationships among the most prominent genes, serving as a summary of the core molecular architecture of the placental processes studied.

Gene	Degree	Betweenness Centrality	Closeness Centrality	Neighborhood Connectivity
PECAM1	28	0.09	0.64	16.5
IL6	27	0.12	0.64	16.4
MMP9	25	0.03	0.57	17.0
CDH1	24	0.12	0.61	15.6
NOTCH1	23	0.03	0.54	17.2
FLT1	23	0.02	0.54	18.0
MMP2	23	0.02	0.57	17.7
ENG	21	0.02	0.55	18.6
TEK	21	0.01	0.52	17.9
ITGB1	21	0.05	0.56	17.8
IGF1	20	0.03	0.54	18.9
ANGPT2	19	0.01	0.52	19.2
TFRC	18	0.10	0.54	15.0
JAG1	18	0.01	0.50	18.8
ANGPT1	16	0.00	0.48	19.8
SLC2A1	16	0.08	0.53	16.6
DLL4	15	0.00	0.47	18.8
ABCG2	14	0.05	0.51	17.2
EFNB2	14	0.01	0.46	18.9
PDGFB	14	0.00	0.47	20.2
PGF	13	0.00	0.46	20.3
PTK2	13	0.02	0.48	19.2
COL18A1	12	0.00	0.46	20.5
NOTCH4	12	0.01	0.49	17.7
MCAM	10	0.01	0.47	20.9
SLC3A2	10	0.03	0.45	8.9

Gene	Degree	Betweenness Centrality	Closeness Centrality	Neighborhood Connectivity
SDC1	9	0.00	0.47	22.0
ABCB1	9	0.02	0.48	18.0
SLC7A5	9	0.06	0.47	9.8
EGFL7	8	0.00	0.43	20.1
PIEZO1	7	0.11	0.50	11.6
SLC46A1	7	0.01	0.39	7.7
VCL	6	0.00	0.46	19.7
CCN1	6	0.00	0.43	21.2
TRPV4	6	0.10	0.47	11.5
ABCC2	5	0.00	0.38	10.2
SLC2A3	5	0.01	0.43	11.2
SLC19A1	5	0.00	0.36	7.6
SLC40A1	5	0.01	0.45	13.2
PKD2	5	0.11	0.36	4.2
YAP1	5	0.00	0.42	16.8
SLC38A2	5	0.00	0.39	8.8
SLC11A2	4	0.00	0.38	10.0
SLC7A8	4	0.00	0.38	10.0
NTN1	3	0.00	0.36	12.3
IFT88	3	0.04	0.27	2.7
TRPV6	3	0.00	0.33	4.7
FOLR1	3	0.00	0.37	10.0
TRPC6	3	0.00	0.34	5.3
KIF3A	2	0.00	0.27	4.0
ATP1A1	2	0.00	0.33	9.5
DYNC1H1	1	0.00	0.21	3.0

Tables 1 & 2: All genes within the network were analyzed for key centrality measures, including degree (the number of connections a gene has), betweenness centrality (its control over information flow), and closeness centrality (its proximity to other genes). The genes were ranked by their degree, from most to least connected.

While a gene's betweenness centrality typically decreases as its degree falls, this was not the case for three key mechanosensing genes: TRPV4, PKD2, and PIEZO1. Despite having a degree of less than 10, these genes maintained a notable betweenness centrality, which implies

a significant regulatory role within the network. In contrast, no genes related to angiogenesis or transport demonstrated this property, suggesting that these specific mechanosensing genes may serve as critical regulators, influencing communication between different parts of the network even without a high number of direct connections.

4. Challenges

While this systems-level approach provided a comprehensive overview of placental pathways, several challenges were encountered. The manual curation of data from a diverse set of literature proved to be a time-intensive process, and inconsistencies in experimental designs and reporting across studies required careful data standardization. Furthermore, the sheer complexity of the resulting bioinformatics networks, with numerous nodes and edges, presented a challenge in itself, requiring a multi-layered analytical approach to distill the most meaningful biological insights. The interpretation of centrality metrics, particularly for genes with both low degree and high betweenness, required a deep understanding of network theory and its biological implications to accurately propose a regulatory role for these genes.

5. Future Work

Building upon the findings of this analysis, future work should focus on experimentally validating the key functional connections and regulatory roles that have been identified. Specifically, the regulatory function of the key mechanosensing genes TRPV4, PKD2, and PIEZO1 should be investigated in vitro using techniques such as CRISPR-Cas9 knockdown or knockout in trophoblast cell lines. Furthermore, future studies could expand the scope to include more extensive datasets from patient cohorts with placental disorders like preeclampsia and intrauterine growth restriction (IUGR). This would allow for a direct comparison of the expression levels and network dynamics of the identified pathways, ultimately strengthening the clinical relevance of our findings. A particularly novel area for future investigation is to explore the role of these identified pathways and regulatory genes in pregnancy-associated breast cancer, given the shared hormonal and signaling mechanisms between placental development and mammary gland tissue during pregnancy. This would provide a valuable link between placental health and broader maternal health outcomes.

6. Conclusion

This study provides a comprehensive molecular map of placental physiology, beginning with a detailed literature review that categorized key genes into four functional groups: mechanosensing, transporter, angiogenesis, and pregnancy hormones. A systematic bioinformatics workflow, utilizing pathway enrichment and network analysis, consolidated these genes into four primary functional clusters, which were further analyzed to visualize the significance of individual pathways and the extent of gene sharing between different functional groups. This analysis culminated in the construction of a protein-protein interaction network, which identified the most central and highly interconnected genes across all identified pathways. A final key finding emerged from the centrality analysis, which revealed that three specific mechanosensing genes—TRPV4, PKD2, and PIEZO1—act as critical regulatory hubs

within the network. Despite having a low number of direct connections, their significant control over information flow suggests a central, coordinating role for mechanosensing in orchestrating vital placental functions, including development, transport, and angiogenesis.

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