**Analysis 2: Tumor invasive process**

**Cluster\_1**

Enrichment Result of Cluster\_1 (LLM Summary)

Integrin-Mediated Cell Adhesion and Signaling

**Pathway Analysis:**

This module centers on integrin-mediated adhesion and associated signaling, emphasizing the structural and regulatory mechanisms that coordinate cell–matrix interactions and signal transduction at the plasma membrane. Enrichment of pathways such as “integrin binding,” “focal adhesion,” and “cell-matrix adhesion” highlights the central role of integrins and their associated complexes in anchoring cells to the extracellular matrix (ECM) and transmitting mechanical and biochemical cues that govern cellular behavior. The inclusion of “integrin complex,” “cell-substrate junction,” and “cell-substrate adhesion” points to the assembly of multiprotein adhesion sites, including focal adhesions, which integrate cytoskeletal connections with receptor-mediated signaling.

Integrin-mediated signaling pathways are critical for linking ECM engagement to the activation of intracellular cascades such as PI3K-Akt, FAK-Src, and MAPK, which regulate survival, migration, proliferation, and differentiation. The presence of “plasma membrane signaling receptor complex” and “protein complex involved in cell adhesion” underscores the dynamic interplay between integrins and growth factor or cytokine receptors in coordinating environmental sensing and cytoskeletal responses. Dysregulation of these adhesion and signaling systems contributes to pathological conditions including cancer metastasis, fibrosis, and impaired wound healing by altering cellular motility and matrix interactions.

Collectively, this module delineates the molecular framework of integrin-based adhesion and signaling, uniting structural connectivity and biochemical communication essential for tissue integrity, morphogenesis, and adaptive responses to the extracellular environment.

Representative module name: Integrin-Mediated Cell Adhesion and Signaling Complex.

**Gene Analysis:**

The listed genes collectively describe an extensive signaling and structural network that underlies integrin-mediated cell adhesion, cytoskeletal organization, and cross-talk with growth factor and cytokine signaling. The multitude of integrin subunits (ITGAs and ITGBs) and extracellular matrix components (COL1A1, FN1, VTN, LAMA/LAMB/LAMC chains) define the physical interface between cells and their surroundings, orchestrating adhesion, migration, and tissue integrity. Adaptor and focal adhesion proteins such as TLN1, PXN, VCL, FLNA, and ZYX link integrins to the actin cytoskeleton, supporting mechanical stability and signal transduction through FAK (PTK2), SRC, and ILK complexes. Downstream signaling is amplified through canonical kinase pathways, including PI3K/Akt (PIK3CB, PIK3R1), MAPK (BRAF, MAP2K1, MAPK1), and PKC (PRKCA, PRKCZ), integrating environmental and growth factor cues from receptors such as EGFR, ERBB2/3, PDGFRB, and TGFBR1/2. Immune-related elements (CD3D, CD4, ZAP70, VAV1) contribute to cell adhesion dynamics and receptor clustering during immune synapse formation, reflecting broader involvement in immunological communication. The participation of ECM regulators and proteases such as MMP14 and TIMP1, along with regulators of small GTPase signaling (RAC1, CDC42, RHOA, ROCK1), highlights a reciprocal relationship between matrix remodeling and motility. This integrin-centered system not only controls cell shape and movement but also couples external mechanical and biochemical signals to gene expression and survival pathways. The most noteworthy genes—such as ITGB1, PTK2, SRC, and FN1—represent critical nodes coordinating adhesion mechanics with signal transduction, central to processes including angiogenesis, wound repair, and cancer metastasis. Collectively, this gene set defines a comprehensive cell–ECM signaling axis that integrates structural anchorage with dynamic cellular responses.

**Cluster\_2**

Enrichment Result of Cluster\_2 (LLM Summary)

Immune Cell Activation and Adhesion Signaling

Pathway Analysis:

This module integrates signaling and adhesion processes that coordinate immune cell activation, communication, and effector function. The enrichment of pathways such as “immune response-activating cell surface receptor signaling pathway,” “antigen receptor-mediated signaling pathway,” and “regulation of T cell activation” underscores the central role of receptor-mediated signaling in orchestrating adaptive immune responses. These pathways involve activation through T cell and B cell antigen receptors and co-stimulatory molecules, enabling cytokine production, proliferation, and differentiation. Concurrently, terms like “leukocyte cell-cell adhesion,” “positive regulation of cell-cell adhesion,” and “positive regulation of leukocyte cell-cell adhesion” indicate the formation and strengthening of immunological synapses and intercellular junctions that facilitate antigen recognition and coordinated immune signaling.

The inclusion of “positive regulation of cell development” and “positive regulation of cell activation” reflects the engagement of intracellular cascades that govern immune cell maturation, activation thresholds, and lineage-specific differentiation. Adhesion receptors such as integrins and selectins, together with co-receptors like CD28 or ICAM family members, are likely key mediators of these processes, linking cell adhesion to downstream activation via pathways such as NF-κB and MAPK. The combined regulation of adhesion and receptor signaling promotes immune cell recruitment, activation, and coordination required for effective pathogen clearance and immunological memory.

Collectively, this module represents a functional framework coupling adhesion dynamics with signaling pathways that regulate immune cell activation and communication.

Representative module name: Immune Cell Adhesion and Activation Signaling Network.

**Gene Analysis:**

The genes listed collectively form a robust immune signaling and adhesion network that coordinates activation, communication, and effector function of immune cells. Central immune signaling components such as CD3D, CD3E, CD3G, CD247, LAT, LCP2, LCK, ZAP70, and VAV1 constitute the T cell receptor (TCR) complex and its proximal signaling cascade, driving downstream pathways including MAPK (MAPK1, MAP2K1/2), PI3K-Akt (PIK3CA, AKT1, IRS2), and PKC (PRKCA, PRKCB, PRKCQ) to promote T cell activation, cytokine secretion, and clonal expansion. Parallel engagement of JAK–STAT and Ras/Raf cascades (JAK1-3, BRAF, KRAS, HRAS) mediates responses to cytokines and growth factors such as IL2, IFNG, TGFB1, VEGFA, and FGF2, reflecting a close coupling between immune activation and tissue remodeling. Integrins and adhesion molecules (ITGAM, ITGB2, ITGAL, ITGB1, FN1) act with focal adhesion kinases (PTK2, PTK2B, SRC) to anchor immune cells to the extracellular matrix and other cells, coordinating immunological synapse formation and migration. Laminins (LAMA/LAMB/LAMC chains) and ECM interactors like DAG1 and SDC4 highlight structural cross-talk between immune and stromal compartments. Regulatory molecules such as CTNNB1, SMURF1, and TGFB1 modulate immune cell growth, migration, and tolerance, ensuring controlled activation to prevent excessive inflammation. Matrix metalloproteinases (MMP8, MMP14) and chemokines (CXCL13, PF4) further shape immune cell recruitment and tissue infiltration. Collectively, this gene set integrates receptor signaling, kinase cascades, and adhesion-mediated coordination, forming the molecular foundation of immune synapse formation, leukocyte trafficking, and inflammatory regulation. Key players such as ZAP70, LCK, PI3K, and integrins exemplify this cross-talk between adhesion and activation essential for effective immune responses.

**Cluster\_3**

Enrichment Result of Cluster\_3 (LLM Summary)

Extracellular Matrix Remodeling and Chemotactic Signaling

**Pathway Analysis:**

This module represents a coordinated network of signaling, extracellular matrix organization, and cell motility processes that collectively regulate tissue remodeling and immune cell migration. Enrichment of “chemotaxis,” “taxis,” and “leukocyte migration” points to directed cell movement driven by chemical cues, particularly in immune and inflammatory contexts. Pathways such as “extracellular matrix organization” and “collagen-containing extracellular matrix” indicate structural remodeling of the extracellular environment necessary for cell trafficking, adhesion, and repair. The presence of “positive regulation of protein phosphorylation,” “positive regulation of MAPK cascade,” and “phosphatidylinositol 3-kinase/protein kinase B signal transduction” underscores the role of intracellular signaling networks that translate extracellular stimuli into cytoskeletal reorganization and motile responses via MAPK and PI3K/Akt pathways.

“External encapsulating structure organization” further suggests contributions to barrier formation or matrix-mediated tissue integrity, linking cellular signaling to biomechanical properties of tissues undergoing active remodeling. These integrated mechanisms support both homeostatic and pathological processes, including immune surveillance, wound healing, and tumor invasion, where modulation of matrix structure and motility signaling determines cellular positioning and interaction with the microenvironment.

Collectively, this module illustrates the interplay between extracellular matrix dynamics, chemotactic signaling, and kinase-mediated regulation of cell movement and tissue architecture.

Representative module name: Extracellular Matrix Remodeling and Chemotactic Signaling Network.

**Gene Analysis:**

The gene set represents a multifaceted signaling network linking extracellular matrix remodeling, chemotaxis, and intracellular kinase cascades that regulate cell migration, immune activation, and tissue repair. The abundance of collagen genes (COL1A1–COL7A1, COL11A1/2, COL18A1) and laminin subunits (LAMA1–LAMA5, LAMB1–LAMB3, LAMC1–LAMC3) reflects dynamic extracellular matrix organization essential for structural integrity, mechanotransduction, and migration guidance. Matrix metalloproteinases (MMP1–MMP17, MMP24) and their inhibitors (TIMP1, TIMP2) mediate controlled ECM degradation, enabling cell motility and tissue remodeling during inflammation or development. Integrins and their adapters (ITGA and ITGB families, ILK, FN1, DAG1, PTK2) form focal adhesion complexes that link cytoskeletal elements to signaling cascades driven by PI3K-Akt (PIK3CA, AKT1), MAPK (BRAF, MAPK1/3), and PKC (PRKCA, PRKCQ), coordinating motility and adhesion responses. Chemokines (CXCL9–CXCL13) and their receptor CXCR3 direct immune cell chemotaxis, while growth factors and receptors such as VEGFA/VEGFC, HGF/MET, EGF/EGFR, and PDGFRs regulate angiogenesis and repair. Small GTPases (RAC1, RHOA, CDC42) and cytoskeletal regulators (CTNNB1, IQGAP1, FLNA) provide mechanistic control over shape and migration. Additionally, immune effectors including IFNG, CD4, ZAP70, and SYK suggest integration of immune and stromal signaling during inflammatory remodeling. Altogether, this module defines an interconnected system where ECM turnover, chemotactic signaling, and kinase-mediated control converge to guide immune cell movement, vascular remodeling, and tissue adaptation. The most influential components—integrin–ECM interactions, PI3K/MAPK signaling, and MMP activity—collectively underscore how extracellular and intracellular networks synchronize motility, adhesion, and repair responses across immune and structural contexts.

**Cluster\_4**

Enrichment Result of Cluster\_4 (LLM Summary)

Growth Factor and Hormone Receptor Signaling

**Pathway Analysis:**

This module encompasses signaling pathways governed by peptide hormones and growth factors, highlighting coordinated regulation of cellular proliferation, differentiation, and metabolic adaptation. The enrichment of “epidermal growth factor receptor signaling pathway,” “ERBB signaling pathway,” and “vascular endothelial growth factor receptor signaling pathway” points to activation of receptor tyrosine kinase (RTK) cascades that drive cell growth, angiogenesis, and tissue maintenance. The inclusion of “insulin receptor signaling pathway,” “insulin-like growth factor receptor signaling pathway,” and related responses to insulin or peptide hormones underscores the integration of metabolic and mitogenic cues that modulate glucose uptake, anabolism, and survival.

“Collagen-activated signaling pathway” connects extracellular matrix dynamics to receptor-mediated signaling, illustrating how integrins and receptor kinases cooperatively regulate cell behavior in response to structural cues. These pathways are known to converge on downstream signaling modules, including PI3K/Akt and MAPK cascades, which fine-tune cellular responses based on environmental and hormonal input. The presence of both systemic (hormone-driven) and local (matrix- or growth factor–dependent) pathways suggests a broader biological theme of coordinating metabolic status with proliferative and structural remodeling demands.

Dysregulation of these signaling networks contributes to pathological processes such as cancer progression, insulin resistance, and aberrant vascular growth, emphasizing their importance in maintaining cellular and tissue homeostasis.

Representative module name: Growth Factor and Hormone Receptor Signaling Network.

**Gene Analysis:**

The genes in this module collectively form an extensive receptor tyrosine kinase (RTK)–centered signaling network that integrates growth factor, hormone, and extracellular matrix cues to regulate proliferation, differentiation, and metabolism. Central signaling nodes such as EGFR, ERBB2/3/4, IGF1R, INSR, MET, PDGFRA/B, and KDR mediate responses to peptide ligands including EGF, IGF1, insulin, and VEGFA/C/D, initiating downstream cascades such as PI3K-Akt (PIK3CA, AKT1, IRS1/2) and MAPK (BRAF, RAF1, MAP2K1, MAPK1/3) to coordinate growth, survival, and nutrient utilization. Collagens (COL1A1, COL4A1–6, COL6A1) and integrins (ITGA1, ITGA5, ITGB3) link extracellular matrix composition to receptor signaling, while adaptor and scaffolding proteins including GRB2, SHC1, IQGAP1, GAB1, and PXN enable efficient transmission of phosphorylation-dependent signals across the plasma membrane. Additional regulators such as PRKCA/CB, SRC, PTK2/2B, and STAT1 integrate mitogenic and cytokine pathways, while JAK1–3 and VAV1 bridge metabolic and immune signaling. The inclusion of TGFB1 and TNFSF10 highlights cross-regulatory loops connecting growth signaling and apoptotic or differentiative cues. Matrix remodeling enzymes (MMP9, CTSK, TIMP1) and vascular regulators (FLT4, VEGFs) further reflect coupling between proliferation and tissue structural adaptation. Together, this gene network exemplifies a hierarchical coordination of growth factor–driven and ECM-mediated signals that support development, angiogenesis, and tissue maintenance. The most noteworthy genes—EGFR, IGF1R, AKT1, and MAPK1—represent key convergence points linking extracellular cues to intracellular growth and survival pathways, whose dysregulation underlies oncogenesis, insulin resistance, and aberrant vascular remodeling.

**Cluster\_5**

Enrichment Result of Cluster\_5 (LLM Summary)

Angiogenesis and Vascular–Epithelial Growth Regulation

**Pathway Analysis:**

This module integrates processes governing endothelial and epithelial cell proliferation, migration, and vascular development, defining a coordinated program of angiogenesis and tissue growth regulation. Core pathways such as “endothelial cell migration,” “regulation of angiogenesis,” and “positive regulation of vasculature development” highlight mechanisms essential for new blood vessel formation and remodeling. These processes rely on the activation of endothelial motility, cytoskeletal rearrangement, and cell–matrix interactions, mediated by signaling molecules including VEGF, FGF, and angiopoietins. The enrichment of “epithelial cell proliferation” and its regulatory terms indicates parallel control of epithelial expansion, which often occurs in concert with vascular development to support tissue regeneration and morphogenesis.

“Regulation of endothelial cell migration” and “positive regulation of angiogenesis” underscore fine-tuned control by proangiogenic cues that stimulate endothelial sprouting and lumen formation, processes critical in wound healing and development. Likewise, “regulation of vasculature development” encapsulates both the initiation and stabilization phases of vascular network maturation, integrating perfusion demands with tissue oxygen and nutrient requirements. These mechanisms are also subject to cross-talk with inflammatory and metabolic signals that influence vessel growth and remodeling dynamics.

Collectively, the pathways describe a biological module centered on vascular and epithelial regeneration, capturing the interplay between proliferative expansion and controlled angiogenic signaling that underpins tissue repair, organogenesis, and pathological neovascularization.

Representative module name: Angiogenesis and Vascular–Epithelial Growth Regulation Network.

**Gene Analysis:**

The listed genes collectively define a molecular network that coordinates angiogenesis, epithelial proliferation, and vascular remodeling through tightly regulated growth factor, integrin, and kinase signaling. Core angiogenic mediators such as VEGFA, VEGFC, PDGFB, FGF2, and HGF, acting through receptors including KDR, FLT4, MET, EGFR, and ERBB2, drive endothelial cell proliferation, migration, and vessel maturation. Downstream signaling cascades—PI3K-Akt (PIK3CA, AKT1, IRS2), MAPK (RAF1, MAP2K1/2, MAPK1), and PKC (PRKCA, PRKCB)—link extracellular cues to cytoskeletal rearrangements and proliferation control. Integrins (ITGA4, ITGA5, ITGB1–3, ITGB8) and focal adhesion components (PXN, PTK2, PTK2B) integrate mechanical and biochemical inputs from the extracellular matrix (COL4A2, COL4A3, LAMA5, LAMB1, LAMC1, HSPG2) to modulate endothelial and epithelial cell adhesion and motility. Rho GTPases (RHOA, RAC1, CDC42) and their regulators guide cytoskeletal dynamics essential for sprouting and lumen formation, while TGFβ pathway components (TGFB1, TGFBR1, TGFBR2) and ESR1 provide cross-regulatory control between morphogenetic and proliferative programs. Additional modulators like MMP14 and PLG remodel the extracellular environment, enabling vessel invasion and stabilization. Chemokines (CXCL10, CXCL13, CCL11) and their receptor CXCR3 link angiogenic growth to inflammatory and immune responses. Altogether, this gene set represents a highly integrated signaling and structural framework that drives endothelial and epithelial growth, tissue regeneration, and tumor vascularization. Notably, VEGFA, AKT1, and TGFB1 emerge as key central regulators coupling angiogenic signaling with growth and matrix remodeling processes fundamental to development and repair.

**Cluster\_6**

Enrichment Result of Cluster\_6 (LLM Summary)

Myeloid Cell Activation and Membrane Signaling Regulation

**Pathway Analysis:**

This module centers on myeloid leukocyte activation and membrane-associated regulatory processes that coordinate immune signaling and protein trafficking. The presence of “myeloid leukocyte activation” underscores the involvement of macrophages, neutrophils, and related immune cells in initiating inflammatory responses, phagocytosis, and cytokine release. Terms such as “cytoplasmic side of plasma membrane,” “extrinsic component of plasma membrane,” and “extrinsic component of cytoplasmic side of plasma membrane” denote the localization of signaling and adaptor proteins that mediate receptor-dependent signal transduction and immunomodulatory activity.

The enrichment of “phosphatase binding” and “protein phosphatase binding” suggests dynamic balance of phosphorylation and dephosphorylation events that shape immune receptor signaling cascades, including those downstream of toll-like receptors, Fc receptors, and integrins. The inclusion of pathways like “positive regulation of protein transport,” “positive regulation of protein localization,” and “positive regulation of establishment of protein localization” indicates active trafficking and recruitment of signaling complexes to the plasma membrane, essential for rapid immune activation and cytoskeletal reorganization.

Together, these processes reflect an integrated network through which myeloid cells mobilize signaling components and receptor-associated proteins to the membrane to ensure efficient immune surveillance and response. Dysregulation of this system may contribute to inadequate pathogen clearance or chronic inflammation.

Collectively, the module highlights the interface between signal transduction, membrane compartmentalization, and immune effector recruitment in myeloid cell activation.

Representative module name: Myeloid Cell Activation and Membrane-Associated Signaling Regulation.

**Gene Analysis:**

The listed genes form a complex network regulating myeloid cell activation, membrane-associated signaling, and immune-mediated communication. Core signaling nodes such as CSF1, CSF1R, and CSF2 drive macrophage proliferation, differentiation, and activation, while FCER1A, FCER1G, and SYK mediate Fc receptor–dependent responses central to phagocytosis and cytokine release. GTPases including RHOA, CDC42, and ARF6 orchestrate cytoskeletal rearrangements and vesicular trafficking that facilitate receptor localization and immune synapse formation. Integrins (ITGAM, ITGB1, ITGB2, ITGB6, ITGB8) and associated scaffolding proteins such as FN1, FLNA, and PXN link membrane adhesion with intracellular signaling through kinases like PTK2 (FAK) and SRC, coordinating migration and immune effector functions. Downstream signaling cascades including PI3K–Akt (PIK3CA/B/C/G, AKT1, PTEN) and MAPK (MAP2K2, MAPK1, MAPK3) connect receptor activation to cell survival, cytokine synthesis, and phagocytic capacity. The JAK–STAT axis (JAK1–3, STAT1) and TGFB1/TGFBR2 pathways further integrate inflammatory and regulatory cues, balancing activation with immune resolution. Membrane organization is underpinned by cadherins (CDH1, CDH2) and catenins (CTNNA1, CTNNB1, CTNND1), ensuring stable intercellular interactions during immune responses. Growth factor signals from EGFR, ERBB2/4, MET, and VEGFA/VEGFC provide cross-talk between immune cells and the tissue microenvironment, linking inflammation to regeneration and angiogenesis. Collectively, this gene set defines a multifaceted regulatory system coupling receptor-mediated signaling, membrane trafficking, and adhesion dynamics to myeloid cell activation and intercellular communication. Key molecules such as CSF1R, SYK, SRC, and PI3K serve as pivotal hubs ensuring efficient immune coordination and tissue homeostasis.

**Cluster\_7**

Enrichment Result of Cluster\_7 (LLM Summary)

Phosphoinositide Kinase and Growth Factor Signaling

**Pathway Analysis:**

This module captures a signaling network centered on phosphatidylinositol lipid metabolism and kinase-mediated phosphorylation, which collectively regulate growth factor and insulin signaling pathways. Enrichment of “lipid kinase activity,” “phosphatidylinositol biosynthetic process,” and “phosphatidylinositol phosphate biosynthetic process” highlights the generation of phosphoinositides—key signaling lipids that serve as membrane-bound second messengers controlling cell growth, metabolism, and vesicular trafficking. The inclusion of “phosphatidylinositol-mediated signaling” and “phosphatidylinositol kinase activity” underscores the central roles of PI3K and related kinases in activating downstream effectors such as Akt, which mediate metabolic adaptation, protein synthesis, and cell survival.

Pathways including “peptidyl-serine phosphorylation” and “response to epidermal growth factor” further connect lipid signaling to broader phosphorylation networks and receptor tyrosine kinase signaling, demonstrating points of crosstalk between phosphoinositide metabolism and EGFR pathway activation. The regulation of insulin receptor signaling, along with “response to insulin” and “regulation of cellular response to insulin stimulus,” emphasizes the role of this network in metabolic control, glucose uptake, and cellular energy homeostasis. These processes are critical in maintaining physiological metabolic responses but, when dysregulated, contribute to insulin resistance, metabolic syndrome, and cancer.

Collectively, this module represents a tightly regulated signaling axis that integrates phosphoinositide metabolism with growth factor and insulin-mediated phosphorylation cascades to coordinate cellular metabolism, proliferation, and survival.

Representative module name: Phosphoinositide Kinase and Growth Factor Signaling Network.

**Gene Analysis:**

The genes listed constitute a core regulatory network governing phosphoinositide lipid metabolism, phosphorylation signaling, and receptor-mediated control of cellular growth, metabolism, and survival. Central to this system are phosphoinositide kinases (PI4KA, PI4KB, PIP5K1A/B/C, PIK3CA/B/C/G, PIK3R1, PIK3R6), which generate key signaling lipids that recruit and activate kinases such as AKT1 and RPS6KB1, linking membrane signaling to metabolic control and protein synthesis. Growth factor and receptor tyrosine kinase signaling via EGFR, ERBB2, ERBB4, PDGFA/B, and their adaptors (NCK1, IQGAP1) activates the MAPK and PI3K/Akt cascades, further driving proliferation and survival. Parallel serine/threonine kinases—including PRKCB, PRKCQ, and PRKCZ—support phosphorylation-dependent crosstalk between these pathways. Negative regulators such as PTEN, PTPN1, and PTPN11 provide feedback to fine-tune signal intensity and maintain cellular homeostasis. Downstream mediators MAPK1, MAPK3, BRAF, and RAF1 connect phosphatidylinositol signaling to transcriptional outputs that control cell cycle progression, differentiation, and stress responses under the influence of hormones including insulin and growth factors. Structural and matrix-related components such as COL1A1 and DMD, along with cytoskeletal regulators like ROCK1, integrate signaling with cellular architecture and motility, suggesting a broader role in tissue organization. The involvement of TGFBR1 and IFNG highlights points of communication with inflammatory and developmental pathways. Altogether, this network coordinates growth factor and insulin responses with lipid-based signaling and phosphorylation dynamics, forming a fundamental axis of metabolic regulation, signal transduction, and cytoskeletal remodeling. Key nodes such as PIK3CA, AKT1, and PTEN represent central modulators of metabolic homeostasis and oncogenic potential.

**Cluster\_8**

Enrichment Result of Cluster\_8 (LLM Summary)

Insulin and IGF Signaling in Glucose and Glycogen Metabolism

**Pathway Analysis:**

This module centers on insulin and insulin-like growth factor (IGF) signaling in the regulation of glucose and glycogen metabolism, reflecting coordinated control of cellular energy storage and nutrient utilization. Enrichment of “insulin receptor binding” and “insulin-like growth factor receptor binding” underscores receptor-mediated pathways that activate glucose uptake and metabolic enzyme regulation, primarily through downstream cascades such as PI3K/Akt signaling. Pathways including “positive regulation of D-glucose transmembrane transport” and “regulation of D-glucose import” highlight the modulation of glucose transporter activity, ensuring adequate glucose availability for glycolysis and biosynthetic processes.

The inclusion of “regulation of polysaccharide metabolic process,” “positive regulation of glycogen biosynthetic process,” and “positive regulation of glycogen metabolic process” emphasizes the balance between glycogen synthesis and breakdown, reflecting insulin’s central anabolic role in promoting storage of carbohydrates under nutrient-rich conditions. These pathways link receptor activation with enzymatic control of glucose and glycogen homeostasis, involving regulatory proteins such as glycogen synthase kinase 3 (GSK3) and glucose transporters (GLUTs). The interplay between insulin and IGF signaling pathways ensures integration of metabolic cues with growth and proliferation, maintaining tissue energy supply and responding to hormonal fluctuations.

Dysregulation of these processes contributes to metabolic disorders such as insulin resistance, type 2 diabetes, and associated cardiovascular complications.

Together, this module defines a core metabolic signaling axis coupling insulin/IGF receptor activity with glucose transport and glycogen metabolism.

Representative module name: Insulin and IGF Signaling in Glucose and Glycogen Metabolism.

**Gene Analysis:**

The genes in this set form a tightly interconnected signaling network that governs insulin and insulin-like growth factor (IGF)–mediated regulation of glucose and glycogen metabolism, linking nutrient sensing with cellular growth and energy homeostasis. Central receptors INSR and IGF1R, together with their ligands INS and IGF1, initiate cascades mediated by IRS1, IRS2, and SHC1 that activate PI3K–Akt (PIK3R1, AKT1) and MAPK (BRAF, RPS6KB1) pathways. These downstream effectors coordinate glucose uptake, glycogen synthesis, and anabolic metabolism by promoting glucose transporter activity and regulating glycogen synthase and other metabolic enzymes. Regulatory phosphatases PTPN1 and PTPN11 fine-tune tyrosine phosphorylation, ensuring appropriate signal duration and intensity, while adaptor proteins YWHAG and YWHAH stabilize active kinases and maintain phosphorylation-dependent signaling complexes. Cross-talk with PRKCB, SRC, and TGFB1 integrates insulin signaling with broader cellular functions such as proliferation, differentiation, and stress responses, reflecting insulin’s dual role in metabolic control and growth regulation. Growth factors such as EGF and PDGFB expand this network’s influence by engaging receptor tyrosine kinases that converge on shared PI3K–Akt and MAPK nodes. Dysregulation within this axis leads to impaired insulin sensitivity, aberrant glucose utilization, and metabolic or proliferative disorders. Collectively, these genes exemplify a core signaling circuit that coordinates hormonal and growth factor inputs to regulate energy balance, biosynthesis, and cellular adaptation, with AKT1, INSR, and IRS1 serving as key mediators linking receptor activation to metabolic output and survival pathways.

**Cluster\_9**

Enrichment Result of Cluster\_9 (LLM Summary)

Epithelial–Mesenchymal Differentiation and Morphogenesis Regulation

**Pathway Analysis:**

This module integrates developmental and signaling processes that regulate epithelial, connective tissue, and neuronal cell fate, highlighting a network underlying tissue morphogenesis and differentiation. Pathways such as “regulation of epithelial cell differentiation” and “regulation of morphogenesis of an epithelium” emphasize control of epithelial development and organization, processes fundamental to organ formation, barrier integrity, and regeneration. The inclusion of “cartilage development” and “connective tissue development” indicates parallel regulation of mesenchymal and structural tissue differentiation, underscoring coordination among germ-layer–derived lineages during morphogenesis.

Processes like “odontogenesis” represent specialized developmental programs that exemplify epithelial–mesenchymal interactions crucial for organogenesis, such as tooth development, where coordinated signaling from fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), and Wnts direct both epithelial and mesenchymal cell differentiation. The enrichment of “regulation of neuron apoptotic process” and “negative regulation of neuron apoptotic process” denotes control of neuronal survival and maintenance, possibly linking morphogen and trophic factor pathways to nervous system patterning and homeostasis. “Chemoattractant activity” and “positive chemotaxis” further suggest guidance mechanisms that coordinate cell migration and tissue architecture during development and repair.

Together, these pathways reflect a dynamic interplay between differentiation, survival signaling, and cell motility that drives organ-specific morphogenesis and homeostasis. Disruption of these processes can contribute to developmental anomalies, fibrosis, or neurodegenerative conditions.

Representative module name: Epithelial–Mesenchymal Differentiation and Morphogenesis Regulation Network.

**Gene Analysis:**

The gene set represents an integrated morphogenetic and signaling network that governs epithelial–mesenchymal differentiation, tissue remodeling, and organ development. Structural components such as collagens (COL1A1–COL6A3) and laminins (LAMA5, LAMB1) form the extracellular matrix framework supporting epithelial integrity and mesenchymal differentiation, while integrins (ITGA1, ITGA2, ITGB3, ITGB6, ITGB8) and focal adhesion regulators (VCL, PTK2B, SRC) mediate adhesion and mechanotransduction. Growth factors and receptors, including TGFB1/TGFBR1/2, PDGFA/B-PDGFRs, FGF2, HGF, and MET, orchestrate cell proliferation, differentiation, and migration essential for tissue morphogenesis and regeneration. Downstream effectors in PI3K/Akt (PIK3CA) and MAPK (BRAF, KRAS, MAPK3) signaling channels integrate developmental cues with cytoskeletal regulation governed by CDC42, RHOA, and ROCK1. The inclusion of NGF, GDNF, and NTRK1 reflects trophic support and neuroepithelial cross-talk critical for neuronal survival and patterning, while aquaporins (AQP3, AQP5) mark epithelial functional maturation. ECM remodeling enzymes (MMP2, MMP9, MMP13) and their inhibitor TIMP1 fine-tune matrix turnover during morphogenesis, angiogenesis, and repair. Cross-communication among pathways mediated by TGFB1, WNT5A, and S1PR receptors ensures coordination of differentiation, migration, and morphogenetic polarity. Additionally, VEGFA, VEGFC, and KDR emphasize vascular integration with epithelial and connective tissue development. Collectively, this gene network links extracellular matrix organization, morphogen signaling, and cell–matrix interactions that define tissue growth, organogenesis, and repair. The most pivotal players—TGFB1, PDGF, and integrin-associated kinases—serve as nodal integrators driving epithelial–mesenchymal coordination and tissue patterning across developmental and regenerative contexts.

**Cluster\_10**

Enrichment Result of Cluster\_10 (LLM Summary)

TGF-β Signaling in Cardiac and Muscle Development

**Pathway Analysis:**

This module is characterized by pathways involved in cardiac and muscle tissue development, regulated primarily through transforming growth factor beta (TGF-β) signaling. Terms such as “heart morphogenesis,” “cardiac muscle tissue development,” and “trabecula morphogenesis” highlight its role in shaping heart structure, chamber formation, and muscle fiber organization during embryogenesis. The enrichment of “muscle organ development,” “striated muscle tissue development,” and “muscle tissue development” indicates broader regulation of myogenesis, encompassing differentiation of cardiac and skeletal muscle progenitors. Central to this network, the “TGF-β receptor signaling pathway” and its downstream responses mediate morphogenetic and proliferative cues, influencing cardiomyocyte specification, extracellular matrix remodeling, and vascular patterning.

The inclusion of “response to transforming growth factor beta” and “cellular response to transforming growth factor beta stimulus” implies an active interplay between developmental signaling and mechanical or biochemical context, consistent with the known roles of TGF-β in modulating epithelial–mesenchymal transition, fibrosis, and tissue integrity. Dysregulation of these processes contributes to congenital heart defects, cardiomyopathies, and maladaptive remodeling under stress conditions.

Collectively, this module represents a developmental signaling framework coupling TGF-β–mediated pathways with cardiac and muscle morphogenesis, integrating transcriptional, structural, and environmental signals required for proper organogenesis.

Representative module name: TGF-β–Mediated Cardiac and Muscle Development Network.

**Gene Analysis:**

The included genes form a coordinated signaling and structural network central to cardiac and muscle tissue development, driven predominantly by TGF-β and growth factor–mediated pathways. Core components such as TGFB1, TGFBR1, and TGFBR2 activate downstream MAPK, RHOA/ROCK1, and SMURF1 regulatory cascades that control myogenesis, extracellular matrix remodeling, and cell differentiation. Structural and matrix genes including COL1A1, COL3A1, COL5A1, and COL6A3 provide the connective framework essential for tissue integrity and mechanical resilience, while integrins (ITGA7, ITGA11, ITGB1, ITGB5, and ITGB8) and cytoskeletal regulators such as FLNA, PXN, and ZYX couple extracellular cues to intracellular signaling via focal adhesion and kinase-mediated communication. Growth factor signaling nodes, including FGF2, VEGFA, PDGFRA/B, IGF1, and their receptors, interact closely with MAPK3 and RPS6KB1 pathways to coordinate cell proliferation, differentiation, and vascularization during cardiac and muscle morphogenesis. ERBB3/4, WNT5A, and CTNNB1 highlight cross-talk with developmental signaling systems that pattern cardiac structure and muscle fiber formation. Mechanical and calcium-dependent mediators such as DAG1, DMD, and MYL2 further integrate structural regulation with contractile maturation, critical for cardiac function. Notably, ENG (endoglin) and JAK2 reinforce the modulation of endothelial and vascular components that accompany myocardial development. Collectively, this gene set defines an interconnected framework linking extracellular matrix synthesis, integrin and receptor kinase signaling, and TGF-β regulatory mechanisms to orchestrate cardiac and skeletal muscle maturation. The most noteworthy genes—TGFB1, ITGB1, PDGFRB, and VEGFA—serve as principal regulators integrating growth, remodeling, and angiogenic cues essential for heart development and repair.