**Analysis 3: in development (Club cell repairing)**

**Cluster\_1**

Enrichment Result of Cluster\_1 (LLM Summary)

Synaptic and Cytoplasmic Protein Translation in Neural Function

**Pathway Analysis:**

This module is characterized by the enrichment of pathways associated with translation and ribosomal function, particularly within cytoplasmic and synaptic compartments. The dominant presence of terms such as “cytoplasmic translation,” “ribosome,” and “structural constituent of ribosome” indicates a core emphasis on the machinery responsible for protein synthesis. Sub-pathways specifying “cytosolic ribosome” and its small subunit further pinpoint active engagement of ribosomal components in mRNA decoding and peptide elongation, reflecting elevated translational capacity within the cell soma and neuronal processes.

Notably, the inclusion of “translation at presynapse,” “translation at postsynapse,” and “translation at synapse” suggests that these translational activities extend to local protein synthesis in neurons. This localized translation is critical for synaptic plasticity, memory formation, and rapid response to synaptic signaling, as supported by studies showing ribosome localization and activity at synaptic sites. The appearance of the “myelin sheath” term may reflect translational demands of oligodendrocytes or myelinated axons, where local protein synthesis supports membrane maintenance and metabolic coupling with neurons.

Collectively, these pathways delineate a functional module centered on translational regulation and synapse-associated protein production, implicating it in neural communication, adaptability, and maintenance of neuron–glia interactions.

Representative module name: Synaptic and Cytoplasmic Translation Machinery.

**Gene Analysis:**

The listed genes collectively represent a core network underlying protein synthesis, cytoskeletal dynamics, and cellular stress adaptation, particularly within neurons and glia. Numerous ribosomal proteins (RPL and RPS family members) and translation factors such as EIF4A1, EIF4A2, and SLBP highlight a strong enrichment in translational machinery, consistent with elevated protein synthesis and ribosome biogenesis at both cytoplasmic and synaptic sites. Chaperone and folding-related genes, including HSP90AA1, HSPA5, HSPA8, HSPD1, CCT2, CCT5, and TCP1, indicate active protein quality control, ensuring proper folding of nascent polypeptides and structural proteins critical for synaptic maintenance. Metabolic enzymes such as GAPDH, PKM, LDHB, and PHGDH, together with mitochondrial components like CYCS, MRPL12, MRPL18, and SLC25A4, suggest coupling between translational activity and energy metabolism to meet the high bioenergetic demands of neuronal signaling. Actin cytoskeletal genes (ACTB, ACTG1, TUBA1B, TUBB4B, GSN) and regulators such as ARF6 and ANXA2 support cytoskeletal remodeling essential for axon guidance and synaptic plasticity. Calcium-binding and signaling proteins (CALM2, CALR) further link translational control with synaptic responsiveness. Notably, RBM3, an RNA-binding protein induced by neuronal activity and cold stress, suggests adaptive translational reprogramming contributing to neuroprotection and plasticity. Altogether, this gene set reflects a biologically coherent module centered on ribosomal translation, chaperone-supported protein folding, and cytoskeletal coordination, underpinning localized protein synthesis and metabolic adaptability in neurons. The most noteworthy features are the integration of energy metabolism with translational control and their implication in synaptic function and plasticity.

**Cluster\_2**

Enrichment Result of Cluster\_2 (LLM Summary)

Chaperone-Mediated Protein Folding and Proteostasis Regulation

**Pathway Analysis:**

This module centers on protein homeostasis, specifically ATP-dependent chaperone-mediated folding processes essential for maintaining proteome stability and functional integrity. The enrichment of terms related to the chaperonin-containing T-complex (CCT or TRiC) and “de novo protein folding” highlights the involvement of molecular chaperones in the co- and post-translational folding of nascent polypeptides. These complexes ensure efficient folding of cytoskeletal proteins, actins, and tubulins, as well as other structurally complex substrates, thereby supporting cellular architecture and signaling fidelity.

The presence of “unfolded protein binding” and “chaperone-mediated protein folding” emphasizes cellular mechanisms for preventing misfolding and aggregation, particularly under stress conditions that challenge proteostasis. ATP-dependent chaperones, such as HSP60, HSP70, and the CCT complex, contribute to energy-driven folding cycles that enhance substrate specificity and promote refolding of damaged proteins.

Interestingly, the inclusion of pathways regulating “protein localization to telomere” may indicate a connection between protein folding and chromatin-associated processes. Molecular chaperones have been shown to influence telomere maintenance indirectly by stabilizing telomere-associated proteins or ensuring proper assembly of telomeric complexes, thereby linking proteostasis with genomic stability.

Collectively, these pathways denote a tightly coordinated network of molecular chaperones that safeguard protein folding, prevent proteotoxic stress, and potentially modulate nuclear processes critical for cellular longevity and genome maintenance.

Representative module name: Chaperone-Mediated Protein Folding and Proteostasis Maintenance.

**Gene Analysis:**

The listed genes collectively form a network dedicated to protein homeostasis, emphasizing ATP-dependent chaperone-mediated folding, assembly, and quality control of nascent and stress-denatured proteins. Central to this module are subunits of the chaperonin-containing T-complex (CCT2, CCT5, CCT7, CCT8, TCP1), which cooperate in folding cytoskeletal proteins such as actin and tubulin, maintaining structural integrity and signal transduction. Key molecular chaperones, including HSP90AA1, HSP90B1, HSPA5, HSPA8, HSPD1, and HSPE1, collectively represent cytosolic, endoplasmic reticulum, and mitochondrial folding systems that preserve proteome stability under both normal and stress conditions. CALR and SDF2L1 highlight the ER-localized quality control arm, where they assist in glycoprotein folding and calcium-dependent signaling, linking proteostasis to cellular stress responses. CLU acts as an extracellular or secretory chaperone, preventing aggregation of misfolded proteins, especially during oxidative or inflammatory stress. NPM1 and DNAJC9 contribute nuclear chaperone functions, coordinating nucleolar protein assembly, histone dynamics, and ribosome biogenesis, thereby connecting protein folding machinery to genomic and translational regulation. CD74 illustrates the immunological dimension of this network, as it regulates trafficking and stability of MHC class II molecules, integrating chaperone activity with antigen presentation. Together, these genes form a highly conserved, multi-compartmental proteostasis system that links molecular folding, stress adaptation, and immune signaling. The most noteworthy feature is the integration of cytosolic, organellar, and secretory chaperones into a unified quality-control network that safeguards cellular stability, ensuring resilience against proteotoxic and environmental stress.

**Cluster\_3**

Enrichment Result of Cluster\_3 (LLM Summary)

Mitotic Chromosome Segregation and Spindle Dynamics

**Pathway Analysis:**

This module is defined by pathways associated with mitotic chromosome dynamics and spindle apparatus regulation, emphasizing precise control of nuclear division and genome integrity. Enrichment of terms such as “mitotic nuclear division,” “sister chromatid segregation,” and “chromosome separation” indicates coordination of events governing equal partitioning of replicated chromosomes during cell division. Processes including “attachment of spindle microtubules to kinetochore” and its regulation highlight the essential role of kinetochore–microtubule interactions in ensuring bipolar tension and accurate chromosome alignment at the metaphase plate.

The inclusion of “mitotic spindle elongation” and “regulation of chromosome organization” reflects mechanisms facilitating spindle stability and elongation, critical for anaphase progression and cytokinetic fidelity. Misregulation of these processes can lead to aneuploidy, a hallmark of many cancers and developmental abnormalities, underscoring their biological significance. Regulatory pathways controlling “chromosome separation” further suggest involvement of cohesin cleavage, anaphase-promoting complex (APC/C) activation, and checkpoint surveillance mechanisms that prevent premature segregation.

Overall, this module represents a core network orchestrating mitotic chromosome segregation and spindle dynamics. It likely reflects heightened proliferative activity, mitotic checkpoint engagement, or responses to genomic instability, depending on biological context.

Representative module name: Mitotic Chromosome Segregation and Spindle Regulation.

**Gene Analysis:**

The genes in this set form a highly coordinated network governing mitotic progression, chromosome segregation, and spindle apparatus organization, representing the molecular foundation of faithful cell division. Central regulators such as CDK1, CCNB1, and CCNB2 drive the G2/M transition and initiate mitotic entry, while AURKA, AURKB, and PLK1 coordinate centrosome maturation, spindle assembly, and kinetochore–microtubule attachment. Components of the spindle checkpoint complex, including BUB3, MAD2L1, CDC20, and CENPF, ensure accurate chromosome alignment and segregation through anaphase-promoting complex (APC/C) regulation, preventing premature chromatid separation. Structural and motor proteins such as PRC1, KIF23, RACGAP1, and NUSAP1 maintain spindle midzone stability and cytokinesis, ensuring physical separation of daughter cells. The inclusion of SMC2, SMC4, and TOP2A highlights the role of condensin and topoisomerase complexes in chromosomal condensation and decatenation, critical for genome integrity. Chaperonin subunits CCT2, CCT5, CCT7, CCT8, and TCP1 underscore a connection between cytoskeletal protein folding and mitotic machinery setup, supporting microtubule and actin dynamics. Proteasome-associated ubiquitin-conjugating enzymes UBE2C and UBE2S facilitate proteolytic turnover of mitotic regulators, while LMNA and BANF1 link nuclear structure reassembly to post-mitotic nuclear organization. Collectively, these genes depict a proliferative transcriptional program ensuring precise mitotic control, cytoskeletal coordination, and nuclear remodeling. The most noteworthy elements are CDK1, AURKA/B, and PLK1, which form the mitotic signaling core frequently upregulated in proliferative states and cancers, reflecting this module’s relevance to both normal cell cycle progression and tumorigenesis.

**Cluster\_4**

Enrichment Result of Cluster\_4 (LLM Summary)

Mitochondrial Bioenergetics Coupled to Cell Cycle Progression

**Pathway Analysis:**

This module integrates pathways central to mitochondrial energy metabolism and cell cycle progression, suggesting a functional coupling between bioenergetic output and proliferative control. Enrichment of “oxidative phosphorylation,” “electron transport chain,” and “oxidoreductase complex” highlights the core role of mitochondrial respiration in ATP generation through sequential electron transfer and proton gradient formation. These processes underpin cellular energy homeostasis and redox balance, which are essential for sustaining anabolic metabolism and macromolecule synthesis during cell proliferation.

The concurrent enrichment of “positive regulation of cell cycle,” “positive regulation of mitotic cell cycle,” and related terms indicates that enhanced mitochondrial activity may drive or support progression through key cell cycle transitions. Experimental evidence shows that oxidative phosphorylation influences cell cycle regulators, including cyclins and CDKs, through ATP-dependent signaling and reactive oxygen species (ROS)–mediated modulation of checkpoint pathways. Elevated respiratory activity can therefore promote DNA synthesis and mitotic entry by ensuring sufficient metabolic resources and signaling cues.

Together, these pathways suggest a tightly coordinated program that couples mitochondrial oxidative metabolism with proliferative signaling, characteristic of cells undergoing active growth or metabolic adaptation. This module likely reflects metabolic rewiring associated with development, regeneration, or tumorigenesis, where efficient energy production is integrated with cell cycle control mechanisms.

Representative module name: Mitochondrial Bioenergetics and Cell Cycle Regulation.

**Gene Analysis:**

The genes listed form a coherent network linking mitochondrial oxidative phosphorylation with cell cycle progression and mitotic control, representing a metabolic–proliferative interface critical for cellular growth and survival. Mitochondrial-encoded genes such as MT-ATP6, MT-CO1, MT-CO3, MT-CYTB, MT-ND2, MT-ND4, and MT-ND5, along with nuclear-encoded components including NDUFA1, UQCR10, CYCS, and POR, reflect an active respiratory electron transport chain driving ATP production and redox homeostasis. This energetic output supports biosynthetic and signaling demands of proliferating cells. Complementary antioxidant systems involving SOD2 and CAT mitigate reactive oxygen species generated by oxidative metabolism, maintaining redox balance crucial for genomic stability. The presence of canonical mitotic regulators—including CDK1, CCNB1, AURKA, AURKB, CDC20, MAD2L1, BIRC5, and UBE2C—indicates synchronized activation of cell cycle checkpoints with metabolic readiness. Structural proteins such as SMC2, SMC4, NUSAP1, and RACGAP1 ensure accurate chromosome segregation and cytokinesis, while NPM1 and LAMIN B1 (LMNB1) contribute to nuclear organization during division. Metabolic enzymes like LDHA and LDHB link glycolytic flux to mitochondrial respiration, potentially integrating aerobic glycolysis with oxidative phosphorylation. Stress and signaling mediators including HMGB1, CALR, and HES1 suggest broader ties to apoptosis regulation, unfolded protein responses, and differentiation control. Collectively, this gene module supports the notion that proliferating cells maximize mitochondrial efficiency while coordinating energy generation with cell cycle execution. Notably, the co-enrichment of mitochondrial respiratory genes with mitotic kinases such as AURKA and CDK1 underscores a fundamental coupling between bioenergetics and cell division, relevant to both normal tissue renewal and tumor metabolism.

**Cluster\_5**

Enrichment Result of Cluster\_5 (LLM Summary)

DNA Helicase Activity and Chromatin Assembly Maintenance

**Pathway Analysis:**

This module is characterized by enrichment of pathways associated with DNA helicase function, single-stranded DNA binding, and molecular chaperone activities, reflecting processes essential for DNA metabolism and chromatin maintenance. Helicases with ATP hydrolysis activity drive the unwinding of duplex DNA during replication, repair, and recombination, ensuring proper progression of replication forks and genome stability. Terms such as “forked DNA-dependent helicase activity” and “single- or double-stranded DNA helicase activity” highlight the dynamic interplay between helicases and replication intermediates, crucial for resolving topological stress and preventing replication fork collapse.

The inclusion of “single-stranded DNA binding” suggests stabilization of exposed DNA regions and recruitment of replication factors, as exemplified by replication protein A (RPA) complexes that coordinate helicase and polymerase functions. Meanwhile, “molecular carrier,” “protein carrier chaperone,” and “histone chaperone activity” imply regulation of protein or nucleoprotein assembly, particularly in chromatin remodeling and nucleosome reassembly following replication or repair. Histone chaperones contribute to re-establishing proper chromatin architecture, linking helicase-mediated DNA unwinding with epigenetic continuity.

Collectively, this module represents the molecular machinery underlying DNA unwinding, stabilization, and chromatin reassembly, processes fundamental to replication fidelity and genome integrity. Dysregulation of these functions is implicated in genomic instability syndromes and oncogenesis, underscoring their vital role in nuclear maintenance.

Representative module name: DNA Helicase and Chromatin Chaperone Machinery.

**Gene Analysis:**

The included genes form a coherent network associated with DNA replication, helicase activity, and chromatin remodeling, integrating nucleic acid metabolism with chaperone-assisted protein maintenance. Core replication factors such as MCM3, MCM5, MCM6, and MCM7 compose the replicative helicase complex that unwinds DNA at replication origins, while RFC5 contributes to clamp loading for polymerase processivity, ensuring accurate and efficient DNA synthesis. Chromatin assembly factors including ASF1B, NAP1L1, and histone-binding proteins like PTMA and HMGB1 facilitate nucleosome assembly and remodeling following replication or repair, thereby preserving epigenetic organization. Structural maintenance proteins SMC2 and SMC4 further support chromosomal condensation and segregation, linking helicase-driven replication dynamics to genome architecture. Molecular chaperones such as HSP90AA1, HSPA5, HSPA8, and CCT subunits (CCT2, CCT5, CCT7, CCT8, TCP1) maintain the stability and folding of key nuclear and cytoskeletal proteins under conditions of replication stress. The presence of factors such as HELLS and TRF suggests roles in chromatin remodeling and telomere maintenance, underscoring a connection between DNA unwinding and epigenetic fidelity. RNA-binding and nuclear transport regulators ALYREF, HNRNPA1, HNRNPA2B1, and KPNA2 hint at coordinated mRNA processing and nucleo-cytoplasmic trafficking, supporting synthesis of replication and repair components. Clusterin (CLU) and CALR add stress-responsive and calcium-dependent chaperone functions, while G3BP1 marks RNA–protein complex stabilization during genotoxic stress. Overall, this gene set defines a multifunctional nuclear proteostasis and chromatin maintenance network, coupling helicase-mediated DNA replication with transcriptional regulation and chromatin integrity. The most noteworthy elements, the MCM complex and ASF1B, exemplify the direct link between replication fork dynamics and nucleosome restoration crucial for genome stability.

**Cluster\_6**

Enrichment Result of Cluster\_6 (LLM Summary)

Deoxyribonucleotide and Pyrimidine Biosynthesis Pathways

**Pathway Analysis:**

This module encompasses nucleotide and deoxyribonucleotide metabolic pathways, indicating a functional emphasis on the biosynthesis and turnover of pyrimidine and deoxyribose phosphate derivatives. The enrichment of terms such as “nucleoside triphosphate metabolic process,” “deoxyribonucleotide biosynthetic process,” and “pyrimidine nucleoside triphosphate metabolic process” highlights active regulation of nucleotide pool homeostasis necessary for DNA replication, repair, and energy-dependent enzymatic reactions.

The presence of “2'-deoxyribonucleotide metabolic process” and “deoxyribose phosphate biosynthetic process” emphasizes the direct link to DNA precursor synthesis. Maintaining balanced deoxyribonucleotide triphosphate (dNTP) pools is critical for fidelity during DNA synthesis, as imbalances can lead to mutagenesis or replication stress. Enzymes such as ribonucleotide reductase and thymidylate synthase are central to these processes, transforming ribonucleotides into deoxyribonucleotides and coordinating with cell cycle cues to meet replicative demands.

In addition, pathways involving “pyrimidine-containing compound metabolic process” reflect the integration of pyrimidine biosynthesis and catabolism, connecting nucleotide metabolism to broader cellular energetics and signaling networks. Alterations in these biochemical routes are often observed in rapidly proliferating cells, including cancer and regenerating tissues, where increased nucleotide demand supports DNA replication and repair.

Overall, this module captures the core metabolic framework that fuels genomic synthesis and maintenance, linking nucleotide metabolism to proliferative and homeostatic cellular functions.

Representative module name: Deoxyribonucleotide and Pyrimidine Metabolism Network.

**Gene Analysis:**

The genes in this module form a cohesive metabolic network responsible for deoxyribonucleotide synthesis, pyrimidine metabolism, and the energetic support required for DNA replication and repair. Central to this system are key nucleotide biosynthetic enzymes such as RRM1, RRM2, TYMS, DUT, DCTPP1, DTYMK, and TK1, which collectively generate and balance deoxyribonucleotide triphosphate (dNTP) pools to maintain replication fidelity and genomic stability. IMPDH2 contributes to purine nucleotide synthesis, reinforcing the coordinated regulation of nucleotide availability across both pyrimidine and purine pathways. Mitochondrial genes including MT-ATP6, MT-ND2, MT-ND4, MT-ND5, and NDUFA1 indicate active oxidative phosphorylation supporting the ATP demand of nucleotide synthesis and DNA biosynthesis. GAPDH and PKM link glycolysis to biosynthetic flux, illustrating the metabolic coupling between energy generation and anabolic nucleotide production. The inclusion of NME1, a nucleoside diphosphate kinase, further connects energy metabolism to nucleotide homeostasis through phosphate group transfer reactions. Chaperone and adaptive stress response genes such as HSPA8 and NUPR1 underscore mechanisms protecting enzyme function and metabolic integrity under replicative or oxidative stress. RAN’s involvement in nuclear transport supports the import of replication and repair factors required for DNA synthesis. TMSB4X may assist in cytoskeletal organization and subcellular trafficking during proliferative activity. Overall, this gene set highlights a tightly regulated metabolic axis that integrates mitochondrial energy production, glycolytic flux, and dNTP biosynthesis. The most noteworthy members—RRM1, RRM2, and TYMS—serve as central nodes controlling DNA precursor supply, crucial for sustaining replication, repair, and cellular proliferation.

**Cluster\_7**

Enrichment Result of Cluster\_7 (LLM Summary)

Immune Cell Migration and Tissue Remodeling

**Pathway Analysis:**

This module integrates pathways associated with leukocyte migration, extracellular matrix composition, and lipid or organic acid metabolism, indicating an overarching theme of immune cell trafficking and tissue remodeling. Enrichment of terms such as “positive regulation of leukocyte migration,” “mononuclear cell migration,” and “myeloid leukocyte migration” underscores the activation and directional movement of immune cells toward inflammatory or repair sites, processes essential for host defense and tissue homeostasis. “Cell chemotaxis” further supports a strong chemokine-mediated guidance mechanism coordinating immune surveillance.

The inclusion of “collagen-containing extracellular matrix” suggests structural and signaling contributions from the extracellular environment during immune cell infiltration, as matrix components modulate cell adhesion, migration, and cytokine gradients. Terms linked to “calcium-dependent protein binding” highlight intracellular signaling pathways that regulate cytoskeletal rearrangements and adhesion molecule activity required for effective motility.

Metabolic processes, including “organic acid” and “monocarboxylic acid biosynthetic process,” as well as “lipase inhibitor activity,” imply metabolic reprogramming that supports cell migration and local inflammation. Lipid-derived mediators such as prostaglandins or fatty acid derivatives can modulate leukocyte chemotaxis and vascular permeability, providing a biochemical interface between metabolism and immunity.

Collectively, these pathways depict a coordinated network linking immune cell migration, extracellular matrix dynamics, and metabolic adaptation, reflective of environments undergoing inflammation, regeneration, or immune surveillance.

Representative module name: Immune Cell Migration and Metabolic Remodeling Network.

**Gene Analysis:**

The listed genes collectively define a multifunctional network centered on immune cell migration, extracellular matrix remodeling, and metabolic adaptation to inflammation or tissue stress. Chemokines such as CCL20, CXCL5, CXCL15, and CXCL17 orchestrate leukocyte chemotaxis, directing immune cells toward inflamed or injured tissues, while adhesion molecules including ICAM1 and PECAM1 facilitate transendothelial migration and immune surveillance. Annexin family members (ANXA1–5) and calcium-binding S100 proteins (S100A1, A6, A10, A11, A14, and others) regulate calcium-dependent signaling and cytoskeletal reorganization essential for motility and membrane trafficking. Enzymes such as CTSB, CTSC, and CTSL mediate proteolysis within the extracellular matrix, whereas SPARC, THBS1, and CLU contribute to structural remodeling and cell–matrix communication. The metabolic enzymes LDHA, LDHB, PKM, PHGDH, and PSAT1 reflect glycolytic and serine biosynthetic activity, signifying metabolic reprogramming linked to inflammatory activation and energy-demanding cell migration. FABP5, FMO3, GSTM1/2, MGST1, and ALDH1A1 underscore lipid and xenobiotic metabolism, providing redox and signaling intermediates that modulate immune responses. Proteins such as HSP90AA1, HSPA8, CALR, and MIF function in stress signaling and cytokine regulation, integrating metabolic and immune stimuli. Structural and signaling molecules including AGER (RAGE) and HMGB1/2 amplify inflammatory cascades connecting tissue injury to immune recruitment. Altogether, this gene set represents an integrated response coordinating leukocyte trafficking with metabolic flexibility and extracellular remodeling during inflammation or regeneration. The most noteworthy components are chemokines, annexins, and S100 proteins, which collectively drive immune cell mobility and intercellular signaling within dynamic tissue environments.

**Cluster\_8**

Enrichment Result of Cluster\_8 (LLM Summary)

Protease Activation and Fibroblast-Mediated Tissue Remodeling

**Pathway Analysis:**

This module reflects processes linking proteolytic activation, calcium-binding protein interactions, and fibroblast proliferation, indicative of coordinated tissue remodeling and inflammatory regulation. The enrichment of “zymogen activation” suggests heightened protease activity, a hallmark of extracellular matrix turnover, coagulation cascades, or inflammatory signaling. Zymogen activation of serine proteases, for instance, modulates processes such as fibrinolysis and complement activation, which shape local tissue architecture and immune cell recruitment.

The presence of “S100 protein binding” points to regulatory interactions involving calcium-binding S100 family proteins, known to influence cytoskeletal dynamics, inflammation, and cellular proliferation through signaling with receptors such as RAGE (receptor for advanced glycation end-products). These interactions can modulate fibroblast behavior, aligning with the enrichment of “fibroblast proliferation” and its regulation. Activated fibroblasts represent key effectors in wound healing, extracellular matrix deposition, and, when deregulated, fibrotic disease or tumor stroma formation.

“Regulation of binding” further suggests fine-tuning of protein–protein and receptor–ligand interactions, integrating protease activation and S100-mediated signaling into broader control of cellular adhesion and communication.

Together, these pathways converge on a theme of regulated proteolysis and calcium-dependent signaling that drive fibroblast proliferation and tissue remodeling, processes central to wound repair and pathological fibrosis.

Representative module name: Protease Activation and Fibroblast Remodeling Signaling.

**Gene Analysis:**

The genes in this module form a coordinated network linking regulated proteolysis, calcium-binding signaling, and fibroblast proliferation, suggesting a role in tissue remodeling, inflammation, and cellular stress adaptation. The inclusion of proteases such as CTSH and CTSL and the receptor PLAUR indicates active participation in proteolytic cascades that remodel the extracellular matrix and regulate cell migration during wound repair and fibrotic responses. S100 family members (S100A1, S100A6, S100A10, S100A11) interact with AGER (RAGE) and ANXA2 to mediate calcium-dependent signaling, influencing cytoskeletal reorganization, inflammation, and fibroblast activation. Key cell cycle regulators including AURKA, AURKB, CDK1, CCNA2, CCNB1, CKS1B, and CKS2 highlight proliferative components that may drive fibroblast expansion or tissue renewal. MIF, HMGB1, and HMGB2 act as proinflammatory mediators released upon cellular stress or injury, reinforcing immune signaling that accompanies tissue repair. Structural and stress response proteins such as STMN1 and SOD2 integrate cytoskeletal regulation with oxidative stress protection, while FTH1 contributes to redox homeostasis by sequestering iron. THBS1 (thrombospondin-1) and HOPX further link extracellular interactions to fibroblast differentiation and matrix organization. The chaperone TMBIM6 and nuclear proteins NME1, NUPR1, and RAN connect stress resistance and nuclear-cytoplasmic transport to proliferative signaling. Overall, this module represents a fibroinflammatory program coupling protease activity, redox signaling, and cell cycle progression to promote tissue remodeling and wound resolution. The most noteworthy elements—S100 proteins, AURK/CDK regulators, and proteolytic mediators—collectively underscore the integration of proliferation and matrix interaction in cellular responses to injury.

**Cluster\_9**

Enrichment Result of Cluster\_9 (LLM Summary)

Lipid Transport and Cholesterol Metabolic Regulation

**Pathway Analysis:**

This module encompasses pathways involved in the regulation of lipid and sterol transport, cholesterol metabolism, and fatty acid processing, highlighting a coordinated network for lipid homeostasis and intracellular trafficking. Enrichment of terms such as “positive regulation of lipid transport,” “regulation of cholesterol transport,” and “positive regulation of sterol transport” emphasizes active modulation of lipid mobilization between cellular compartments and the circulation. These processes are fundamental for maintaining membrane composition, signaling lipid availability, and supporting energy metabolism.

The inclusion of “positive regulation of steroid metabolic process” and “positive regulation of cholesterol metabolic process” indicates dynamic control of lipid-derived signaling molecules, such as steroid hormones and oxysterols, which influence gene expression, inflammatory responses, and metabolic adaptation. Cholesterol trafficking between the plasma membrane, endoplasmic reticulum, and mitochondria is critical for steroidogenesis and regulation of lipid-sensing pathways, including those mediated by liver X and sterol regulatory element-binding proteins (LXRs and SREBPs).

“Medium-chain fatty acid metabolic process” reflects the integration of fatty acid catabolism and lipid remodeling, potentially linking peroxisomal and mitochondrial metabolism to sterol dynamics. “Regulation of lipid localization” underscores lipid sorting mechanisms that ensure correct distribution of lipids between organelles, essential for cellular signaling and membrane fluidity.

Together, these pathways define a metabolic and regulatory framework coupling lipid transport with sterol and fatty acid metabolism, supporting cellular energy balance and systemic metabolic function.

Representative module name: Lipid Transport and Sterol Metabolic Regulation Network.

**Gene Analysis:**

The listed genes collectively define a regulatory network governing lipid metabolism, cholesterol trafficking, and fatty acid processing, integrating lipid transport with metabolic and signaling functions essential for cellular and systemic homeostasis. Key lipid-binding and transfer proteins such as SCP2, PRELID1, and DBI facilitate intracellular lipid and phospholipid trafficking, maintaining membrane lipid composition and supporting steroid and cholesterol transport between organelles. Enzymes including CES1D, CES1F, CES1G, and ACOT7 participate in lipid hydrolysis and fatty acid turnover, crucial for mobilizing stored lipids and regulating metabolic flux. FDPS and POR are central to sterol and isoprenoid biosynthesis, essential for cholesterol production and membrane biosynthetic pathways, as well as redox balance and xenobiotic metabolism. Structural and signaling molecules such as CD36, APOC1, and PLIN2 mediate lipid uptake, storage, and lipoprotein remodeling, linking intracellular lipid utilization with extracellular lipid transport dynamics. The calcium- and phospholipid-binding ANXA2 and the antioxidant enzyme PON1 contribute to membrane stabilization and protection from oxidative damage, while THBS1 connects lipid signaling to cell–matrix communication and vascular remodeling. MIF introduces an inflammatory and redox-sensitive regulatory component that coordinates immune and metabolic responses during lipid flux changes. Together, this gene set encapsulates a finely tuned lipid regulatory network coupling ester hydrolysis, fatty acid metabolism, and cholesterol transport to oxidative and inflammatory cues. The most noteworthy genes, including FDPS, CD36, and APOC1, exemplify the integration of metabolic and signaling control mechanisms essential for lipid homeostasis and energy regulation across tissues.

**Cluster\_10**

Enrichment Result of Cluster\_10 (LLM Summary)

Antiviral Defense and Proinflammatory Immune Regulation

**Pathway Analysis:**

This module integrates immune response, host–pathogen interaction, and proinflammatory signaling pathways, suggesting coordinated regulation of antiviral defense and cytokine-driven inflammation. The inclusion of “viral process,” “viral life cycle,” and “positive regulation of viral process” indicates engagement of host cellular machinery in viral replication or modulation, possibly reflecting activation of innate sensing and response mechanisms. Pathways related to type I interferon production, interleukin-12, and tumor necrosis factor (TNF) signaling underscore a robust antiviral and proinflammatory network. Type I interferon pathways are central to restricting viral infection through the induction of interferon-stimulated genes, while IL-12 and TNF contribute to activating natural killer and T cells, bridging innate and adaptive immunity.

The presence of “biological process involved in symbiotic interaction” suggests recognition of intracellular or extracellular microorganisms, consistent with immune monitoring of both commensal and pathogenic entities. “Regulation of sprouting angiogenesis” may link inflammatory cytokines such as TNF and type I interferons to endothelial remodeling, as inflammation-induced angiogenesis is a common response to infection and tissue injury. Additionally, “positive regulation of DNA binding” could reflect transcriptional activation of immune genes via interferon regulatory factors (IRFs) and NF-κB.

Overall, the pathways converge on a theme of host immune activation in response to viral or microbial stimuli, balancing antiviral defense, cytokine signaling, and vascular adaptation.

Representative module name: Antiviral and Inflammatory Response Regulation.

**Gene Analysis:**

The included genes collectively define a functional network associated with innate immunity, inflammation, and cellular stress responses, strongly aligning with antiviral and proinflammatory defense mechanisms. Several genes, such as IFITM3, ISG15, and BST2, are interferon-stimulated and directly restrict viral replication by inhibiting viral entry, assembly, or release, while ICAM1, CXCL5, and PLAUR mediate leukocyte recruitment and adhesion, underscoring immune cell activation and tissue infiltration during infection. Molecules like AGER (RAGE), HMGB1, and S100A1 act as damage-associated molecular patterns that activate NF-κB signaling, linking cellular stress to inflammatory cytokine production. Chaperones and stress-response proteins including HSP90AA1, HSPA8, and HSPD1 stabilize immune regulators and maintain proteostasis during immune activation. Components such as CD36, CLU, and THBS1 connect inflammation with lipid metabolism and extracellular matrix interactions, reflecting immune and metabolic crosstalk during tissue remodeling. Nuclear and nucleic acid–related proteins including BANF1, NCL, TOP2A, and G3BP1 likely participate in stress granule formation, viral RNA handling, and transcriptional control of immune effectors. Additionally, MIF, LGALS9, and HES1 integrate metabolic and signaling cues that fine-tune macrophage activity and inflammatory resolution. Glycolytic enzymes such as GAPDH and PKM may also serve dual roles in metabolic adaptation and immune signaling under cellular stress. Overall, this gene set represents a highly responsive module that coordinates antiviral restriction, cytokine production, and stress adaptation through metabolic and signaling integration. Notably, IFITM3, ISG15, and HMGB1 emerge as key genes bridging antiviral defense with inflammatory amplification.