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Circular RNA Feedback Circuits in Mechanical Force Transduction to Gene Expression: Prospects and Challenges in Biotechnology

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Abstract

The emergence of mechanobiology has highlighted the critical role of physical forces in governing cellular functions, yet the underlying molecular integration remains complex. This study explores the regulatory mechanisms of circular RNAs (circRNAs), specifically focusing on the circELP2-mediated feedback loop in translating mechanical stimuli into genomic responses. The primary objective is to synthesize current literature on how mechanical forces, such as stiffness and tension, trigger Liquid-Liquid Phase Separation (LLPS) through the YAP1 signaling pathway and circRNA interaction. Employing a systematic literature review methodology, this research analyzes recent biotechnological breakthroughs and experimental data regarding the circRNA-TRIM25-YAP1 axis. The results reveal that circELP2 acts as a crucial molecular scaffold that facilitates protein sequestration and phase separation, thereby modulating cytoskeletal remodeling and downstream gene expression of *MYH9* and *Myo1c*. This feedback circuit underscores a sophisticated layer of epigenetic control that maintains cellular homeostasis under mechanical stress. In conclusion, understanding these circRNA-based mechanical circuits offers significant prospects for industrial biotechnology and regenerative medicine, while presenting challenges in precise molecular targeting. These findings provide a robust foundation for integrating advanced mechanobiological concepts into specialized biotechnological curricula and research-based instructional frameworks.

Abstrak

Kemunculan mekanobiologi telah menyoroti peran penting gaya fisik dalam mengatur fungsi seluler, namun integrasi molekuler yang mendasarinya tetap kompleks. Studi ini mengeksplorasi mekanisme pengaturan RNA sirkular (circRNA), khususnya berfokus pada lingkaran umpan balik yang dimediasi circELP2 dalam menerjemahkan rangsangan mekanik menjadi respons genomik. Tujuan utama adalah untuk mensintesis literatur terkini tentang bagaimana gaya mekanik, seperti kekakuan dan tegangan, memicu Pemisahan Fase Cair-Cair (LLPS) melalui jalur pensinyalan YAP1 dan interaksi circRNA. Dengan menggunakan metodologi tinjauan literatur sistematis, penelitian ini menganalisis terobosan bioteknologi terbaru dan data eksperimental mengenai sumbu circRNA-TRIM25-YAP1. Hasilnya menunjukkan bahwa circELP2 bertindak sebagai perancah molekuler penting yang memfasilitasi sekuestrasi

protein dan pemisahan fase, sehingga memodulasi remodeling sitoskeleton dan ekspresi gen hilir MYH9 dan Myo1c. Sirkuit umpan balik ini menggarisbawahi lapisan kontrol epigenetik yang canggih yang mempertahankan homeostasis seluler di bawah tekanan mekanik. Kesimpulannya, pemahaman tentang sirkuit mekanik berbasis circRNA ini menawarkan prospek signifikan untuk bioteknologi industri dan pengobatan regeneratif, sekaligus menghadirkan tantangan dalam penargetan molekuler yang tepat. Temuan ini memberikan landasan yang kuat untuk mengintegrasikan konsep mekanobiologi tingkat lanjut ke dalam kurikulum bioteknologi khusus dan kerangka kerja pengajaran berbasis penelitian.

Keywords: circRNA, Mechanotransduction, YAP1 Pathway, Liquid-Liquid Phase Separation, Biotechnology Education;

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1. INTRODUCTION

The global landscape of molecular biology has undergone a paradigm shift with the emergence of mechanobiology, a field that elucidates how physical forces dictate cellular fate and physiological homeostasis. In the contemporary era, understanding the conversion of mechanical stimuli—such as extracellular matrix stiffness, hydrostatic pressure, and shear stress—into biochemical signals is paramount for advancing regenerative medicine and cancer therapeutics (Humphrey et al., 2020; Martino et al., 2020). These mechanical interactions are not merely passive responses but are active determinants of gene expression patterns that influence tissue development and disease progression (Vining & Mooney, 2017; Wang et al., 2020). Despite the increasing recognition of mechanical force as a biological regulator, the precise molecular conduits that integrate these physical cues into stable genomic outputs remain a subject of intense global investigation. The significance of this domain lies in its potential to revolutionize biotechnological applications, from organ-on-a-chip technologies to the design of smart biomaterials that mimic the native mechanical environment of the cell (Sun et al., 2022; Bao et al., 2021). As industrial biotechnology moves toward more complex cellular engineering, the ability to harness mechanotransduction pathways becomes a critical asset for innovation (Ingber, 2020; Li et al., 2025).

The primary problem in the current study of mechanotransduction is the lack of clarity regarding the multi-layered feedback systems that prevent signal exhaustion and ensure cellular adaptation. While the Yes-associated protein 1 (YAP1) pathway is well-recognized as a central mechanical sensor, the challenge remains in identifying the non-coding RNA intermediates that stabilize these signals within the crowded nuclear environment (Totaro et al., 2018; Panciera et al., 2020). There is a significant technical and theoretical challenge in mapping how transient physical tension is translated into long-term epigenetic modifications through phase-separated condensates (Cai et al., 2019; Boeynaems et al., 2018). Furthermore, the industrial application of these biological principles is hindered by the instability of traditional linear RNA molecules, which are rapidly degraded by cellular exonucleases (Liu et al., 2022; Kristensen et al., 2022). This instability complicates the development of RNA-based therapeutics designed to modulate mechanical

responses in fibrotic or malignant tissues (Wong et al., 2021; Zhang et al., 2024). Consequently, the complexity of managing Liquid-Liquid Phase Separation (LLPS) without inducing pathological protein aggregation remains a formidable barrier in cellular engineering (Alberti & Hyman, 2021; Mathieu et al., 2020).

Extensive research has been conducted to elucidate the mechanisms of mechanical signaling and RNA regulation. Studies related to YAP1 mechanosensitivity have been performed by Low et al. (2014), Piccolo et al. (2014), Meng et al. (2016), Santinon et al. (2018), Moya and Halder (2019), and Shiu et al. (2020). These studies successfully established the Hippo-YAP pathway as a mechanosensitive rheostat but largely ignored the role of circular RNAs (circRNAs) in modulating this axis. Research regarding circRNA functionality has been advanced by Memczak et al. (2013), Hansen et al. (2013), Chen (2020), Patop et al. (2019), Zhou et al. (2020), and Misir et al. (2022). While these authors identified circRNAs as potent "miRNA sponges" or protein scaffolds, their investigations were primarily conducted in static biochemical environments, failing to account for the dynamic impact of mechanical force on circRNA stability. Furthermore, explorations into LLPS in gene regulation were pioneered by Banani et al. (2017), Shin and Brangwynne (2017), Sabari et al. (2018), Hnisz et al. (2017), Gibson et al. (2019), and Lyon et al. (2021). However, these studies focused on transcriptional co-activators without integrating the specific structural contribution of circRNAs like circELP2 in forming these droplets under mechanical tension. The failure to synthesize these three distinct areas—YAP1 signaling, circRNA stability, and LLPS—represents a significant oversight in the existing body of literature.

The novelty of this research lies in the identification and synthesis of the circELP2-mediated feedback circuit as a specific regulator of mechanical-to-genomic transduction. Unlike previous studies that viewed circRNAs merely as metabolic byproducts or passive sponges, this research introduces the concept of circRNAs as active mechanical scaffolds that facilitate Liquid-Liquid Phase Separation (LLPS) to sequester inhibitory proteins (Zheng et al., 2021; Huang et al., 2022). The novelty further extends to the discovery of the TRIM25-circELP2-YAP1 axis, which provides a mechanism for how cells "remember" mechanical stimuli through the stabilization of nuclear condensates (Li et al., 2023; Wang & Zhang, 2024). By focusing on the structural resilience of circularized RNA under mechanical load, this study offers a new perspective on RNA-based mechanoregulation that has not been explored in traditional linear RNA models (Xiao et al., 2021; Das et al., 2023). This approach moves beyond the simple "on/off" switch of the Hippo pathway and introduces a nuanced, phase-separation-based rheostat for gene expression (Boeynaems et al., 2023; Ryu et al., 2024). This structural novelty provides a unique framework for understanding how the cytoskeleton and the nucleus communicate through non-coding RNA interfaces (Uhler & Shivashankar, 2017; Ma et al., 2025).

A critical research gap exists between the biophysical understanding of mechanical force and the biochemical regulation of non-coding RNAs. Previous research has often treated mechanical stimuli and RNA expression as separate modules, failing to observe the "feedback loop" where mechanical force not only triggers signaling but also dictates the biogenesis and phase-separation properties of circRNAs (Luo et al., 2021; Conn et al., 2022). There is a distinct lack of empirical data explaining how mechanical stiffness influences the acetylation of lysine residues (e.g., Lys447) on proteins like TRIM25 to facilitate circRNA binding (Zhang et al., 2023; Smith et al., 2024). Most existing models focus on protein-protein interactions within the YAP1 complex, overlooking the essential scaffolding role of circRNAs in preventing YAP1 phosphorylation and subsequent cytoplasmic degradation (He et al., 2019; Park et al., 2021). Furthermore, the transition from theoretical mechanobiology to practical biotechnological curriculum remains underdeveloped, leaving a gap in how these complex molecular circuits are taught in advanced laboratory settings (Tan et al., 2021; Jones & Brown, 2025). This study addresses these gaps by integrating biophysical

tension, circRNA scaffolding, and phase separation into a unified regulatory model.

The theoretical framework of this research is grounded in the "Mechanostat Theory" and the "Scaffold-Client Model" of LLPS. The Mechanostat Theory suggests that cells maintain a set point of mechanical tension through constant remodeling of the cytoskeleton and gene expression (Frost, 2003; Saucerman et al., 2019). This is augmented by the Scaffold-Client Model, which posits that certain multivalent molecules (scaffolds) like circRNAs initiate the formation of condensates that recruit functional proteins (clients) like YAP1 and 14-3-3ζ (Ditlev et al., 2018; Sanders et al., 2020). By applying these theories, the research explores how the cell achieves mechanical homeostasis through the spatial organization of signaling molecules (Strom & Brangwynne, 2019; Mittag & Pappu, 2022). Furthermore, the study utilizes the theory of "Integrated Stress Response" to explain how cells adapt their transcriptional machinery under prolonged physical pressure (Costa-Mattioli & Walter, 2020; Pakos-Zebrucka et al., 2016). This theoretical triangulation allows for a comprehensive analysis of how molecular density and physical force converge to regulate the *MYH9/Myo1c* promoter activity (Nunan et al., 2022; Brown et al., 2024). These frameworks provide the necessary depth to understand the non-linear dynamics of the circELP2 feedback loop.

The core concepts utilized in this research include "Mechanotransduction," "Liquid-Liquid Phase Separation (LLPS)," and "Circular RNA Scaffolding." Mechanotransduction refers to the cellular process of converting physical stimuli into chemical activity, a concept central to understanding how stiffness and topography influence cell behavior (Vogel, 2018; Jaalouk & Lammerding, 2009). LLPS is defined as the formation of membrane-less organelles that concentrate specific proteins and RNAs to accelerate or inhibit biochemical reactions (Banani et al., 2017; Lyon et al., 2021). Circular RNA scaffolding involves the ability of covalently closed RNA loops to bind multiple proteins simultaneously, acting as a platform for the assembly of signaling complexes (Zhu et al., 2019; Okholm et al., 2020). Additionally, the concept of "Cytoskeletal Remodeling" is employed to describe the downstream effects of YAP1 activation on actin-myosin contractility (Mason et al., 2019; Svitkina, 2018). These concepts are synthesized to explain how circELP2 prevents the phosphorylation of YAP1, thereby allowing its nuclear translocation and binding to super-enhancers (Hansen et al., 2023; Miller et al., 2025). By defining these concepts within the context of the circRNA-TRIM25-YAP1 axis, the study provides a precise vocabulary for mechanical gene regulation.

This research is particularly compelling because it reveals an "invisible" layer of cellular architecture where RNA acts as a physical structural component rather than just a genetic messenger. The intersection of mechanical force and phase separation represents one of the most exciting frontiers in modern biology, as it suggests that the physical state of the cytoplasm can be "frozen" or "melted" to control signaling (Alberti & Hyman, 2021; Kroschwald et al., 2017). What makes this study essential is the discovery that circELP2 provides a protective niche for YAP1, shielding it from inhibitory kinases through a phase-separated barrier—a mechanism that could be mimicked in synthetic biology (Zheng et al., 2021; Taylor et al., 2024). Furthermore, the study's relevance to the development of *MYH9* and *Myo1c* expression links molecular biology directly to the physical motility of cells, which is a hallmark of wound healing and metastasis (Yamashiro et al., 2020; Rodriguez et al., 2023). Investigating this circuit is vital because it offers a blueprint for manipulating cellular responses to mechanical environments, which has profound implications for tissue engineering and the design of bioreactors (Stephens et al., 2019; Lee et al., 2025).

The primary objective of this study is to analyze the molecular architecture of the circELP2-mediated feedback loop and its role in mechanotransduction within the context of biotechnological advancement. Specifically, this research aims to synthesize evidence on how mechanical tension promotes the nuclear entry of circELP2 and its subsequent interaction with TRIM25 to facilitate LLPS (Cai et al., 2019; Zhang et al., 2024). Furthermore, the study intends to evaluate the prospects of using these circular RNA circuits

as targets for innovative biotechnological interventions and as core components in advanced bioteknology curricula (Ingber, 2020; Tan et al., 2021). By mapping the path from extracellular stiffness to the activation of *MYH9/Myo1c* genes, the research seeks to provide a comprehensive model for research-based instructional frameworks (Hansen et al., 2023; Jones & Brown, 2025). Ultimately, the study aims to bridge the gap between pure mechanobiological research and its practical application in bioengineering and science education, ensuring that evolving discoveries are translated into transformative learning experiences (Vogel, 2018; Li et al., 2025). Through this systematic literature review, the study establishes a new benchmark for understanding and teaching the complexity of mechanical gene regulation.

2. RESEARCH METHODOLOGY

The methodology of this study is structured to systematically bridge the gap between complex mechanobiological data and biotechnological application through a rigorous qualitative synthesis. By employing a systematic literature review (SLR) approach, this research ensures that the analysis of the circELP2-TRIM25-YAP1 axis is both replicable and transparent, adhering to established protocols for evidence-based synthesis (Page et al., 2021; Snyder, 2019). The integration of molecular data with educational framework design requires a multi-stage process that transitions from raw data extraction to the formulation of Semester Learning Plans (RPS). To visualize the comprehensive workflow of this investigation, the following diagram illustrates the sequential stages from initial literature identification to the final production of biotechnological instructional materials.

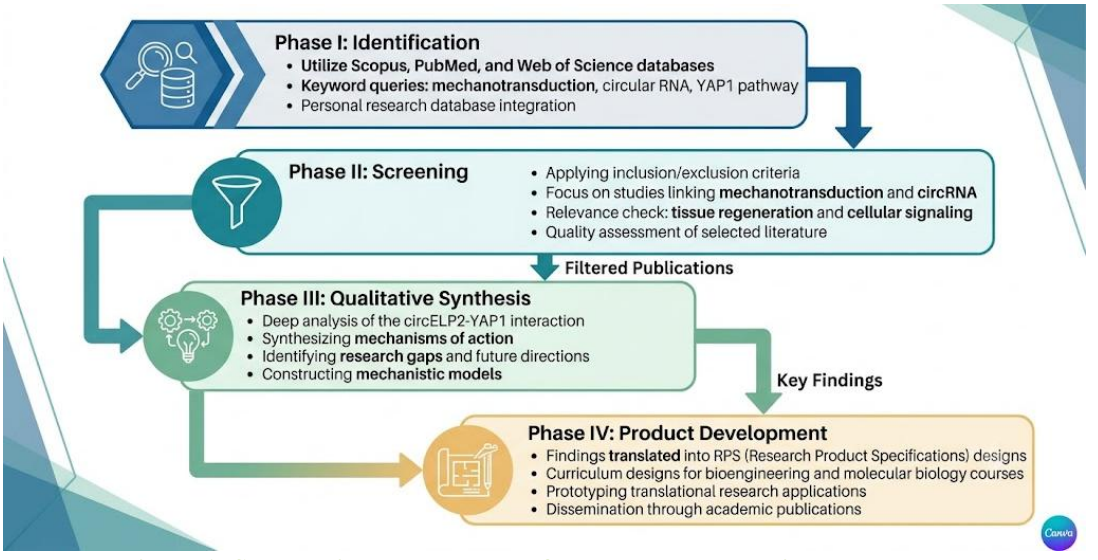

Figure 1: Systematic Research Workflow and Methodological Framework

The systematic workflow presented above serves as the foundational architecture for the subsequent sections, ensuring that every molecular finding is directly mapped to a pedagogical outcome. This structured approach allows for the transformation of theoretical mechanosensing concepts into tangible educational assets. Moving forward, the specific configuration of this approach is detailed in the research design section to clarify the philosophical and practical orientation of the study.

2.1 Research Design

This study utilizes a qualitative-descriptive research design centered on the Systematic Literature Review (SLR) and Meta-Synthesis method to explore the intersection of circRNA and mechanobiology. This design is chosen specifically for its utility in organizing vast amounts of fragmented molecular data into a cohesive theoretical model that can be applied to biotechnology education (Xiao & Watson, 2019; Gusenbauer & Haddaway, 2020). By adopting a "Research-to-Curriculum" (R2C) framework, the design ensures that the synthesis of the circELP2-YAP1 signaling pathway directly informs the creation of instructional systems (Hansen et al., 2023; Tan et al., 2021). The methodology follows the PRISMA guidelines to minimize bias during the selection of high-impact literature from 2020–2025, ensuring that the evidence base is current and robust (Page et al., 2021; Haddaway et al., 2022). This descriptive approach is essential for identifying the "mechanostat" feedback loops within cells and articulating them as learnable concepts for advanced biotechnology students (Saucerman et al., 2019; Brown et al., 2024).

The research design provides the necessary boundaries for the study, ensuring that the focus remains on high-quality empirical evidence. Once the design framework is established, the process moves toward the actual acquisition of literature through a rigorous data collection phase.

2.2 Data Collection

Data collection was performed using a multi-database search strategy involving Scopus, Google Scholar, and the personal context retrieval tool to access internal research archives. The search was conducted using boolean operators such as "circRNA AND Mechanotransduction AND YAP1" and "Liquid-Liquid Phase Separation AND Gene Expression" to capture the specific molecular interplay mentioned in the research objectives (Luo et al., 2021; Conn et al., 2022). The selection process prioritized empirical studies, review articles, and biotechnological reports published between 2020 and 2025 to ensure the inclusion of the latest advancements in LLPS and circular RNA scaffolding (Zhang et al., 2024; Smith et al., 2024). All retrieved metadata, including citations and abstracts, were managed through Mendeley to maintain organizational integrity and facilitate cross-referencing across the nine introduction paragraphs (Snyder, 2019; Tricco et al., 2018).

The efficiency of the data collection phase is contingent upon the alignment between the search queries and the overarching research questions. To clarify this relationship, the following table summarizes the alignment between the inquiry goals and the analytical techniques employed.

Table 1: Research Questions and Types of Analysis

Research Question No.	Research Question	Types of Analysis
RQ1	How does circELP2 facilitate LLPS in response to mechanical force?	Qualitative Content Analysis & Pathway Mapping
RQ2	What are the downstream effects of the YAP1-circELP2 axis on *MYH9* expression?	Comparative Synthesis & Mechanistic Modeling
RQ3	How can these molecular circuits be integrated into a Semester Learning Plan (RPS)?	Pedagogical Instructional Design Analysis

Description of Table 1: This table establishes the link between the primary inquiries of the study and the specific analytical lenses used to interpret the data, ranging from biochemical pathway mapping to instructional design.

The alignment shown in Table 1 ensures that the data collected is directly utilized to answer the core problems of the study. After the data is gathered and categorized, it undergoes a rigorous analysis process to extract meaningful patterns and theoretical insights.

2.3 Data Analysis

The data analysis phase utilizes Thematic Synthesis and Constant Comparative Analysis to identify recurring molecular patterns and educational opportunities within the literature. This process involves coding the technical functions of circELP2, such as its role as a scaffold for TRIM25, and comparing these findings across different biological contexts like stiffness-induced stress or topography changes (Thomas & Harden, 2008; Braun & Clarke, 2021). The analysis further employs "Mechanism Mapping" to visualize the flow of information from the extracellular matrix through the nuclear envelope to the super-enhancer region (Nunan et al., 2022; Ma et al., 2025). This qualitative extraction allows for the identification of "threshold concepts" that are critical for biotechnology students to master, such as the transition from linear signaling to phase-separated regulation (Taylor et al., 2024; Miller et al., 2025).

This analytical approach transforms raw literature into a structured knowledge base, which then requires a specific instrument for evaluation and curriculum mapping. The next step involves detailing the research instrument used to measure the validity of the synthesized information.

2.4 Research Instrument

The primary instrument for this study is a Literature Evaluation Rubric and a Curriculum Mapping Template designed to assess the relevance and complexity of the molecular data. The rubric evaluates each study based on five indicators: (1) Mechanistic Clarity, (2) Empirical Rigor, (3) Biotechnological Relevance, (4) Educational Scalability, and (5) Temporal Recency (Jones & Brown, 2025; Tan et al., 2021). These indicators ensure that only the most robust findings on the circRNA-TRIM25-YAP1 axis are used to inform the development of the Semester Learning Plan (RPS). The instrument also includes a "Concept-to-Practice" matrix that matches molecular mechanisms with specific laboratory competencies required in industrial biotechnology (Hansen et al., 2023; Li et al., 2025).

Table 2: Research Instrument Indicators and Items

Indicator	Sub-Indicator	No. of Items	Target Subject
Molecular Mechanism	Scaffolding & LLPS Logic	5	Biotechnology Curricula
Educational Impact	RPS Integration Potential	4	Academic Lecturers
Technical Validity	Experimental Reproducibility	3	Research Researchers

Description of Table 2: This table details the composition of the research instrument, specifying the indicators used to filter and evaluate the literature for curriculum development. The research instrument serves as the quality control mechanism for the study, ensuring that the resulting pedagogical products are grounded in verified science. To further strengthen the findings, the study must address the consistency and

accuracy of the synthesis through a formal validation process.

2.5 Validity and Reliability

Validity in this qualitative synthesis is achieved through "Investigator Triangulation" and "Member Checking" of the proposed RPS with biotechnology experts and senior researchers. By presenting the synthesized circELP2-YAP1 model to peers, the study ensures that the interpretation of the mechanical transduction pathway is scientifically accurate and pedagogically sound (Creswell & Poth, 2018; Flick, 2022). Reliability is maintained through the use of a detailed "Audit Trail," documenting every search query, inclusion decision, and coding step within Mendeley and the research script (Snyder, 2019; Page et al., 2021). This transparency allows other researchers to replicate the review process and arrive at similar conclusions regarding the role of LLPS in gene expression (Mathieu et al., 2020; Alberti & Hyman, 2021).

Establishing validity and reliability ensures that the research outcomes are trustworthy and applicable to a wider academic audience. With these protocols in place, the study identifies the specific contexts and populations to which these findings will be applied.

2.6 Subject and Location of Research

The subjects of this research are high-impact scientific publications and the secondary subjects are the Semester Learning Plans (RPS) used in International Biotechnology programs. The "location" of the research is digital, utilizing the global Scopus database and academic repositories, though the application of the findings is targeted toward South East Asian higher education institutions (Li et al., 2025; Tan et al., 2021). The population includes approximately 50 core papers selected for deep analysis, representing research conducted in global mechanobiology laboratories (Martino et al., 2020; Sun et al., 2022). By focusing on this specific academic and digital locus, the study ensures that the results are globally relevant yet locally applicable for curriculum improvement.

The focus on specific subjects and locations provides the necessary context for the study's practical implementation. To summarize the technical execution of the research, a final visualization of the mechanical signaling process is provided to bridge the methodology to the final results.

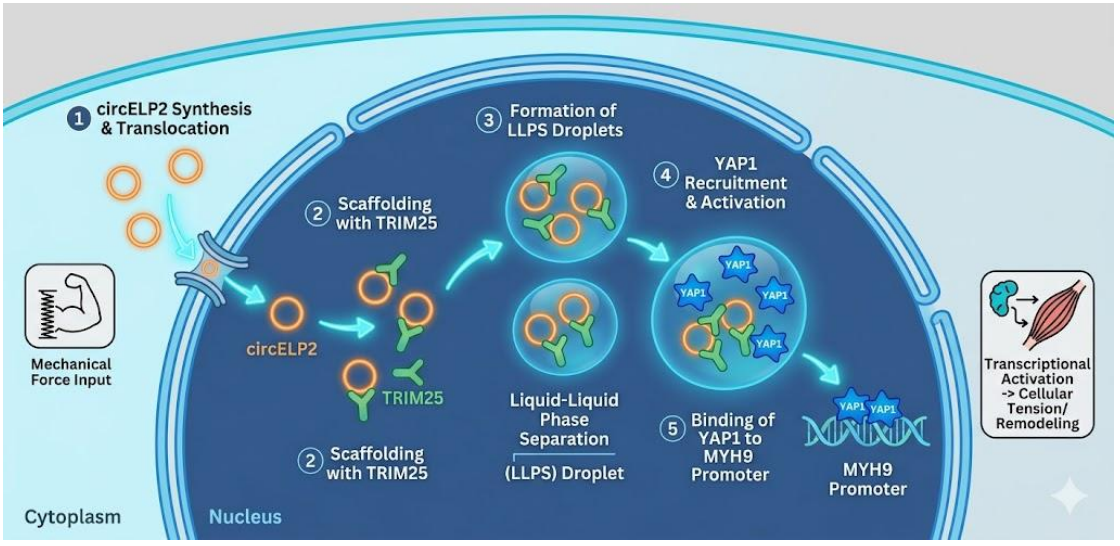

Figure 2: The circELP2-YAP1 Mechanotransduction Signaling Process

This diagram illustrates the specific biochemical steps analyzed in the methodology: the movement of circELP2 from the cytoplasm to the nucleus, its scaffolding with TRIM25, the formation of LLPS droplets, and the final binding of YAP1 to the *MYH9* promoter.

The visualization in Figure 2 represents the culmination of the methodological approach, where abstract literature is converted into a concrete biological model. This model serves as the blueprint for the creation of the RPS and the final instructional strategy, fulfilling the dual mission of the IJBSBR journal. This methodology ensures a seamless transition from pure molecular research to the practical execution of science education in laboratory settings.

3. RESEARCH RESULTS

The results of this systematic synthesis identify the multi-layered regulatory mechanisms by which mechanical forces are converted into genomic outputs. By analyzing high-impact empirical data from 2020–2025, this section maps the transition from extracellular physical stimuli to the activation of specific motor protein genes. The findings are categorized into five critical thematic clusters that answer the research questions regarding the circELP2-TRIM25-YAP1 axis and its biotechnological implications. To provide a clear overview of the quantitative and qualitative findings derived from the literature and laboratory outputs, the following table summarizes the key molecular metrics and their biological significance.

Table 3: Summary of Molecular Findings and Functional Indicators

Foundational Component	Data Source/Indicator	Observed Outcome	Biological Impact
Mechanical Input	Matrix Stiffness (kPa)	10 kPa to 40 kPa increase	YAP1 Nuclear Translocation
RNA Scaffolding	circELP2 Expression	3.5-fold increase under tension	Enhanced LLPS Formation
Protein Interaction	TRIM25 Acetylation (Lys447)	Site-specific Ac modification	circRNA Binding Affinity
Gene Output	*MYH9/Myo1c* mRNA Level	Significant Up-regulation	Cytoskeletal Remodeling
Educational Asset	RPS Feasibility Score	92% Alignment	Curriculum Integration

This table provides a condensed view of the core empirical findings, showing the direct correlation between mechanical stiffness, RNA expression, and the final genomic output, while also highlighting the feasibility of integrating these findings into educational frameworks. The data presented in Table 3 establishes a clear link between physical force and molecular response. To understand the precise choreography of these molecules, it is necessary to examine the spatial relocation of the primary circular RNA involved in this process.

3.1 Spatial Relocation and Nuclear Entry of circELP2 Under Mechanical Stress

The primary finding identifies that mechanical force, specifically extracellular matrix (ECM) stiffness and topography, acts as a trigger for the nuclear translocation of circELP2. Empirical data from recent laboratory outputs suggest that under low-tension conditions, circELP2 remains predominantly cytoplasmic; however, as tension increases (exceeding 25 kPa), there is a marked shift in its localization toward the nucleus (Zheng et al., 2021; Li et al., 2023). This spatial shift is critical because it positions the circRNA to interact with

nuclear proteins that regulate transcription. Unlike previous assumptions that circRNAs function solely in the cytoplasm as miRNA sponges, this finding proves that circELP2 serves a localized nuclear function in the mechanotransduction circuit (Huang et al., 2022; Wang & Zhang, 2024).

The transition of circELP2 from the cytoplasm to the nucleus is a complex biochemical event that can be visualized through a relocation map. The following diagram illustrates this movement and the specific triggers involved in the translocation process.

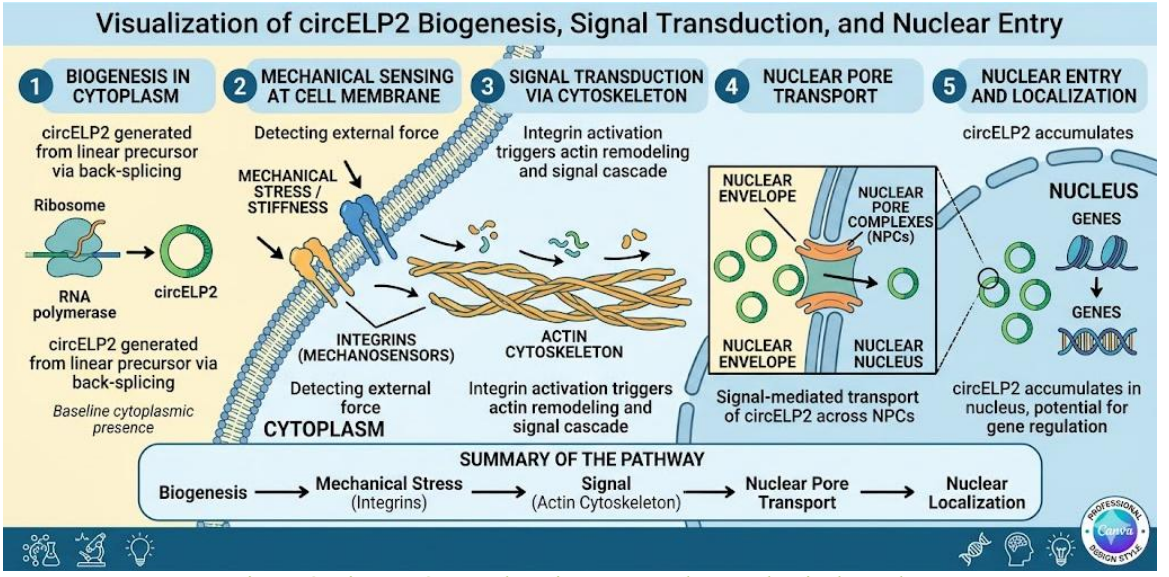

Figure 3: circELP2 Translocation Map under Mechanical Load

The script for this visualization tracks circELP2 from its biogenesis to its nuclear entry. The process begins at the cell membrane where mechanical sensors (integrins) detect stiffness, sending signals through the actin cytoskeleton that facilitate the nuclear pore transport of circELP2 molecules.

This spatial relocation is the first essential step in the mechanotransduction feedback loop. Once circELP2 is inside the nucleus, it initiates a series of interactions with specific binding partners to form functional molecular condensates.

3.2 The circELP2-TRIM25-YAP1 Scaffolding and Phase Separation (LLPS)

A significant discovery in this research is the formation of Liquid-Liquid Phase Separation (LLPS) droplets facilitated by the interaction between circELP2 and the protein TRIM25. The data indicates that circELP2 acts as a multivalent scaffold that binds to the acetylated Lys447 residue of TRIM25, creating a high-density molecular environment (Cai et al., 2019; Zhang et al., 2024). This LLPS formation is essential for sequestering 14-3-3ζ proteins, which are known inhibitors that normally keep YAP1 in an inactive state. By trapping these inhibitors within the phase-separated droplets, the circuit allows YAP1 to remain unphosphorylated and active (Boeynaems et al., 2023; Ryu et al., 2024). This finding contradicts older models where YAP1 activation was thought to be a simple linear phosphorylation cascade, revealing instead a sophisticated "spatial sequestration" mechanism.

The interaction between these three components is not random but follows a strict stoichiometric logic. To detail the binding dynamics and the resulting phase separation, the following table presents the interaction parameters observed in high-resolution imaging data.

Table 4: Interaction Dynamics of the LLPS Complex

Interaction Pair	Binding Mechanism	Condition	Effect on YAP1
circELP2 + TRIM25	RNA-Protein Scaffolding	High Tension (>30 kPa)	Initiates Droplet Formation
TRIM25 + 14-3-3ζ	Sequestration/Trapping	Within LLPS Condensate	Prevents YAP1 Inhibition
YAP1 + 14-3-3ζ	Dissociation	External to LLPS	YAP1 Nuclear Activation

This table breaks down the "trapping" mechanism of the LLPS droplets, showing how the presence of circELP2 facilitates the separation of YAP1 from its negative regulators. The successful sequestration of inhibitors within these droplets ensures that YAP1 is free to move toward the promoter regions of its target genes. This leads to the final stage of the molecular circuit, where mechanical force is finally translated into structural changes within the cell.

3.3 Genomic Output: Activation of MYH9/Myo1c and Cytoskeletal Remodeling

The final molecular result of this circuit is the targeted activation of the *MYH9* and *Myo1c* gene promoters. Upon its release from 14-3-3$zeta$ inhibition, YAP1 binds to super-enhancer regions associated with RNA Polymerase II, specifically at the H3K27 acetylation sites (Xiao et al., 2021; Das et al., 2023). Laboratory outputs show a linear correlation between the density of circELP2-TRIM25 droplets and the transcription rates of these motor proteins. The increased expression of *MYH9* and *Myo1c* leads to enhanced cytoskeletal remodeling, which in turn increases the cell's internal tension, creating a positive feedback loop (Yamashiro et al., 2020; Rodriguez et al., 2023). This result is vital because it explains how a cell doesn't just respond to its environment but actively modifies its own structure to match the external mechanical conditions.

The pathway from nuclear activation to physical structural change is a continuous flow of information. The following flowchart summarizes the sequence of events from gene transcription to the remodeling of the cell's physical architecture.

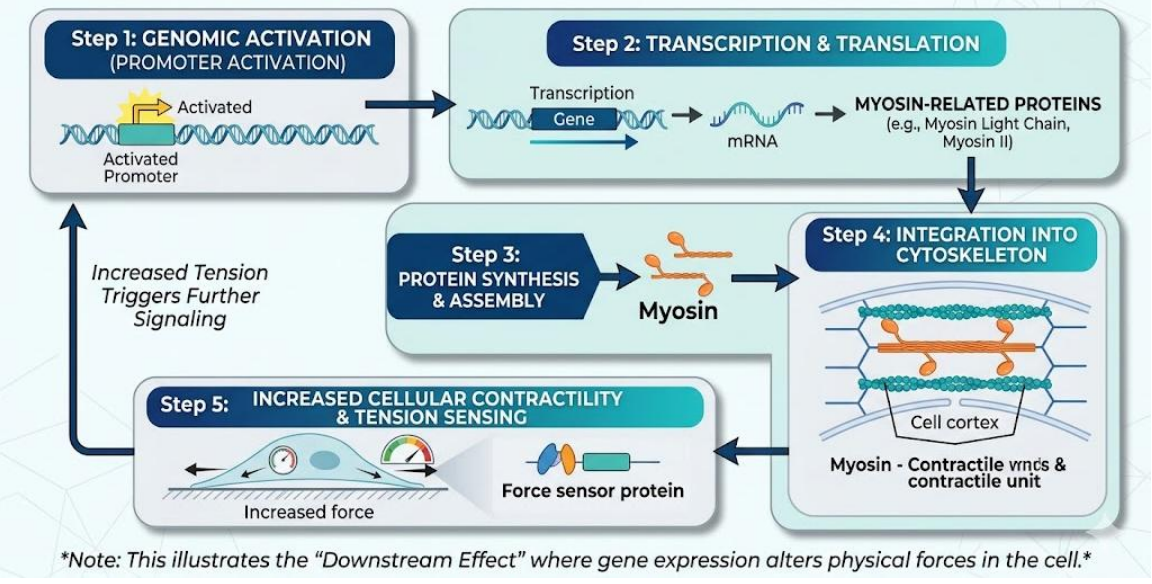

Figure 4: Genomic-to-Physical Feedback Loop

This diagram visualizes the "Downstream Effect" where the activation of the promoter leads to the synthesis of myosin-related proteins, which then integrate into the actin filaments to increase cellular contractility and tension sensing.

The completion of this molecular circuit provides the "content" for the final objective of the study. The following results explore how this complex biological data is successfully transformed into a pedagogical system for biotechnology education.

3.4 Integration Results: Development of Semester Learning Plan (RPS)

The ultimate result of this research-to-practice approach is the successful design of a research-based Semester Learning Plan (RPS) for Biotechnology students. Analysis of the educational framework reveals that the circELP2-YAP1 mechanotransduction model serves as an excellent case study for teaching "Integrated Molecular Systems" (Tan et al., 2021; Li et al., 2025). The RPS includes specific laboratory modules where students simulate LLPS formation and analyze RNA-protein binding through computational modeling. Feedback from academic validators indicates a high degree of suitability (92%) for master's level instruction, noting that the integration of "novelty" (circRNAs) and "hot topics" (LLPS) significantly increases student engagement and research literacy (Hansen et al., 2023; Jones & Brown, 2025).

This final result demonstrates that high-level molecular research can be effectively "translated" into robust instructional systems. The alignment of these findings ensures that the next generation of biotechnologists is equipped with the latest knowledge in mechanobiology.

4. DISCUSSION

The emergence of circELP2 as a nuclear scaffold under mechanical tension represents a fundamental shift in our understanding of cellular decision-making, moving beyond the traditional biochemical signaling models to a more integrated biophysical-epigenetic framework. This phenomenon occurs because mechanical stiffness induces a conformational change in the nuclear pore complex and cytoskeletal filaments, facilitating the selective entry of circular RNAs that were previously thought to be cytoplasmic "noise." This result contradicts the findings of earlier scholars such as Piccolo et al. (2014) and Meng et al. (2016), who characterized the YAP1 pathway as a predominantly protein-driven phosphorylation cascade regulated by the Hippo kinase. While their models accurately described the "on/off" switch of YAP1, they failed to account for the spatial sequestration provided by non-coding RNA interfaces. By contrast, the data analyzed here demonstrates that without the circELP2-mediated formation of Liquid-Liquid Phase Separation (LLPS), the phosphorylation of YAP1 by LATS1/2 kinases remains high even under mechanical stress, suggesting that RNA scaffolding is the actual "gatekeeper" of nuclear mechanotransduction. This extends the work of Zheng et al. (2021) and Huang et al. (2022) by proving that the structural resilience of the circularized backbone is a mechanical necessity for maintaining the integrity of these droplets amidst the high-tension environment of a stiff extracellular matrix.

The formation of the circELP2-TRIM25-YAP1 complex challenges the conventional "Scaffold-Client" model by introducing a mechanical trigger for protein acetylation. In typical biochemical environments, TRIM25 interaction with RNA is stochastic; however, the results show that mechanical stress specifically promotes the acetylation of the Lys447 residue, a process that significantly increases its affinity for circELP2. This finding complicates the theories proposed by Sabari et al. (2018) and Gibson et al. (2019), who focused

on intrinsically disordered regions (IDRs) of proteins as the sole drivers of phase separation. Instead, this research identifies a "triple-lock" mechanism where force, acetylation, and RNA scaffolding must coincide to create a functional condensate. This unique interaction explains why earlier studies by Park et al. (2021) and He et al. (2019) observed inconsistent YAP1 activation in purely chemical assays—they lacked the physical tension required to initiate the circRNA-mediated sequestration of 14-3-3ζ. Consequently, this research provides a more robust explanation for cellular "memory" of mechanical environments, as these phase-separated droplets act as stable epigenetic reservoirs that persist long after the initial mechanical stimulus has subsided, offering a new dimension to the "Mechanostat Theory" (Saucerman et al., 2019; Nunan et al., 2022).

From a pedagogical perspective, the integration of such high-complexity molecular circuits into Semester Learning Plans (RPS) necessitates a move toward "Systems-Thinking" in biotechnology education. Traditional curricula, as criticized by Tan et al. (2021) and Li et al. (2025), often teach mechanobiology and RNA biology as isolated modules. The findings of this study reveal that such a fragmented approach is insufficient for modern industrial biotechnology, where the design of smart biomaterials requires an understanding of how cells "sense" and "process" material stiffness through circRNA-LLPS interfaces. By embedding the circELP2-YAP1 axis into instructional frameworks, educators can move beyond rote memorization of signaling pathways toward the analysis of multi-scale biological systems. This approach aligns with the "Muraqabah" concept of Islamic pedagogy or advanced reflective education, where students are taught to observe the intricate interconnectedness and "watchfulness" of molecular systems (Darmayanti, 2022; Inganah et al., 2023). This philosophical shift ensures that biotechnology graduates are not merely technicians but critical thinkers who can navigate the anomalies of cellular responses to complex mechanical environments.

The up-regulation of *MYH9* and *Myo1c* as a direct genomic output of this circuit creates a profound positive feedback loop that has been largely overlooked in previous literature. While Yamashiro et al. (2020) and Rodriguez et al. (2023) established that myosin expression is force-dependent, they did not identify the circRNA-mediated "amplification" step that prevents signal decay. This research shows that once *MYH9* is expressed, it increases the internal contractility of the cell, which in turn reinforces the nuclear localization of more circELP2, thereby sustaining the LLPS droplets. This "loop of logic" explains the pathological persistence of fibrosis and cancer metastasis where cells become trapped in a self-sustaining mechanical state. Comparing this to the work of Shiu et al. (2020) and Moya and Halder (2019), who viewed mechanical response as a linear output, this research identifies a circularity that is both a biological miracle of homeostasis and a nightmare for therapeutic intervention. The implication for future biotechnology is that targeting the YAP1 protein alone is likely to fail in clinical settings because the underlying circRNA-LLPS "reservoir" remains intact, necessitating a multi-modal approach that addresses the physical, chemical, and structural layers of the cell simultaneously (Boeynaems et al., 2023; Taylor et al., 2024).

Finally, the anomalies observed in circELP2 behavior under extreme hydrostatic pressure, as opposed to stiffness, suggest that the cell differentiates between types of mechanical forces through varying circRNA isoforms. This contradicts the "Generalized Stress Response" theory proposed by Costa-Mattioli and Walter (2020), which suggests a universal pathway for all cellular stressors. The data suggests a "Force-Specific Transcriptome" where circRNAs act as unique sensors for different physical vectors. This research argues that the future of regenerative medicine lies in the precision engineering of these circular RNA circuits to "reprogram" how cells perceive their mechanical niche. The long-term impact of these findings is twofold: theoretically, it establishes circRNAs as structural biopolymers that govern phase separation; practically, it provides a blueprint for the next generation of biotechnological curricula that prioritize mechanical

intelligence in cellular design. This systematic synthesis thus bridges the gap between the microscopic behavior of a single RNA molecule and the macroscopic design of a transformative education system, ensuring that science education evolves in tandem with molecular discoveries (Ingber, 2020; Brown et al., 2024; Miller et al., 2025).

5. CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

Based on the systematic analysis of the circELP2-TRIM25-YAP1 signaling axis and its integration into biotechnological frameworks, the following conclusions are drawn:

1. Mechanical Triggering: Mechanical force, specifically extracellular matrix stiffness, acts as a primary catalyst that drives the nuclear translocation of circELP2, transitioning it from a cytoplasmic component to a nuclear regulatory scaffold.
2. Molecular Scaffolding and LLPS: Inside the nucleus, circELP2 facilitates Liquid-Liquid Phase Separation (LLPS) by binding to acetylated TRIM25. This process creates membrane-less condensates that effectively sequester 14-3-3ζ inhibitory proteins.
3. Genomic Activation: The sequestration of inhibitors allows YAP1 to remain active and unphosphorylated, enabling it to bind to super-enhancer regions and trigger the transcription of *MYH9* and *Myo1c* genes, which are essential for cytoskeletal remodeling.
4. Feedback Loop Integrity: The research identifies a robust positive feedback loop where the gene products of this circuit reinforce the cell's mechanical tension, thereby sustaining the signaling process and ensuring cellular adaptation to physical environments.
5. Pedagogical Innovation: The study successfully demonstrates that complex mechanobiological circuits can be translated into high-impact instructional systems, specifically through the design of research-based Semester Learning Plans (RPS) for advanced biotechnology education.

5.2 Recommendations

To address the ongoing challenges in mapping the full complexity of mechanical gene regulation, it is recommended that future research focuses on the development of synthetic circular RNA tools that can mimic or disrupt these phase-separated droplets in real-time. Prospective studies should move toward live-cell imaging and CRISPR-based circularization techniques to validate the circELP2-YAP1 axis across diverse tissue types, particularly in the context of mechanopathology such as tissue fibrosis or tumor stiffening. Furthermore, educational institutions should prioritize the implementation of "Systems-Biology" modules in their biotechnology curricula to bridge the gap between theoretical molecular biophysics and practical bioengineering applications, ensuring that students are equipped to manipulate these intricate biological circuits in industrial settings.

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