口头报告

Regulation of meiotic recombination by phase separation

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Sexual reproduction gives rise to genetic diversity among progeny, partly through meiotic recombination, which mixes genetic information from two parental genomes to create unique combinations of alleles. Large segments of DNA are exchanged through crossover recombination between homologous chromosomes. During meiotic prophase, each homologue pair must undergo at least one crossover (crossover assurance) to segregate faithfully. Only a limited subset of recombination intermediates become crossovers, and these are widely spaced or limited to one per chromosome pair (crossover interference). Mechanisms that regulate crossover number and spacing remain poorly understood. We reveal that in *C. elegans*, 'recombination nodules', protein assemblies that stabilize recombination intermediates and promote crossover formation, assemble in part through biomolecular condensation and are stabilized by CDK-2 kinase activity. Additionally, we find that essential components of these nodules move along the synaptonemal complex (SC), a unique liquid crystalline compartment that assembles between paired chromosomes, and do not freely exchange between SCs in the same nucleus. Our findings reveal that recombination nodules behave as active droplets and support a model in which coarsening of these droplets via protein translocation along liquid crystalline SCs underlies crossover patterning. Our study provides new insights into the regulation of crossover formation and patterning during meiosis and uncovers a novel role for liquid-liquid phase separation (LLPS) in subcellular signal propagation and pattern formation.

Key words: phase separation; coarsening; patterning; chromosome; cell division; recombination; crossover

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Membrane binding and phase separation of the ACAP4 BAR-PH domain coordinate cell migration

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ArfGAPs (Arf-specific GTPase-activating proteins) regulate cell migration through interactions with small G proteins, including Arfs. Among ArfGAPs, the BAR (Bin/Amphiphysin/Rvs) domain plays a key role in membrane binding and curvature induction, yet the molecular mechanisms underlying these processes remain unclear. Here, we investigate the function of the BAR domain and its adjacent PH (pleckstrin homology) domain of ACAP4 in cell migration. We demonstrate that the BAR-PH tandem of ACAP4 induces membrane curvature, promotes cell migration, and undergoes liquid-liquid phase separation (LLPS), forming condensates in vitro and exhibiting membrane-associated distribution in cells. The crystal structure of the ACAP4 BAR domain, determined at 2.8 Å resolution, reveals multiple positively charged surface patches. Structural modeling further identifies conserved positively charged residue pairs in the PH domain, which collectively mediate electrostatic interactions essential for both phase separation and membrane localization. Mutagenesis experiments confirm that these regions are required for ACAP4's subcellular localization and pro-migratory activity. Furthermore, we identify that the actin-binding protein Ezrin interacts with a specific C-terminal region of ACAP4 to regulate its function. Ezrin binding enhances phase separation and enables full-length ACAP4 to associate with membranes and promote cell migration, particularly when co-expressed with activated Ezrin (T567D). Together, our findings uncover the molecular basis by which ACAP4 coordinates membrane remodeling and cytoskeletal dynamics, offering new insights into the mechanisms that drive cell migration.

Key words: cell migration; BAR-PH; phase separation; ArfGAP

口头报告

Small-molecule cocktail 5SM induces heart regeneration by upregulating TGFβ/BMP signaling

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Zebrafish and neonatal mammals possess a remarkable capacity for cardiac regeneration following injury, a property that is largely absent in adult mammals. We have recently identified a cocktail of five small molecules (5SM) that promote adult cardiomyocyte (CM) proliferation and heart regeneration. However, the underlying mechanisms through which 5SM induces CM proliferation remain incompletely understood. In this study, we demonstrated an essential role for TGFβ/BMP signaling in mediating 5SM-induced heart regeneration. Harmine, one component of 5SM, plays a dominant role in upregulating TGFβ/BMP signaling by inhibiting DYRK1B. Inhibition of DYRK1B releases PRKACA, which then activates CREB phosphorylation, subsequently upregulating the expression of *Tgfβ2, Tgfβ3, Bmp2*, and *Bmp7* in CMs. Exogenous treatment with any of these proteins—TGFβ2, TGFβ3, BMP2, or BMP7—enabled cultured CMs to re-enter the cell cycle, while pharmacological inhibition of either the TGFβ or BMP pathways markedly diminished the effect of 5SM on CM proliferation in vitro and in vivo. CM-specific knockout of *Smad4* impaired the regenerative effects of 5SM following myocardial infarction (MI) in adult mice. Based on the autocrine loop and pro-proliferative effects of TGFβ/BMP signaling, the ligands induced by 5SM ultimately bind to their receptors in CMs, leading to CM proliferation. In summary, our work establishes that TGFβ/BMP signaling mediates the effect of harmine in promoting CM proliferation and gains novel insights into the DYRK1B-PKA-CREB axis in heart regeneration.

Key words: 5SM; heart regeneration; TGFβ/BMP signaling; DYRK1B

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Wnt specifically induces FZD5/8 endocytosis and degradation and the involvement of RSPO-ZNRF3/RNF43 and DVL

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Ligand-induced receptor endocytosis and degradation play critical roles in controlling signal strength and duration and are typical negative regulatory mechanisms used by receptor tyrosine kinase pathways. Frizzled (FZD) proteins are the principal receptors of the Wnt signaling pathway. However, whether Wnt ligands induce FZD endocytosis and degradation remains elusive. The transmembrane E3 ubiquitin ligases ZNRF3 and RNF43 were reported to promote the endocytosis and degradation of FZDs to inhibit Wnt signaling, and their function is antagonized by R-spondin (RSPO) proteins. However, the dependency of RSPO-ZNRF3/RNF43-mediated FZD endocytosis and degradation on Wnt stimulation, as well as the specificity of this degradation for different FZD, remains unclear. Here, we demonstrated that Wnt specifically induces FZD5/8 endocytosis and degradation in a ZNRF3/RNF43-dependent manner. RSPO1 enhances Wnt signaling by specifically stabilizing FZD5/8. Wnt promotes the interaction between FZD5 and RNF43. We further demonstrated that DVL proteins promote ligand-independent endocytosis of FZD but are dispensable for Wnt-induced FZD5/8 endocytosis and degradation. Our results demonstrate that Wnt signaling may use a similar strategy to that of receptor-tyrosine kinase pathways, in which ligands bind to and activate receptors and simultaneously induce receptor endocytosis and degradation to control signaling strength and duration. Our results reveal a novel negative regulatory mechanism of Wnt signaling at the receptor level and illuminate the mechanism by which RSPO-ZNRF3/RNF43 regulates Wnt signaling, which may provide new insights into regenerative medicine and cancer therapy.

Keywords: Wnt signaling; FZD5/8; ZNRF3/RNF43; DVL proteins; ligand-induced receptor endocytosis.

口头报告

Fibroblast bioelectric signaling drives hair growth

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Hair loss affects millions globally, significantly impacting quality of life and psychological well-being. Despite its prevalence, effective strategies for promoting human hair growth remain elusive. By investigating Congenital Generalized Hypertrichosis Terminalis (CGHT), a rare genetic disorder characterized by excessive hair growth, we discover that chromatin deletions or duplicate inversion disrupt the topologically associating domain (TAD), leading to the upregulation of the potassium channel *KCNJ2* in dermal fibroblasts. Mouse genetics demonstrate that KCNJ2-mediated membrane hyperpolarization in dermal fibroblasts promotes hair growth by enhancing fibroblasts Wnt signaling responses, involving reduction in intracellular calcium levels. Notably, fibroblast membrane potential oscillates during normal hair cycle, with hyperpolarization specifically associated with the growth phase. Inducing fibroblast membrane depolarization delays the growth phase, while KCNJ2-mediated hyperpolarization rescues hair loss in aging and androgenetic alopecia models. These results uncover a previously unrecognized role of fibroblast bioelectricity in tissue regeneration, offering novel therapeutic avenues for hair loss treatment.

Key words: Bioelectric signaling; Hair follicle regeneration; KCNJ2; Fibroblast niche

口头报告

Decihpering cell signaling: from single molecule to network kinetics

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Abstract:

Cell signaling is tightly regulated in both time and space and often involves complex feedback loops. Here we introduce two innovative strategies to elucidate signal transduction in living cells:

1. We have developed biosensors for GTPase activity utilizing environment-sensitive fluorescent dyes that undergo spectral changes suitable for ratiometric imaging in live cells. This single-molecule ratiometric imaging approach allows us to track the spectral shifts of individual molecules in real-time. We quantitatively mapped the recruitment and activity of single Cdc42 molecules across the cell, particularly at the cell edge, and investigated the mechanisms by which nanoscale Cdc42 clusters regulate its activity. Furthermore, we determined the activation kinetics of Cdc42 at the single-molecule level.

2. Multiplexed imaging is an essential tool in biological research, allowing visualization and analysis of multiple biomolecular targets within a single specimen. We introduce a fluorescence lifetime-based cell barcoding technique that is straightforward to implement and significantly reduces spectral overlap. With single excitation, we achieved the discrimination of over 100 types of cells in a single dish. Using this barcoding system, we systematically evaluated the regulation of Ca^{2+}, cAMP, and ATP at different cellular sites immediately following perturbation of various GPCRs. Additionally, we investigated how the mechano-properties of the substrate influence the molecular-scale organization of integrin-based focal adhesions.

口头报告

Macrophage-derived dendrite-like pseudopods enhance bacterial ingestion in response to high-dose infections

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Macrophages, critical innate immune cells, exhibit remarkable adaptability during pathogen infections. The relationship between their morphological plasticity and physiological functions remains elusive. Gram-negative bacteria pose a significant pathogenic threat due to their general antimicrobial resistance, leading to severe diseases and symptoms such as sepsis. Notably, stimulation with lipopolysaccharide (LPS), a characteristic marker and an important outer membrane component of Gram-negative bacteria, enhances the ability of macrophages to engulf pathogens. However, it remains unclear whether host macrophages have evolved distinct strategies to strengthen the ingestion of invading Gram-negative bacteria. Here, we discovered an unprecedented macrophage adaptation paradigm in a few hours upon severe Gram-negative bacterial infections, characterized by the formation of dendrite-like pseudopods (DLPs). Using in vitro, microfluidic, and in vivo infection models, we demonstrate that the DLPs enhance bacterial uptake by expanding the macrophage searching radius, thereby bolstering host defense. Mechanistically, Toll-like receptor 4 (TLR4) activation by Gram-negative bacterial lipopolysaccharide (LPS) upregulates the expression of macrophage-specific RhoGEF via NF-κB. Consequently, periodic cycles of actin assembly and disassembly propel the elongation of DLPs, whereas vimentin intermediate filaments stabilize them. Importantly, infusion the DLPs-equipped macrophages into Salmonella-infected mice reduced bacterial burden and infection severity. Together, our findings underscore the dynamic response of macrophages to massive infections, augmenting immune defense against pathogenic bacteria.

Key words: macrophage; dendrite-like pseudopods; pathogen ingestion; actin filaments; vimentin intermediate filaments

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Ints7 deficiency activates DNA damage response to elicit resurgence of endogenous retrovirus MERVL and anastasis of embryonic stem cells

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The murine endogenous retrovirus *MERVL* is dynamically activated in a small population of in vitro-cultured mouse embryonic stem cells (mESCs) exhibiting totipotent-like features. Yet, the relationship between *MERVL* activation and cell fate decisions of mESCs is incompletely understood. Through a genome-wide knockout screen, we discovered that *MERVL* activity is intrinsically linked to DNA damage response pathways. Loss of Ints7, a backbone subunit of the Integrator complex, elevated DNA damage and triggered *MERVL* expression. Mechanistically, Ints7 depletion induced phosphorylation of Kap1, increased chromatin accessibility at *MERVL* loci, and activated the p53-Dux axis to drive *MERVL* transcription. Intriguingly, DNA damage-induced *MERVL* resurgence followed the cleavage of caspase-3, often accompanying a process known as anastasis—cell survival after transient apoptotic signaling. Collectively, our study uncovered that *MERVL* activation in mESCs is integrated into the cellular circuit for decision-making in response to DNA damage, suggesting that sub-lethal caspase activation can influence developmental potential of stem cells.

口头报告

Regulation of R-loop homeostasis by ubiquitin ligase ARIH2

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R-loop is a three-stranded nucleic acid structure consisting of an RNA:DNA hybrid and a displaced single-stranded DNA. It is important for many cellular signaling pathways, but could be a threat to genome integrity if dysregulated. Although protein ubiquitylation plays critical roles in many cellular activities, less is known about the functions of ubiquitylation in regulation of R-loop homeostasis. We showed that ARIH2, an RBR type of ubiquitin ligases, plays a crucial role in R-loop regulation. Knocking down ARIH2 could enhance cellular R-loop level, indicating that ARIH2 is a key player to mediate R-loop metabolism. Moreover, the enzymatic activity of ARIH2 is important for R-loop regulation as well. Previous study has shown that ARIH2 is activated by associating with the neddylated Cullin5 protein complex. Surprisingly, our data indicate that the Cullin5 protein complex is irrelevant to R-loop regulation, suggesting a new venue for ARIH2 activation. Interestingly, we found that ARIH2 could be activated by the ATM kinase and this phosphorylation-dependent activation pathway is required for ARIH2's role in R-loop regulation. Furthermore, we found that ARIH2 mediates DNA damage-induced Chk2 phosphorylation. Importantly, the regulation of Chk2 phosphorylation by ARIH2 is controlled by R-loop. Together, our data suggest a positive regulatory mechanism involving the signaling cascade of ATM-ARIH2-Chk2 in coordinating protein ubiquitylation, R-loop and DNA damage responses. We will also discuss the role of ARIH2 in sensitivity of cancer cells to cancer drugs and DNA damage agents.

口头报告

TGFβ-activated PDHB promotes mitochondrial pyruvate metabolism and contributes to human endoderm differentiation via ATP-dependent BRG1

Cell fate determination is closely linked to global metabolic changes. The metabolic changes during germ layer differentiation from human pluripotent stem cells are recently characterized. However, it is largely unclear whether and how the metabolic changes affect differentiation process. Here, we reveal that the metabolic switch with decreased lactate production and increased mitochondrial pyruvate metabolism, which is controlled by TGFβ-activated PDHB, is necessary for the definitive endoderm differentiation from human pluripotent stem cells. The inhibition of glucose utilization or blocking pyruvate entry into mitochondria significantly impair endoderm differentiation. In contrast, inhibiting lactate production can increase endoderm differentiation efficiency. Mechanistically, inhibiting glucose utilization and pyruvate mitochondrial metabolism during endoderm differentiation leads to a marked reduction in intracellular ATP levels. This decrease adversely affects the function of ATP-dependent chromatin remodeling complex BAF, thereby hindering the differentiation process. The BAF complex, centered around the helicase BRG1, promotes the expression of lineage-related genes by opening the local chromatin during endoderm induction. Overall, our findings demonstrate that TGFβ-PDHB-mediated glucose metabolic reprogramming regulates human definitive endoderm differentiation through alterations in ATP levels and the function of BAF complex.

口头报告

蛋白质进入线粒体的分子路径

Abstract

Most mitochondrial proteins are imported from the cytosol as pre-proteins. The translocation of these proteins across the mitochondrial double membranes is primarily controlled by the TOM complex in the outer membrane and the TIM complexes in the inner membranes. Notably, more than 50% of proteins follow the pre-sequence pathway involving the TOM and TIM23 complexes. However, it was unclear how these complexes are engaged in protein translocation, especially regarding the translocation pathway in the TIM23 complex. To elucidate the molecular details of the pre-sequence pathway through the TOM and TIM23 complexes, we assembled the TOM-TIM23 supercomplex with a translocating protein substrate in vivo. Structural and biochemical characterization of the assembly revealed a new polar-rich pathway in the TOM complex. Furthermore, our findings suggested that the pathway formation subunit in TIM23 is Tim17 and Mgr2, challenging the generally accepted notion of Tim23 being the core translocase subunit. Our very recent data on protein translocation in the inner membrane reveals that the assembly of the TIM23 complex is modulated by substrate hydrophobicity, which enable dynamic regulation of protein sorting toward either the matrix or membrane. In summary, our findings propose a paradigm-shifting model of the mitochondrial pre-sequence pathway.

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Off-DNA Aberrant Condensates (ODACs) of Mutant Transcription Factors in Genetic Diseases

The phenotypic complexity of genetic disorders often obscures their molecular mechanism, leaving fewer than 5% of rare diseases with approved therapies. While aberrant biomolecular condensates and dysregulated liquid-liquid phase separation (LLPS) are increasingly implicated in pathogenesis, mechanistic links to clinical heterogeneity remain unresolved. Here, we bridge TCF4 mutations to symptom severity in Pitt-Hopkins syndrome (PTHS) by integrating clinical, neuropathological, and multi-scale experimental models including cerebral organoids. We demonstrate that the length of intrinsically disordered regions (IDRs) in TCF4 dictates disease severity through aberrant condensate formation (off-DNA aberrant condensates, ODACs). These ODACs sequester essential transcriptional regulators, exacerbating neurodevelopmental pathology. Strikingly, ODAC dissolution reduces molecular trapping and ameliorates phenotypic severity, revealing a causal role of condensate dysfunction. We further identify analogous ODAC-driven mechanisms across diverse genetic disorders, implicating a unifying pathological paradigm. Our work establishes ODACs as a therapeutic target and provides a framework for addressing condensate-mediated diseases.

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An injury-induced lipid niche licenses dysfunctional RGS1+ efferocytes to impede tissue repair

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Tissue injury profoundly reshapes the local microenvironment through the accumulation of apoptotic debris and its metabolites that should be efficiently cleared by pro-resolving macrophages-mediated efferocytosis to sustain tissue homeostasis. However, how the microenvironmental cues reciprocally regulate efferocytic capacity remains unclear. Here, using a mouse model of ischemia/reperfusion (I/R)-induced kidney injury, we demonstrate that extracellular lipids within the injury microenvironment (IME) are key drivers of macrophage efferocytosis suppression and impaired tissue repair. Single-cell mRNA sequencing identify a transcriptionally distinct subset of Rgs1+ efferocytotic macrophages in the injured tissue, which is dysfunctional for efferocytosis and driven by lipids. Mechanistically, lipids serve as building blocks to fuel palmitoyl transferase DHHC5-mediated palmitoylation of Regulator of G-protein signaling 1 (RGS1, encoded by Rgs1) at cysteine 118, enabling its interaction with and deactivating Rac1, a GTPase required for actin cytoskeletal remodeling during efferocytosis. In addition to the post-transcriptional modification (PTM) mechanism, lipids upregulate Rgs1 and Zdhhc5 through lipid sensor PPARα and c-Jun-mediated transcriptional activation, respectively. Genetic ablation or enzymatic inactivation of DHHC5 diminishes RGS1 palmitoylation, restored Rac1 activity, rescued macrophage efferocytosis, and accelerated renal recovery post-I/R injury. Notably, a rationally designed peptide targeting macrophage RGS1 palmitoylation enhances apoptotic cell clearance, attenuates inflammation, and improves functional recovery. Our findings reveal a dual molecular event by which IME-derived lipids transcriptionally and post-translationally reprogram macrophages to limit efferocytosis, nominating RGS1 as a druggable node to resolve inflammation and restore tissue homeostasis.

Key words: macrophage efferocytosis; injury microenvironment; RGS1; palmitoylation; lipids

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Well-folded AF9 promotes AML cell proliferation and chemoresistance in a liquid-to-gel phase separation dependent manner

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Acute myeloid leukemia (AML) is a hematopoietic malignancy characterized by poor prognosis. In this study, we identified that AML cells with high expression of AF9 exhibit more aggressive disease progression and increased chemoresistance in humanized xenograft mouse models. Mechanistically, we demonstrated that AF9 promotes the assembly of super elongation complexes (SEC) via liquid-gel phase separation (LGPS), thereby enhancing the expression of key oncogenic genes such as CCND1 and AKT1, which in turn drives AML cell proliferation and resistance to chemotherapy.

We further investigated an acetylation-deficient, loss-of-function mutant of AF9(3A), which retains the ability to undergo liquid-liquid phase separation (LLPS) but fails to promote AML cell proliferation. This functional difference is attributed to the TCP-1 ring complex (TRiC), a molecular chaperone essential for AF9 to adopt a folded conformation that enables gel-like condensate formation. In contrast, the misfolded AF9(3A) mutant supports only LLPS, without facilitating SEC formation or leukemic growth.

To therapeutically target this mechanism, we designed a peptide derived from AF9 (residues 59 , 77 and 78), which disrupts AF9–TRiC interaction and impairs AF9 folding. Treatment with this peptide effectively converted AF9-mediated LGPS into LLPS and significantly suppressed AML cell proliferation and chemoresistance both *in vitro and in vivo.*

Overall, our findings reveal that AF9 promotes AML progression and therapy resistance through an LGPS-dependent mechanism. The AF9(59–78) peptide offers a promising therapeutic strategy by selectively disrupting this pathological phase transition.

Key words: AF9; acute myeloid leukemia; liquid-to-gel phase separation; protein folding; cell biology

口头报告

Pathogenic MID1 condensates trigger neuronal apoptosis

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Abstract

Pathogenic protein condensates are increasingly recognized as drivers of cellular dysfunction and neuronal death in various diseases, yet the precise mechanisms by which these aberrant structures directly trigger apoptosis remain largely unclear. Here we demonstrate that disease-causing mutations in the E3 ubiquitin ligase MID1 (TRIM18) promote its aberrant condensation via phase separation into low-fluidity, pathogenic structures. These pathogenic MID1 condensates directly trigger robust neuronal apoptosis. While wild-type MID1 can form transient, less dynamic cytoplasmic condensates upon microtubule dissociation (a process driven by its coiled-coil domain), mutations linked to X-linked Opitz Syndrome (XLOS)—over 80% of which induce this phenotype—generate distinct, highly pathogenic condensates. These structures recruit key apoptotic proteins like BAD and Caspase-9, activating caspase-dependent cell death. Mouse models with XLOS-analogous mutations display hippocampal MID1 condensation, neuronal loss, and neurological deficits. Our findings establish pathogenic MID1 condensates as direct inducers of neuronal apoptosis, defining a critical toxic gain-of-function mechanism in XLOS and offering a compelling model for condensate-mediated neurotoxicity.

Keywords: MID1; protein condensates; neuronal apoptosis; X-linked Opitz syndrome; phase separation

口头报告

Induction of clusterin activates proliferation, migration, and endocytosis of mesothelial cells via LRP2 receptor to resolve liver fibrosis

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Abstract: Liver fibrosis, a common outcome of chronic liver diseases, is generally considered irreversible. Upregulation of clusterin (CLU), a secreted glycoprotein, occurs in several degenerative diseases and is suggested to be protective; however, its potential in treating or reversing liver fibrosis requires investigation. In our study, CLU expression was selectively induced in pericentral senescent hepatocytes and then secreted during liver fibrosis in both patients and mice. Deletion of CLU exacerbated liver fibrosis, whereas treatment with recombinant CLU reversed fibrosis, suggesting that CLU induction feedback inhibits fibrosis progression. Mechanistically, LRP2, the receptor for CLU, is specifically expressed by liver mesothelial cells but not hepatic stellate cells. Recognition of CLU by LRP2 triggers mesothelial cell proliferation and migration from liver surface into the pericentral region, followed by endocytosis of surrounding fibers, thus reversing liver fibrosis. Thereafter, we designed a 20-amino acid peptide mimicking CLU, named CLUtide, and determined its effect in reversing liver fibrosis, suggesting the considerable therapeutic potential. In conclusions, the pericentral senescent hepatocytes secrete CLU to induce the migration and proliferation of mesothelial cells to endocytose fibers by its receptor LRP2, thus reversing liver fibrosis. The engineered CLUtide mimics CLU holds considerable translational and therapeutic potential for resolving liver fibrosis.

Key words: clusterin; liver fibrosis; mesothelial cell; endocytosis; LRP2

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Vitamin A and its analogues modulate MUFAs metabolism to improve ferroptosis and aging by direct targeting of ACSL3

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In this study, we uncover a novel non-canonical function of vitamin A (VA) and its analogues, which operates independently of the well-characterized RAR/RXR nuclear receptor signaling pathway. Through the synthesis and systematic evaluation of a series of newly designed VA analogues, we demonstrate that VA and its derivatives directly bind to and activate acyl-CoA synthetase long-chain family member 3 (ACSL3), a key enzyme that channels monounsaturated fatty acids (MUFAs) into membrane phospholipids. This ACSL3-mediated mechanism elevates the MUFA-to-PUFA ratio in phospholipids, thereby conferring protection against lipid peroxidation and ferroptosis. Strikingly, we further demonstrated that VA and its analogue D3 extend the lifespan of C. elegans in a manner dependent on ACSL3, highlighting the physiological relevance of this pathway in aging. Our findings uncover a previously unrecognized role of the VA family in regulating MUFAs metabolism, establishing a mechanistic link between nutrient signaling, cell death suppression, and organismal longevity.

Key words: vitamin A; ACSL3; lipid metabolism; ferroptosis; longevity

口头报告

Research on the role and mechanism of the small G protein Arl4c in melanoma

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Melanoma is a highly heterogeneous and aggressively invasive malignancy. In recent years, significant progress has been made in melanoma treatment; however, many patients still exhibit poor responses or develop resistance to targeted therapy, immunotherapy, or combination strategies, indicating that the pathogenesis of melanoma requires further investigation.

In this study, bioinformatic analysis identified Arl4c as a differentially overexpressed gene in melanoma, which is closely associated with poor patient prognosis. Although Arl4c is known to be highly expressed and implicated in the progression of various cancers, its role and molecular mechanisms in melanoma remain unclear.

Our results demonstrate that Arl4c is highly expressed in clinical samples of canine melanoma and promotes melanoma cell proliferation and migration in vitro, as well as tumor growth in a murine melanoma model. Mechanistically, Arl4c interacts with the transcription factor GABPA, facilitating its nuclear localization, which in turn enhances YAP gene transcription and promotes YAP protein expression,constituting the Arl4c-GABPA-YAP signaling axis that positively regulates cell proliferation.

In conclusion, this study elucidates the oncogenic role and molecular mechanism of Arl4c in melanoma. Further investigation into the regulatory mechanisms of Arl4c may provide a foundation for its development as a potential diagnostic and therapeutic target in melanoma.

Key words: melanoma; Arl4c; molecular mechanism; proliferation