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P1

Endogenous YAP/TAZ partitioning in TEAD condensates orchestrates Hippo response

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Abstract:

YAP/TAZ are transcriptional coactivators that pair with transcription factor TEADs for modulating Hippo pathway in biological contexts including development, organ size and oncogenesis. Previous works propose the potential role of YAP/TAZ phase separation for transcriptional activation, yet the biomolecular basis and regulatory mechanism of endogenous YAP/TAZ-TEAD condensates remains unclear. Here we carefully dissect their endogenous morphology, and it turns out that YAP/TAZ are

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client proteins recruited to TEAD condensates. TEAD proteins have robust intrinsic potential to phase separate and YAP/TAZ condensates disappear immediately after losing their interaction with TEADs. Moreover, TEADs condensates serve as central organizing hubs to dynamically concentrate active YAP and other markers of transcriptional activation, which provides a straightforward and biophysical perspective for understanding transcription program regulated by YAP/TAZ-TEAD complex. Based on this, we revisited a series of recent characterized TEAD inhibitors and identified that VGLL4 represents a critical regulator contributing to TEAD central pocket inhibitors. Altogether, we demonstrate a fundamental role of TEAD condensates in spatially regulating YAP/TAZ signaling, underscoring its significance in further deciphering TEADs biology and applications in TEAD-targeted therapy.

Key words: TEAD; YAP/TAZ; liquid-liquid phase separation; VGLL4

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P2

Mitotic centrosome scaffold assembly driven by phase separation

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Centrosome functions as the major microtubule organizing centre and the central coordination hub whose dysfunction has been linked to a plethora of human pathologies. Centrosomes are membraneless organelles that form when centrioles assemble pericentriolar material (PCM) around themselves. Spd-2/CEP192 protein, defined by a conserved “Spd-2 domain” (SP2D), plays a critical role in centrosome assembly. Here, we show that the SP2D does not target Spd-2 to centrosomes, but rather promotes PCM scaffold assembly. The SP2D is monomeric in solution, but can form higher-order oligomers upon phosphorylation by PLK1. Structural analyses identify potential self-association interfaces, and targeted disruption of one such interface dramatically perturbs SP2D oligomerisation in vitro and PCM scaffold assembly in vivo. Furthermore, full length Spd-2 undergoes phase separation to form biomolecular condensates. When coexisting with other key PCM components, these condensates can further enrich two distinct types of scaffolds regulated by specific kinases. Together, our findings uncover a phosphorylation-regulated, phase separation-driven mechanism for mitotic centrosome scaffold assembly.

Key words: CSCB, cell biology, cytoskeleton, cell cycle, centrosome.

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P3

Exoribonucleases mediated miRNA overhang cleavage triggers tumorigenesis

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Global downregulation of miRNA expression is common in cancer, and the accumulation of 3' trimmed miRNA isoform represents one underlying mechanism. Since the expression level of multiple exoribonucleases are higher in tumor, we specteculate they function as miRNA trimmers. Ectopic expression of PARN and ERI1 resulted in increased proportion of 1nt-shorter isomiR and reduced miRNA abundance. In vitro, PARN and ERI1 specificly trimmed miRNA 3' overhang and impaired its AGO2 binding affinity. miRNA dysregulation triggered growth arrest and apoptosis, resembling oncogene induced senescence. Disruption of miRNA-mediated post-transcriptional control aberrantly activated target genes, many of which were established oncogenic transcription factors. Taking advantage of our system, we will hopefully discover the key pathway connecting miRNA dysregulation to cancer, and provide a spontaneous tumor model caused by altered miRNA aboundance.

Key words: Nucleases; miRNA; 3' overhang; Cancer; gene regulation.

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P4

CSPG^{4+} M2 Macrophage Drives Metastatic Prostate Cancer Cell Linage Plasticity

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Abstract

Prostate cancer is the second leading cause of cancer-related death in men worldwide. While metastasis is a determinant of mortality, molecular mechanisms driving prostate cancer metastasis remain elusive. Here, we demonstrate that *TMPRSS2-ERG* gene fusion co-occurs with *FOXO1* or *PTEN* gene deletion more frequently in metastatic than primary prostate cancers in patients. We show that male mice of prostate-specific ERG transgene in combination with *Foxo1* or *Pten* knockout (*Pb-ERG/Foxo1*$^{pc-/-}$ or *Pb-ERG/Pten*$^{pc-/-}$) develop prostate cancer metastasis in lung, liver and other soft tissues. Our findings demonstrate that in *Foxo1* or *Pten* deficient conditions, ERG binds to the promoter regions of mouse *KC, Mip2* and their human functional homolog *CXCL8*, transcriptionally promoting their expression and subsequently inducing M2-like macrophage infiltration. Using single cell RNA-seq analyses, we investigate the transcriptome regulation, dynamics of cellular heterogeneity, and microenvironmental factors in genetically engineered mouse metastatic prostate cancer samples. We identify CSPG4/ITGA2/ITGB1 axis is an important cell-chat pathway between macrophage and prostate cancer cell, which promotes prostate cancer cell lineage plasticity.

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Smad7 boosts STING signaling as a self-oligomerizing scaffold

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The cGAS-STING pathway plays a pivotal role in antiviral and antitumor immunity, necessitating precise regulation of the adaptor protein STING. While STING oligomerization is essential for its activation, the mechanisms governing this process remain largely unclear. In this study, we identify Smad7, a negative regulator of TGF-β signaling, as a positive regulator of cGAS-STING signaling. Overexpression of Smad7 in mammalian cells significantly enhances TBK1/STING phosphorylation, IRF3 activation, and the production of type I interferons and interferon-stimulated genes (ISGs) upon pathway stimulation, while knockdown or knockout of Smad7 impairs STING activation. Smad7fl/fl LyzCre/- mice demonstrated weakened antiviral responses and increased lung damage during DNA virus infection. In tumor allografts, depletion of Smad7 in B16-F10 cells eliminated cGAMP-induced STING-mediated antitumor immunity. Mechanistically, Smad7 interacts with transmembrane regions of STING, acting as an oligomerization scaffold. Through its N-terminal disordered region, Smad7 promotes the oligomerization of STING, facilitating the assembly of the STING complex and the recruitment of TBK1/IRF3, thereby amplifying the signaling cascade. Our findings establish Smad7 as a critical positive regulator of cGAS-STING signaling and suggest it as a potential therapeutic target for enhancing antiviral and antitumor immunity.

Key words: cGAS-STING, Smad7, oligomerization, scaffold protein, innate immunity

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P6

Enhancing the Chemical Toolbox for Ferroptosis Pathology Intervention

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Since its initial characterization in 2012, ferroptosis has been linked to a wide array of physiological and pathological states, including organ injuries, degenerative diseases, development, and aging. The growing appreciation of ferroptosis's role in various pathologies has highlighted an urgent need for the development of potent and safe inhibitors suitable for clinical applications. Over the recent years, our research has been dedicated to the discovery of innovative ferroptosis inhibitors through high-throughput screening and integrated chemical-biological research. To date, we have uncovered a diverse series of novel inhibitors with remarkable inhibitory effects, including several drugs already approved by the FDA for different medical conditions.

Curiously, our mechanistic studies have uncovered that these compounds mitigate ferroptosis by engaging various stages of its regulatory pathway. These include: (1) radical trapping agents (RTAs) or prodrugs of RTAs that neutralize lipid reactive oxygen species (ROS); (2) chemicals that modify and stabilize glutathione peroxidase 4 (GPX4); (3) chemicals that modulate the metabolism of polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) to avert lipid peroxidation; (4) innovative inhibitors of ferrotinophagy that impede the interaction between NCOA4 and ferritin.

Among these newly identified inhibitors, Tanshinone compounds stand out for their exceptional anti-ferroptosis potency, with an EC50 ranging from 2 to 10 nM, attributed to a unique "NQO1 gain-of-function" mechanism. The in vivo efficacy of these novel inhibitors has been corroborated across multiple pathological models associated with ferroptosis. Collectively, our research not only broadens

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the spectrum of chemical toolbox for addressing ferroptosis-related pathologies, be it through the introduction of new compounds or the repurposing of existing medications, but also sheds new light on the intricate regulatory mechanisms governing ferroptosis.

Since defined in 2012, ferroptosis has been found to associate with various physiological and pathological conditions, such as organ injuries, degenerative pathologies, development, and aging. The evolving understanding of ferroptosis in pathologies underscores the need for effective and safe ferroptosis inhibitors for clinical use. In past few years, we have focused on developing novel ferroptosis inhibitors by high-throughput screening and chemical-biological studies. So far we have identified multiple series of new ferroptosis inhibitors with potent inhibitory activities, including several FDA-approved drugs that were proposed for other diseases. Interestingly, mechanistic investigations have revealed these compounds suppress ferroptosis by targeting various steps of ferroptosis regulation, including: (1) radical trapping agents (RTA) or prodrugs of RTAs that directly eliminate lipid ROS; (2) chemicals that modify and stabilize GPX4; (3) chemicals targeting PUFAs and MUFAs metabolism to prevent lipid peroxidation; (4) novel ferrotinophagy inhibitors that block NCOA4-ferritin interaction. Among these new inhibitors, Tanshinone compounds exhibit most potent anti-ferroptosis activity (EC50= 2-10 nM) with a novel “NQO1 gain-of-function” mechanism. The in vivo effect of these new inhibitors was also verified in several ferroptosis-associated pathological models. Taken together, our work have expanded the chemical pool for targeting ferroptosis pathologies with either novel compounds or repurposing of known drugs. In addition, our studies also provide new insight of regulatory mechanisms of ferroptosis.

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P7

Oncometabolite 5-IP7 inhibits inositol 5-phosphatase to license protumorigenic E-cadherin endocytosis

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ABSTRACT

E-cadherin downregulation is an epithelial-mesenchymal transition hallmark canonically attributed to transcriptional repression. We delineate a metabolite-driven endocytic route of E-cadherin downregulation in inflammation-driven colorectal cancer (CRC). Specifically, IP6 kinase-2 (IP6K2), a 5-diphosphoinositol pentakisphosphate (5-IP_7) synthase upregulated in CRC patients, is activated via a ROS-Src phosphorylation axis elicited by the colitis inducer dextran sulfate sodium (DSS), generating 5-IP_7 around adherens junction (AJ) to promote E-cadherin endocytosis and unleash β-catenin's nuclear transcriptional activities. Mechanistically, 5-IP_7 inhibits inositol 5-phosphatases such as OCRL via steric competition with the substrate PI(4,5)P_2, thereby promoting PI(4,5)P_2-mediated endocytic adaptor recruitment. Depleting 5-IP_7 or overexpressing a 5-IP_7 binding-deficient OCRL mutant confers resistance to DSS-elicited AJ disruption. Intestinal epithelial-specific IP6K2 deletion attenuates DSS-induced colitis/CRC, whereas an IP6K2 isoform-selective inhibitor protects wildtype but not IP6K2$^{-/-}$ mice against DSS insult. These findings implicate 5-IP_7 as an oncometabolite whose stimulus-dependent synthesis relieves a PI(4,5)P_2 dephosphorylation-based endocytic checkpoint, leading to AJ disassembly and protumorigenic β-catenin activation. Targeting IP6K2 could strengthen intestinal epithelial barrier against inflammation and cancer.

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P8

Deficiency of KMT2D causes autistic-like behavior in mice and zebrafish

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Kabuki syndrome type 1 is a congenital multisystem disorder caused by *KMT2D* mutations. While some studies suggest that *KMT2D* deficiency may lead to autistic-like behaviors, the role of *KMT2D* in social behavior remains unconfirmed due to a lack of animal model evidence. In this study, we developed a mouse knockdown model and a zebrafish knockout model to investigate the role of *KMT2D* in synaptic function and behavioral patterns. We also performed an RNA sequencing analysis to delve into the molecular and cellular mechanisms of *KMT2D*. Results showed that *Kmt2d* deficiency in mouse and zebrafish both exhibited autistic-like behaviors including social behaviors defects and repetitive behavior. Additionally, knockdown of *Kmt2d* in the mouse hippocampus decreases excitatory and increases inhibitory synaptic transmission, disrupting the excitation-inhibition balance—a hallmark of autistic-like behaviors. RNA sequencing analysis revealed that under conditions of low kmt2d expression, differentially expressed genes were associated with glutamatergic and GABAergic synapses, supporting the dysregulation of excitation-inhibition balance in the hippocampus. Taken together, our research elucidates the critical role of KMT2D in modulating animal social behavior, potentially through its impact on synaptic excitation-inhibition balance.

Key words: KMT2D; autism; synaptic; excitation-inhibition balance

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P9

The role and mechanism of receptor-like protein LRTM1 in the negative regulation of cardiomyocyte regeneration

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Background:

One of the core pathological features of myocardial infarction is the loss of cardiomyocytes, and promoting cardiomyocyte regeneration represents a potential therapeutic strategy for post-infarction heart failure.The aim of this research is to uncover the role and mechanisms of Receptor-like Protein LRTM1 in cardiomyocyte regeneration, providing novel therapeutic targets for cardiac repair.

Method:

In this study, we performed two cardiac injury models - apical resection and myocardial infarction operation - in both neonatal and adult mice. Cardiomyocyte-specific Lrtm1 deletion was achieved through combinatorial use of Myh6-MerCreMer and Myh6-iCre transgenic mouse lines with Lrtm1fl/fl conditional alleles. A series of molecular signaling experiments, including RNA sequencing, immunostaining, coimmunoprecipitation and iquid chromatography–mass spectrometry analyses, were conducted. Heart regeneration and cardiac function were evaluated by Masson staining and echocardiography, respectively.

Result:

Integrated analysis of RNA-seq data from P1 and P7 murine hearts, as well as P1 myocardial infarction (MI) versus sham-operated hearts, revealed a negative correlation between LRTM1 (a transmembrane protein) expression and cardiomyocyte proliferative capacity. Notably, LRTM1 exhibited cardiac-specific enrichment, particularly in cardiomyocytes, compared to other organs. These findings implicate LRTM1 as a critical regulator of intrinsic myocardial regeneration. In vitro and in vivo functional studies demonstrated that LRTM1 knockdown enhanced proliferation in neonatal rat primary

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cardiomyocytes, extended the postnatal cardiomyocyte proliferative temporal window in neonatal mice, and promoted cardiomyocyte proliferation in adult MI mice, thereby improving post-MI cardiac function and attenuating pathological ventricular remodeling. Transcriptomic profiling identified LRTM1 knockdown-mediated regulation of multiple cardiomyocyte proliferation-associated processes, including cell cycle progression, metabolism, electrophysiology, and sarcomere organization. Mechanistically, combined RNA-seq and motif enrichment analyses revealed that LRTM1 downregulation suppressed JAK/STAT1 signaling activation by impairing extracellular IFN-α/receptor binding, leading to reduced IRF1 transcription factor expression. This cascade ultimately drives cardiomyocyte proliferation through coordinated modulation of cell cycle-related proteins.

Conclusion:

LRTM1, a novel receptor-like protein, is specifically expressed in cardiomyocytes. Cardiomyocyte-specific knockout of LRTM1 promotes cardiomyocyte proliferation, extends the proliferative time window in neonatal mice and ameliorates post-infarction cardiac remodeling in adult mice via interferon signaling.These findings support a potentially important new therapeutic approach for human heart failure.

Key words: heart regeneration; myocardial infarction; transmembrane protein; interferon; signal transduction

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P10

分泌型 NCAM1 促进泡沫细胞胆固醇外流抑制动脉粥样硬化进展的作用及其机制研究

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背景：动脉粥样硬化（Atherosclerosis, AS）是一种严重危害人类健康的慢性心血管疾病。AS斑块内脂质代谢异常，尤其是斑块内泡沫细胞胆固醇外流异常在AS斑块发生发展中起重要作用。分泌型神经细胞黏附分子1（Secreted Neural cell adhesion molecule1, sNCAM1）与脂质代谢以及冠心病有一定的关系，但其对泡沫细胞胆固醇外流及AS发生发展过程的影响及机制尚不清楚

目的：探究分泌型NCAM1在泡沫细胞胆固醇外流及AS斑块发生发展过程中的作用及机制。

方法：我们对14例急性冠脉综合征（Acute Coronary Syndrome，ACS）、14例慢性冠脉综合征（Chronic Coronary Syndrome，CCS）和12例健康对照的血清样本进行蛋白质谱分析，筛选出sNCAM1在ACS患者血清中表达显著降低，并且其水平与血清高密度脂蛋白胆固醇（high-density lipoprotein cholesterol，HDL-c）水平呈正相关。利用神经元和神经胶质细胞来探究sNCAM1的分泌和释放以及生物学来源。随后利用ApoE-/-小鼠，予高脂饮食构建动脉粥样硬化模型，同时每周尾静脉注射外源性NCAM1重组蛋白，8周后取材分析小鼠血清血脂成分的改变；油红、Masson、HE染色分析主动脉斑块负荷、主动脉根部斑块面积、脂质成分、胶原成分的变化。最后我们构建巨噬细胞源性和平滑肌细胞源性泡沫细胞模型，通过分子生物学实验手段研究sNCAM1在泡沫细胞内的作用，用BODIPY493/503染色检测sNCAM1对泡沫细胞胆固醇聚集以及胆固醇外流的影响。最后结合组学数据、分子间相互作用和分子功能研究的实验技术，对sNCAM1发挥生物学效应的分子机制进行了探究。

结果：sNCAM1在ACS患者血清中表达水平显著降低，且与HDL-c呈正相关；NCAM1主要在神经元和神经胶质细胞中表达，在ox-LDL或缺氧刺激下，神经元细胞表达和分泌NCAM1均减少；注射sNCAM1的ApoE-/-小鼠血清中TC下降，HDL-c上升，主动脉斑块负荷减少，主动脉根部斑块面积减少，脂质成分减少；sNCAM1抑制泡沫细胞形成，促进泡沫细胞胆固醇外流；sNCAM1促进平滑肌源性泡沫细胞中ABCA1的表达，抑制p38 MAPK通路中p-p38的水平。

结论：sNCAM1可抑制泡沫细胞形成，促进胆固醇外流，减缓小鼠动脉粥样硬化过程。

关键词：动脉粥样硬化；胆固醇外流；泡沫细胞；分泌型NCAM1

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P11

SMAD9 recruits HDAC1 to antagonize BMP signaling during cardiac development

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SMAD1, SMAD5, and SMAD9 form a subgroup of receptor-regulated SMADs that act as intracellular mediators of Bone Morphogenetic Protein (BMP) signaling, a crucial pathway for embryonic development. However, it remains poorly understood how these highly homologous SMAD proteins exercise distinct transcriptional regulatory roles in BMP responses. In this study, we identify SMAD9 as a novel negative regulator of BMP-mediated cardiac development. Ectopic expression of SMAD9 in mammalian cells inhibits BMP signaling, leading to impaired cardiomyocyte differentiation. Consistent with these findings, microinjection of SMAD9 mRNA into zebrafish embryos disrupts cardiac morphogenesis, resulting in severe heart looping defects, which can be rescued by the addition of exogenous BMP2. Notably, BMP signaling induces the transcription of SMAD9, indicating an autoregulatory feedback mechanism. At the molecular level, BMP-induced phosphorylation of SMAD9 enhances its interaction with histone deacetylase 1 (HDAC1). This SMAD9-HDAC1 complex binds to BMP-responsive promoters, establishing a repressive chromatin state that suppresses target gene expression. Our findings reveal a previously unrecognized regulatory paradigm wherein SMAD9 functions as a critical feedback inhibitor of BMP signaling, establishing the BMP-SMAD9 axis as an essential regulatory module in cardiac development.

Key words: BMP signaling, SMAD proteins, HDAC1, cardiomyocyte differentiation, cardiac development cell biology

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P12

MSH2 Deficiency Enhances Antitumor Immune Response by Suppressing ELR + CXC Chemokines

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DNA mismatch repair (MMR) is crucial in maintaining genomic stability through repairing base-base and insertion/deletion mismatch in newly synthesized strands during DNA replication. MMR deficiency (dMMR) leads to unrepaired DNA errors, resulting in mutator phenotype and tumor development. dMMR tumors can produce neoantigens to stimulate immune response, rendering them sensitive to immunotherapy. However, although all dMMR tumors express high levels of neoantigens, almost half of dMMR tumors still did not respond to immunotherapy, suggesting that there are additional mechanisms regulating the immune response in dMMR tumors. In the MMR system, the most common defective genes are MLH1 (MutL Homolog 1) and MSH2 (MutS Homolog 2). Studies have found that MLH1 deletion can activate the cGAS-STING pathway to induce immune response. In contrast, MSH2 deficiency fails to activate cGAS-STING, indicating a distinct mechanism by which MSH2 deficiency promotes tumor immunity. To investigate the role of MSH2 deficiency in tumor immunity, RNA-Seq analysis revealed significant downregulation of CXCL8 in MSH2-KO cells, with expression restored upon MSH2 rescue. These findings were validated by RT-qPCR, Western blot, and ELISA, confirming that MSH2 deletion suppresses both mRNA and protein levels of CXCL8 (an ELR$^+$ CXC chemokine). Additionally, MSH2 knockout suppressed mRNA levels of other ELR$^+$ CXC chemokines. Based on these results, we hypothesize that MSH2-deficient tumor may alleviate the immunosuppressive TME by suppressing ELR+ CXC chemokines, thereby enhancing anti-tumor immune responses. This study aims to investigate whether MSH2 deficiency promotes anti-tumor immune responses by repressing ELR$^+$ CXC chemokines and to explore the underlying mechanisms.

Key words: MMR; MSH2; immunotherapy; chemokines

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P12

MSH2 缺陷促进抗肿瘤免疫的机制研究

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DNA错配修复(DNA mismatch repair，MMR)在维持基因组稳定中至关重要，其功能缺失(MMR deficiency，dMMR)会导致突变表型的产生和肿瘤的发生。dMMR肿瘤通过产生新抗原刺激机体免疫应答，使其对免疫治疗敏感。然而，尽管所有肿瘤都会产生新抗原，仍有50% dMMR肿瘤对免疫治疗无效，这表明dMMR还通过其他机制调节免疫应答。MLH1和MSH2是MMR系统中最常见的缺陷基因，研究发现MLH1缺失可以激活cGAS-STING信号通路激活免疫应答，但本研究前期发现MSH2缺失不能激活cGAS-STING信号通路。有趣的是，我们发现MSH2缺失可以抑制含谷氨酸-亮氨酸-精氨酸基序的CXC(ELR+ CXC)趋化因子的转录。本研究旨在阐明MSH2缺陷是否通过抑制ELR+ CXC趋化因子促进肿瘤免疫应答，并探索其可能机制，为临床癌症治疗策略提供新的见解。

关键词：DNA错配修复；MSH2；免疫治疗；趋化因子

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P13

Multiscale dynamics in T Cell antigen recognition

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The immune system relies on a specialized group of immune cells to defend against foreign pathogens, viruses, bacteria, and cancer. T lymphocytes play a central role in adaptive immunity by recognizing exogenous antigens and initiating specific immune responses. As the therapeutic potential for cancer and other immune-related diseases continues to gain attention, T cells and their role in adaptive immunity have become a major research focus. This is particularly true for Chimeric Antigen Receptor (CAR) T cell therapy and transgenic T Cell Receptor (TCR) therapy, which are at the forefront of immunotherapy advancements. With the continuous advancement in our understanding of TCR structure, signaling initiation, and function, mechanical forces have emerged as a crucial factor in T-cell antigen recognition and activation. However, the role of mechanical forces and their underlying mechanisms remain insufficiently understood. To address this knowledge gap, we have developed a mechano-immunological coupling model to investigate the mechanisms of antigen recognition and activation during the adhesion process between T cells and antigen-presenting cells (APC). This model captures the force transfer process from the APC to the T cell and integrates the dynamic adhesion behavior at the interface with the signaling pathways within the T-cell cytoplasm. Our findings reveal that the discrimination ability and sensitivity of antigen recognition are primarily mediated by the mechanical strength of TCR-pMHC (TM) binding by influencing force transmission and the adhesion topology at the interface.

Key words: T cell; multiscale dynamics; discrimination; sensitivity

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Maternal ELL3 loss-of-function leads to oocyte aneuploidy and early miscarriage

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Abstract

Up to an estimated 10% of women experience miscarriage in their lifetimes. Embryonic aneuploidy is a leading cause for miscarriage, infertility and congenital defects. Here we identify variants of ELL3, a gene encoding a transcription elongation factor, in couples who experienced consecutive early miscarriages due to embryonic aneuploidy. Maternal ELL3 knockout leads to mouse oocyte aneuploidy, subfertility and miscellaneous embryonic defects. Mechanistically, we fnd that ELL3 localizes to the spindle during meiosis, and that ELL3 depletion in both mouse and human oocytes increases the incidence of meiotic spindle abnormality. ELL3 coordinates with TPX2 to ensure the proper function of the microtubule motor KIF11. Live imaging analysis shows that ELL3 is paramount for promoting spindle assembly and driving chromosome movement. Together, our fndings implicate maternal ELL3 defciency in causing oocyte aneuploidy and early miscarriage.