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# Editorial: Gene regulation mediated by competing RNA: From benchside to bedside

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Editorial on the Research Topic
Gene regulation mediated by competing RNA: From benchside to bedside

In addition to DNA methylation and chromatin structure, another important level of epigenetic regulation for gene expression is non-coding RNA (ncRNA) (Luo et al., 2019). NcRNAs facilitate post-transcriptional gene regulation *via* competitively interacting with the regulatory elements of target genes (Zhang et al., 2022). The course of various biological processes, the development of diseases, and the susceptibility to therapy are all significantly influenced by competitive ncRNA gene regulation (Panni et al., 2020). Numerous studies have demonstrated that important functional genes could be regulated by these ncRNAs *via* competing endogenous RNA (ceRNA) network (Salmena et al., 2011; Tay et al., 2011; Tay et al., 2014). Moreover, a large number of therapeutic means have been developed based on these mechanisms (Luo and Zhu, 2014). Thus, competitive RNA is expected to be used not only for basic research but also as a promising tool for applications in therapy. In this Research Topic, the essential functions and mechanisms of ncRNAs are further identified and investigated.

Circular RNAs (circRNAs) are ncRNAs that play a regulatory role in many biological processes, such as cell proliferation, senescence, and apoptosis (Visci et al., 2020). Many studies have found that circRNAs can play their regulatory role as microRNA (miRNA) sponges in human physiological and pathological processes (Peng et al., 2021). Whether as a diagnostic biomarker or as a therapeutic target, circRNAs have important values for studying the pathogenesis of diseases owing to their unique properties.

Aberrant alterations in nucleus pulposus cells (NPCs) are the most significant aspect of the pathological process of intervertebral disk degeneration (IDD) (Fontana et al., 2015; Oichi et al., 2020). In this context, Li et al. investigated circRNAs and miRNAs associated

with NPC metabolism under the IDD condition. They identified that circ_0040039 might aggravate IDD by stabilizing miR-874-3p and thus upregulate the miR-874-3p-ESR1 pathway, which lead to NPC degeneration and worsen IDD. In another study, Duan et al. demonstrated that circMTO1 could accelerate the progression of polycystic ovary syndrome (PCOS) by increasing MCL1 expression through interaction with miR-320b, offering novel insights into the development of diagnosis and treatment for PCOS. Furthermore, Cai et al. revealed that hsa_circRNA_0001400 is substantially expressed in cervical cancer tissues and promotes tumor progression *via* the circRNA_0001400-miR-326-Akt pathway. Knockdown of circRNA_0001400 by siRNA might potentially developed as a new method for cervical cancer therapy.

Long non-coding RNAs (lncRNAs), like circRNAs, can serve as miRNA sponges to provide indirect regulation of gene expression (Zhang et al., 2018). Besides, artificial lncRNAs have recently drawn a lot of interest as novel disease therapy tools to be utilized in gene regulatory activities (Tang et al., 2016).

Atrial fibrillation (AF), the most prevalent kind of arrhythmia, poses a great challenge in patient diagnosis and therapy (Hindricks et al., 2021), and further research into the pathophysiology of AF is of urgent need. Liu et al. constructed a ceRNA network associated to AF susceptibility and persistence, and then prioritized the selected lncRNAs using an innovative application of the improved RWR-M algorithm. Myocardial infarction-associated transcripts (MIAT) and LINC00964 were identified as featured lncRNAs in the network. These discoveries are in line with a prior study (Deshmukh et al., 2015), and they also suggested that ceRNA network analysis might shed light on the basic mechanisms underlying AF and offer promising therapeutic and diagnostic tools. In another study, kidney stones are hypothesized to be caused by Randall's plaque (RP) (Daudon et al., 2015). Xia et al. investigated the rate of immune cell infiltration as well as the ceRNA network in RPs from renal stone patients and validated the results both *in vivo* and *in vitro*. They then found that the lncRNA-associated differentially expressed mRNAs were significantly associated with renal interstitial fibrosis in extracellular matrix tissues, regulatory cell responses to growth factor stimulation, and collagen-containing extracellular matrices. In addition, Wu et al. summarized the recent research progress of LINC00467, detailing its biological mechanisms as an oncogene and clinical values as a prognostic predictor in various types of cancers.

MiRNAs as a class of small ncRNAs play a crucial role in downregulating gene expression by competitively interacting with the mRNA 3′UTR region and mediating RNA degradation through the RISC complex (Zhou et al., 2022). MiRNAs have two main applications. On the one hand, artificial miRNAs are often developed as genetic tools based on their downregulation mechanism to affect gene expression (Zhu et al., 2018). On the other hand, miRNAs are often utilized in targeted gene therapy due to the characteristic that miRNA targets can be used to attain tissue or cell-type specific transgene expression (Luo et al., 2015a).

MiRNAs have important roles in the emergence of epilepsy due to their capacity to regulate a variety of mRNAs. Previous studies have shown that miRNAs could alter neuronal excitability, which has an impact on the incidence of epilepsy (Henshall et al., 2016). Su et al. constructed a miRNA-mRNA regulation network that regulates ion channel genes in the mesial temporal lobe epilepsy (mTLE). They identified that miR-27a-3p might control a number of ion channel genes associated with mTLE, pointing to the possibility of using it as a diagnostic biomarker for mTLE.

In addition, the human induced pluripotent stem cells (hiPSCs) and embryonic stem cells (hESCs) are powerful tools for genetic studies in the recent years (Luo et al., 2021a). Some previous studies have illustrated the roles of several lncRNA-miRNA-mRNA circuits in regulating the pluripotent genes in hESCs (Wang et al., 2013; Xu et al., 2016). In this Research Topic, Chen et al. systematically reviewed the current progress in applying iPSC-derived models to study the regulatory role of miRNAs in developmental processes.

As sequencing technologies advance quickly, the expression profiles of different classes of ncRNAs are feasible to be characterized simultaneously in disease models, such as dilated cardiomyopathy (DCM) (Lin et al., 2021). Based on sex differences in DCM, Liu et al. constructed an immune-related ceRNA network including 5 lncRNAs, 6 miRNAs, and 29 mRNAs that might regulate several immune-related signaling pathways. Among these genes, CBL, CXCL12, and IL6ST were found to be connected to immune cell infiltration.

Here we assembled a compendium of 11 manuscripts including nine original researches and two reviews that cover the scope of this Research Topic, summarizing the critical aspects of the gene regulation mediated by competing RNAs in various diseases.

Additionally, we would also like to highlight other novel forms of competing RNA-mediated gene regulation that are yet to be included in the above compendium. Guide RNA (gRNA) is an important class of artificial small ncRNA that competitively bind with elements on the genome with the CRISPR/Cas complex (Luo et al., 2015b). Besides genome editing, the RNA-guided gene targeting technology has also been exploited quickly and extensively for diverse purposes, including gene regulation (Luo et al., 2016).

Recently, RNA viruses, such as SARS-CoV-2, have been found to act as exogenous competing RNAs and thus regulate endogenous gene expression, which may contribute to the disease progression (Bertolazzi et al., 2020). And in the current COVID-19 pandemic, it is of great interest to focus

on the role of SARS-CoV-2 in competing RNA-mediated gene regulation (Luo et al., 2021b).

## Author contributions

YL, DZ, and J-HF wrote and edited the manuscript. All authors have approved the manuscript for publication.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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