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Mammalian ncRNA-disease repository: a global view of ncRNA-mediated disease network

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Dear Editor

Recently, substantial studies have begun to explore the functional diversity and mechanistic roles of ncRNAs in mammals.[1] Now, it has become increasingly apparent that ncRNAs are involved in multiple major biological processes, such as developmental timing, fat metabolism and cell death.[2] Furthermore, the epigenetic and genetic defects in ncRNAs and their processing machinery have been implicated in the etiology of many forms of diseases.[3] Several databases that documented the relevance of the microRNAs(miRNAs) to diseases have been constructed and provided useful results.[4,5] However, miRNAs are just the tip of the iceberg, other ncRNAs such as long non-coding RNAs (lncRNAs), PIWI-interacting RNAs (piRNAs) and small nucleolar RNAs (snoRNAs) have also been demonstrated to contribute to diseases.[3,6] Accumulated evidence suggest the diverse non-coding RNAs (ncRNAs) involved in a wide variety of diseases progression.[3,6,7] It is a key challenge for understanding the precise behavior of diverse ncRNAs in mammalian diseases and deciphering the cross-regulations among disease-associated ncRNAs. Because there was no repository focused on diverse ncRNA-disease relationships in mammals, we have developed a manually curated diverse ncRNA-disease repository (MNDR, www.rna-society.org/mndr/) by integrating evidence in three mammals. Totally, 807 lncRNA-associated, 229 miRNA-associated, 13 piRNA-associated and 100 snoRNA-associated entries for 1149 curated entries were documented for three mammals (866 *Homo sapiens*-associated, 251 *Mus musculus*-associated and 32 *Rattus norvegicus*-associated entries) (Table 1).

Recent investigations indicated there are complex regulations among diverse ncRNAs and protein-coding genes. Such as, *PTEN* gene and the *PTEN* pseudogenes (*ptenp1*, one of lncRNAs) share a high degree of sequence homology, changes in ptenp1 expression levels indirectly affect *PTEN* expression by sequestering *PTEN*-targeting miRNAs.[8]

Table 1 The statistics of the ncRNA-disease entries in MNDR database

Species	lncRNA	miRNA	piRNA	snoRNA	Total
Homo sapiens	753	NA	13	100	866
Mus musculus	50	201	0	0	251
Rattus norvegicus	4	28	0	0	32
Total	807	229	13	100	1149

Thus understanding the mutual regulating pattern among diverse ncRNAs and protein-coding genes, particularly in disease conditions, is a key challenge. Thus, MNDR is not only a knowledge depository but providing us a good opportunity to view the ncRNA-mediated disease network globally (in visualization page: www.rna-society.org/mndr/visualization.html). Diverse ncRNAs and interaction genes were represented as nodes and the regulations were denoted as edges. Based on such a simplified ncRNA-mediated disease network, interesting observations have been achieved. The result showed that snoRNA *htr*, as a hub node, has intensively linked to 21 interaction genes in the network. More important, through *BCL2*, *BCL2L1* and *BAX*, the snoRNA *htr* can communicate with the lncRNA *malat1* (Supplementary Figure 1). Another example is snoRNA *htr* and lncRNA *h19* are linked by *E2F1* and *MYC*. When combined with human disease-associated miRNA evidence from mir2disease database, lncRNAs, miRNAs and snoRNAs, together with their interaction/target genes, can be integrated into bigger expanding ncRNA-mediated disease network. The biggest sub-network has 129 nodes and 149 edges, involving 33 lncRNAs, 1 snoRNA, 19 miRNAs and 76 interaction protein-coding genes(Supplementary Figure 2). In this network, more regulations among diverse ncRNAs directly or indirectly via intermediate genes, lncRNA *dgcr5, har1a* and *har1b*, were connected with *hsa-mir-21* via intermediate gene *REST.* Interestingly, *hsa-mir-21* and snoRNA *htr* were linked by key anti-apoptosis gene *BCL2*. Similar results were observed that

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lncRNA *dgcr5, har1a* and *har1b* can also communicate with snoRNA *htr* through alternative route *NFKB1-hsa-mir-9-REST*. Hence, according to current data, the two pivot protein-coding genes (*BCL2* and *NFKB1*) and several ncRNAs (lncRNA *malat1*, snoRNA *htr* and miRNA *hsa-mir-21*, *has-mir-9*) collectively play an important role in the ncRNA-mediated disease network (Supplementary Figure 2). Importantly, the crosstalk between lncRNA *malat1* and miRNA *hsa-mir-21* can be found conserved in mouse ncRNA-mediated disease network. Above observations indicated diverse ncRNAs could communicate with each other in disease state through some disease-associated genes in mammals, highlighting the complexity, conservative and plasticity of the regulatory relationships between diverse ncRNAs and protein-coding genes in diseases.

Conflict of Interest

The authors declare no conflict of interest.

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