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# 部門公開セミナー

共催：新学術領域研究「配偶子産生制御」

## Major role of DND1 is post-transcriptional gene silencing by recruiting the CCR4-NOT deadenylase complex to the target mRNAs in the germline

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*Dead end homolog 1* (*Dnd1*), also known in humans as *DND microRNA-mediated repression inhibitor 1*, encodes an evolutionarily conserved, germline-specific RNA-binding protein (RBP) containing two RNA recognition motifs (RRMs). The loss of *Dnd1* results in male sterility and high incidence of teratocarcinoma formation in 129Sv mice. While DND1 is believed to target large number of mRNAs and antagonize miRNA-mediated mRNA degradation, the global targets and molecular mechanism of DND1 function remain elusive. Here we show using Photo-Activatable Ribonucleoside enhanced Cross-Linking and ImmunoPrecipitation (PAR-CLIP) that DND1 binds to AU-rich sequences near the poly-A tail in the 3'UTR on mature mRNAs and shares ~78% of the target mRNAs with miRNA/AGOs. In these, 19% of miRNA/AGO-binding sites overlapped with DND1. Unexpectedly, DND1 interacts with the CCR4-NOT deadenylase complex, a major catalytic subunit for miRNA/AGO-dependent mRNA degradation. Furthermore, DND1 induced down-regulation of target transcripts with a concomitant reduction of protein levels and, in contrast to previous reports, reinforce the miRNA/AGO-dependent target destabilization. We further validated this model using mouse germline stem cells (GSCs), which represent an *in vitro* counterpart of spermatogonial stem/progenitor cells (SSCs). We show a significant up-regulation of homologs of human DND1 targets upon knocking down Dnd1 in mouse GSCs, suggesting that molecular function and target specificities of DND1 are conserved between mice and humans. This up-regulation is likely mediated by the CCT4-NOT complex. Loss of *Cnot1*, which encodes a scaffold protein of the CCR4-NOT deadenylase complex, leads to up-regulation of transcripts largely overlapped with the up-regulated transcripts in *Dnd1*-knockdown GSCs. Taken together, the major role of DND1 is to destabilize target mRNAs and reinforce the miRNA-dependent mRNA destabilization. This work represents a necessity for revisiting the PTGR underlying germ cell development as well as TGCT formation.

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