IN BRIEF

RNA

DIS3L2, the final player in let-7 degradation

The pluripotency factor LIN28 maintains stem cells in an undifferentiated state by blocking the expression of let-7 microRNAs (miRNAs). LIN28 achieves this by recruiting 3′ terminal uridylyl transferases, which add a terminal oligouridine tail to pre-let-7 that inhibits its processing and promotes miRNA decay. This study identifies the 3′-5′ endonuclease DIS3L2 as the enzyme responsible for promoting pre-let-7 degradation in mouse embryonic stem (ES) cells. DIS3L2 was found to preferentially degrade uridylated pre-let-7 over unmodified pre-let-7 or unrelated miRNAs *in vitro*. Moreover, siRNA-mediated depletion of DIS3L2 in mouse ES cells resulted in the accumulation of uridylated pre-let-7, whereas knockdown of the exosome 3′-5′ endonucleases EXOSC10 or RRP44 had no effect, confirming that DIS3L2 is the nuclease responsible for carrying out pre-let-7 decay in the LIN28 pathway.

ORIGINAL RESEARCH PAPER Chang, H.-M. *et al.* A role for the Perlman syndrome exonuclease Dis3l2 in the Lin28–let-7 pathway. *Nature* **497**, 244–248 (2013)

DNA REPAIR

A histone signal for mismatch repair

Errors that arise during DNA replication are corrected by the mismatch repair pathway (MMR), which detects base–base mismatches and insertion–deletion loops primarily via MutSα (comprising MutS homologue 2 (MSH2) and MSH6). Previous work had indicated that additional factors to the core MMR machinery, such as histone modifications, are needed for MMR *in vivo*. So Li *et al.* hypothesized that the MSH6 Pro-Trp-Trp-Pro (PWWP) domain, which acts as a 'reader' of trimethylated Lys36 on histone 3 (H3K36me3), is involved in this process. They found that MutSα preferentially binds to H3K36me3 *in vitro* and that the PWWP domain is essential for this. Moreover, H3K36me3 was shown to recruit MutSα to chromatin *in vivo* in G1 and early S phase, which might ensure that MutSα is present when DNA replication errors occur. Importantly, cells lacking H3K36me3 had an increased rate of spontaneous mutations and microsatellite instability (a hallmark of MMR). Therefore, H3K36me3 is involved in MMR by promoting the recruitment of MutSα to chromatin.

ORIGINAL RESEARCH PAPER Li, F. *et al.* The histone mark H3K36me3 regulates human DNA mismatch repair through its interaction with MutSα. *Cell* **153**, 590–600 (2013)

CELL DEATH

RB acts outside the nucleus

The RB tumour suppressor inhibits E2F transcription factors to prevent cell cycle progression and has a role in apoptosis through direct and indirect transcriptional mechanisms. Lees and colleagues now show that RB also functions at mitochondria to directly induce apoptosis. Tumour necrosis factor (TNF) promotes apoptosis via an extrinsic and an intrinsic pathway, the latter of which involves the activation of the BCL-2 protein family members BAX and BAK. These trigger mitochondrial outer membrane permeabilization (MOMP) and the release of pro-apoptotic factors from mitochondria. The authors show that RB associates with mitochondria and enhances apoptosis in response to TNF and that this function is independent of RB-mediated effects on transcription. Instead, RB triggers MOMP by interacting with BAX to promote an activating conformational change in this protein. Importantly, the localization of RB at mitochondria was found to contribute to its tumour-suppressive function.

ORIGINAL RESEARCH PAPER Hilgendorf, K. I. *et al.* The retinoblastoma protein induces apoptosis directly at the mitochondria. *Genes Dev.* **27**, 1003–1015 (2013)