Nature Reviews Molecular Cell Biology | Published online 24 Jan 2018; doi:10.1038/nrm.2018.6

GENE EXPRESSION

AMPK relieves PRC2-mediated silencing

> AMPK directly phosphorylates EZH2, thereby inhibiting PRC2

Intermediary metabolic pathways can affect gene expression by regulating epigenetic modifications, but our understanding of the mechanisms of this regulation and its effects on cell function is limited. Wan *et al.* now show that a major metabolic sensor, AMPK, is a negative regulator of gene silencing mediated by Polycomb repressive complex 2 (PRC2) and that this activity has tumour-suppressive functions.

AMPK regulates cell energy status by limiting cell proliferation and by supporting cell survival in energy-deprivation conditions. To investigate its role in epigenetic regulation, the authors analysed histone methylation in AMPK-knockout mouse embryonic fibroblasts (MEFs). Levels of histone H3 Lys27 trimethylation (H3K27me3) were significantly increased in knockout cells, whereas induction of AMPK reduced H3K27me3 levels in wild-type MEFs as well as in ovarian and breast cancer cell lines. Thus, AMPK is a negative regulator of H3K27me3.

Getty/Imgorthand

PRC2 is the primary H3K27 methyltransferase. Depletion of enhancer of zeste homologue 2 (EZH2), the main PRC2 catalytic subunit, abrogated the increase in H3K27me3 levels in the AMPK knockout cells, as well as after AMPK inhibition. Furthermore, EZH2 target genes were downregulated in the absence of AMPK and upregulated by its activation. This indicated that AMPK regulates gene expression through counteracting EZH2–PRC2-mediated gene silencing.

Next, the authors showed that EZH2 and AMPK physically interact in cells, and that EZH2 is phosphorylated in the presence of AMPK on three residues, one of which, Thr311, is part of a near-canonical motif for AMPK. A phosphomimetic mutant of EZH2 (EZH2-Thr311Glu) had reduced activity in various cancer cell lines, whereas upon the expression of non-phosphorylatable EZH2 mutants (EZH2-Thr311Ala or EZH2-Arg308Leu) H3K27me3 levels were not reduced by AMPK activation. EZH2-Thr311Glu was further shown to exhibit decreased binding to the PRC2 scaffolding component SUZ12, which consequently impaired the assembly of the entire PRC2 complex. Thus, AMPK directly phosphorylates EZH2, thereby inhibiting PRC2 assembly and activity.

EZH2 represses the expression of tumour suppressors and is frequently overexpressed or mutated in various cancers. EZH2-Thr311Ala and EZH2-Arg308Leu showed stronger capability to promote tumorigenesis than wild-type EZH2 (by supporting proliferation, anchorage-independent growth and aggressive phenotypes), whereas EZH2-Thr311Glu displayed compromised activity to support cell transformation. Accordingly, levels of phosphorylated EZH2 correlated with a better prognosis for patients with breast and ovarian cancers, suggesting that AMPK-mediated phosphorylation of EZH2 is a tumour-suppressive mechanism, at least in some contexts.

In summary, by directly phosphorylating EZH2, AMPK opposes PRC2-mediated gene silencing. As EZH2 is frequently upregulated in cancer and drives silencing of tumour suppressor genes, AMPK activation could be a therapeutic strategy for cancer.

Paulina Strzyz

ORIGINAL ARTICLE Wan, L. *et al.* Phosphorylation of EZH2 by AMPK suppresses PRC methyltransferase activity and oncogenic function. *Mol. Cell* http://doi.org/10.1016/j.molcel.2017.12.024 (2017)
FURTHER READING Herzig S. & Shaw R. J. AMPK: guardian of metabolism and mitochondrial homeostasis. *Nat. Rev. Mol. Cell Biol.* http://doi.org/10.1038/nrm.2017.95 (2017) | Blackledge N. P, Rose N. R. & Klose R. J. Targeting Polycomb systems to regulate gene expression: modifications to a complex story. *Nat. Rev. Mol. Cell Biol.* **16**, 643–649 (2015)