TUMORIGENESIS

Taking the hallmark?

DOI:

10.1038/nrc2161

URLs

Myc

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=4609

p27

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=1027

E2F1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=1869

SKP2

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=6502

CKS1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=1163

FOXM1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=2305

Burkitt lymphoma

<http://www.cancer.gov/cancertopics/types/non-hodgkins-lymphoma>

About 70% of all cancers show overexpression of the **Myc** family of transcription factors. A hallmark of Myc-mediated tumorigenesis is thought to be its ability to accelerate proliferation by downregulating the tumour suppressor **p27**, a cyclin-dependent kinase inhibitor. John Cleveland and colleagues have now identified a Myc-dependent pathway that is required to downregulate p27 and hence propagate lymphomagenesis.

Eμ-Myc transgenic mice overexpress *Myc* and develop B-cell lymphomas that resemble human **Burkitt lymphoma**. The **E2F1** transcription factor, a MYC target gene, is thought to be necessary, but not sufficient, for the MYC-mediated downregulation of p27 expression in these mice. Therefore, Cleveland and colleagues wanted to identify proteins other than E2F1 that might function downstream of MYC to mediate p27 downregulation. The expression of p27 is regulated at the transcriptional and protein levels, and MYC-dependent downregulation of p27 appears to be primarily achieved by modulating p27 protein stability. p27 is targeted for proteolysis by S-phase kinase-associated protein 2 (**SKP2**) and cyclin-dependent kinase subunit 1 (**CKS1**), both of which form the p27 phosphodegron binding site of the SCF^{SKP2} ubiquitin ligase holoenzyme. Indeed, using expression profiling of lymphomas from *Eμ-Myc* mice, the authors showed

that *Cks1* and to a lesser extent *Skp2* were overexpressed in precancerous B cells from *Eμ-Myc* mice. Although they showed that the induction of transcription of *Cks1* was MYC-dependent, this was indirect and could not be attributed to E2F1, nor to forkhead box M1 (**FOXM1**), a transcription factor that regulates the expression of *Cks1* and *Skp2*.

So, is MYC-mediated transcription of *Cks1* responsible for the tumorigenic downregulation of p27? Using quantitative reverse transcription PCR and western blotting to analyse 49 lymphomas from *Eμ-Myc* mice and 17 human Burkitt lymphoma samples, Cleveland and colleagues showed that p27 was commonly downregulated whereas CKS1 and SKP2 were overexpressed, suggesting that this expression profile could represent a hallmark of MYC-induced lymphoma. In addition, they showed that *Eμ-Myc;Cks1*^{-/-} mice had a marked delay in lymphoma development and prolonged survival. Next, they confirmed that this MYC-CKS1 pathway increased B-cell proliferation rates *in vivo* owing to p27 downregulation, and that CKS1 was required for MYC to downregulate p27. Importantly, they also showed that lymphomas from *Eμ-Myc;Cks1*^{-/-} mice continued to

express p27 and were less invasive, demonstrating the relevance of the MYC-CKS1 pathway in lymphomagenesis.

The continued expression of p27 in the lymphomas of *Eμ-Myc;Cks1*^{-/-} mice indicates that the MYC-CKS1 pathway cannot be bypassed in this mouse model. Although not fully understood or characterized, Cleveland and colleagues have identified a potentially therapeutically advantageous pathway that might lend itself to anticancer drug targeting.

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ORIGINAL RESEARCH PAPER Keller, U. B. et al. Myc targets Cks1 to provoke the suppression of p27^{Kip1}, proliferation and lymphomagenesis. *EMBO J.* 26 April 2007 (doi: 10.1038/sj.emboj.7601691)

FURTHER READING Nakayama, K. I. & Nakayama, K. Ubiquitin ligases: cell-cycle control and cancer. *Nature Rev. Cancer* 6, 369–381 (2007)