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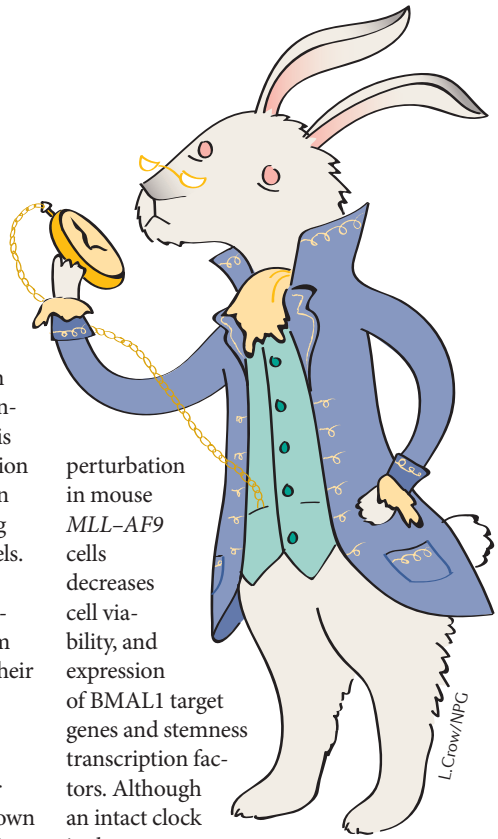
TUMORIGENESIS

Cancer goes tick tock



Circadian rhythms regulated by an endogenous clock are an essential influence over many biological functions; therefore it is not surprising that cancer development is also intimately linked to the daily oscillations of the circadian clock. Two new studies have highlighted different aspects of cancer chronobiology that could have far-reaching implications for therapies.

Using a conditional *Kras*^{G12D};*Trp53*$^{fl/fl}$ mouse model of lung adenocarcinoma, Masri *et al.* have unexpectedly revealed that lung tumours can hijack the clock's control over distal lipid metabolism in the liver. Tumour-bearing mice displayed unique liver transcriptomic and metabolomic signatures compared with their control counterparts, implying that oscillating gene and metabolite expression was out of sync. Interestingly, the deregulation of liver homeostasis observed in tumour-bearing mice, which included a strong reduction in cycling lipids, did not result in changes to core clock gene expression.

In establishing the full extent to which lung adenocarcinoma can rewire liver metabolism, the authors identified the activation of energy sensor AMP-activated protein kinase α (AMPKα), which in turn led to specific suppression of sterol regulatory element binding protein 1 (SREBP1) but not SREBP2 expression. As a consequence, fatty acid biosynthesis was repressed and cholesterol biosynthesis was induced.

In an attempt to determine which tumour-derived factors signal the metabolic reprogramming, Masri *et al.* discovered an upregulated interleukin-6 (IL-6)-dependent pro-inflammatory response, specific to the liver. IL-6 induced Janus kinase (JAK)-dependent phosphorylation of signal transducer and activator of transcription 3 (STAT3), which promoted expression of suppressor of cytokine signalling 3 (*Socs3*). Insulin signalling is known to be modulated by SOCS3 and consistent with this, lung tumorigenesis induced insulin-dependent inhibition of phosphorylated AKT and insulin receptor substrate 1 (IRS1), causing decreased liver-specific insulin levels. The upshot of these changes was a concomitant increase in serum glucose levels, suggesting a mechanism by which tumour cells can satiate their heightened energy requirements.

In contrast to the conventional notion that disruption of circadian rhythms leads to increased tumour development, Puram *et al.* have shown that the maintenance of a leukaemia stem cell (LSC) population in acute myeloid leukaemia (AML) requires intact canonical clock molecular machinery. Combining a serial transplantation mouse model of AML driven by the mixed lineage leukaemia (*MLL*)–*AF9* fusion oncogene with an *in vivo* RNAi screen of transcription factors, the authors identified expected regulators of LSC function, such as homeobox A9 (*HoxA9*), along with the unanticipated circadian rhythm genes *Clock* and *Bmal1*, which function together as a heterodimer to regulate transcription.

Accordingly, circadian *Clock* and *Bmal1* gene knockdown in mouse *MLL–AF9* leukaemia cells reduced proliferation, increased myeloid differentiation and depleted LSCs, as quantified by decreased cell surface expression of the stem cell marker KIT. To validate the circadian-rhythm dependency of AML, Puram *et al.* used a small molecule agonist of transcriptional repressors NR1D1 and NR1D2, which target *Bmal1*, to highlight that circadian circuitry perturbation in mouse *MLL–AF9* cells decreases cell viability, and expression of BMAL1 target genes and stemness transcription factors. Although an intact clock is also present in normal murine haematopoietic cells, crucially the genetic loss of *Bmal1* does not impair haematopoietic function. In contrast, *Bmal1*$^{-/-}$ cells that also expressed *MLL–AF9* reduced survival in secondary, but not primary, recipient mice, revealing that leukaemia maintenance relies on functional circadian pathways. Finally, to confirm the human relevance of their findings, the authors showed that the NR1D1 or NR1D2 agonist more effectively inhibited the viability of a human AML cell line than that of normal haematopoietic stem cells.

Together these studies highlight the emerging complexity of the relationship between cancer and the clock and leave us asking how many other tumour types modulate and/or rely on clock activity for their progression.

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ORIGINAL ARTICLES Masri, S. *et al.* Lung adenocarcinoma distally rewires hepatic circadian homeostasis. *Cell* **165**, 896–909 (2016) | Puram, R. V. *et al.* Core circadian clock genes regulate leukemia stem cells in AML. *Cell* **165**, 303–316 (2016)