

# Cell Cycle News & Views

## A role of miR-33 for cell cycle progression and cell proliferation

Comment on: Cirera-Salinas D, et al. *Cell Cycle* 2012; 11:922–33; PMID:22333591; <http://dx.doi.org/10.4161/cc.11.5.19421>

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MicroRNAs (miRNAs) are non-coding RNAs that downregulate gene expression at the post-transcriptional level. In recent years, their regulatory roles have been receiving much attention. miR33 is one such miRNA, recently identified as a critical regulator of cholesterol homeostasis<sup>1</sup> and insulin signaling.<sup>2</sup> The recent study by Cirera-Salinas et al.<sup>3</sup> described a new role of miR33 for the regulation of cell cycle progression and cell proliferation.

In a previous study, Fernandez-Hernando, the senior author of the current paper, and Moore<sup>1</sup> determined that miR33 is an intronic miRNA located within the gene encoding sterol-regulatory element-binding protein-2 (SREBP-2), the key transcriptional factor for cholesterol biosynthesis and transport. miR33 inhibits high-density lipoprotein biogenesis in the liver and cellular cholesterol efflux.<sup>1</sup> Since SREBPs have also been implicated in the regulation of cell cycle,<sup>4–6</sup> the authors investigated the link between miR33 and cell cycle progression as well as cell proliferation.<sup>3</sup>

Using bioinformatic approaches, the authors predicted potential miR33 target genes involved in cell cycle progression and cell proliferation.<sup>3</sup> Among these predicted genes, they found that overexpression of miR33 inhibits cyclin-dependent kinase 6 (CDK6) and cyclin D1 (CCND1) mRNA expression and reduces cell proliferation. Conversely, inhibiting miR33 increases mRNA expression of CDK6 and cyclin D1 and promotes cell proliferation. Further, the authors found that the level of endogenous miR33 is inversely correlated with the levels of CDK6 and CCND1. Endogenous miR33 levels decreased upon cells' release from mitosis and increased thereafter, whereas CDK6 and CCND1 levels first rose and then declined. Furthermore, miR33 arrested the cell

cycle at G<sub>1</sub>, indicating its role in the transition from G<sub>1</sub> to S phase. Collectively, these observations strongly suggest that miR33 suppresses CDK6 and CCND1 mRNA expression and inhibits its cell cycle progression and cell proliferation.

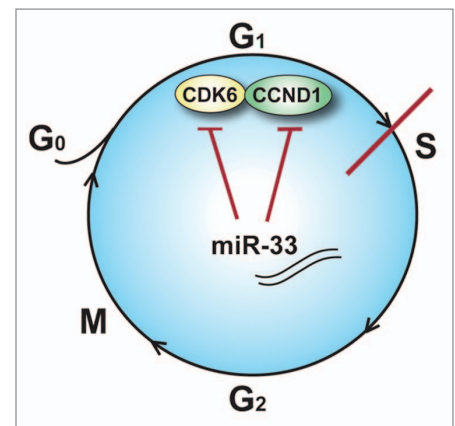
The authors then verified their *in vitro* findings in an *in vivo* model of liver regeneration initiated by a 70% resection of the liver.<sup>3</sup> They showed a significant reduction in hepatic miR33 levels in response to partial hepatectomy and a gradual increase as liver regeneration advanced. Again, hepatic miR33 levels presented an inverse correlation with hepatic CDK6 and CCND1 levels. As the authors suggest, miR33 may play a role in terminating liver regeneration. Furthermore, inhibiting miR33 in the liver by subcutaneous injections of antisense oligonucleotides targeting miR33 every week for one month significantly increased the liver-to-body mass ratio 96 h after partial hepatectomy. These *in vivo* observations are consistent with their *in vitro* findings and indicate a suppressive role of miR33 in liver regeneration.

The authors thus elegantly demonstrated miR33's regulation of cell cycle progression. Several interesting questions arise from this study. First, what regulates miR33 levels to control cell cycle progression? Particularly in response to partial hepatectomy, what suppresses miR33 levels in the first place? Considering the inverse correlation between miR33 levels and CDK6 and CCND1 levels, the first downregulation of miR33 seems essential for liver regeneration. Second, miR33 is abundantly expressed in the liver.<sup>1</sup> In the normal adult liver, hepatocytes are highly differentiated and rarely undergo cell division.<sup>7</sup> Given miR33's suppressive role in cell proliferation described in this study, a high level of miR33 in the normal adult liver may be associated

with the quiescent state of hepatocytes. In addition to its potential role for stopping liver regeneration, the relation of miR33 to quiescent hepatocytes may be an interesting area for investigation.

Third and lastly, in the clinical setting, hepatocyte proliferation is important not only for recovery from resection of healthy livers, but also from liver injury. Thus, to examine miR33's role in hepatocyte proliferation in a model of liver injury will significantly increase clinical relevance of the current findings.

In summary, this study identified miR33 as a regulator of cell cycle progression, cell proliferation and liver regeneration. The study essentially linked the transcript byproduct (miR33) of a major lipid transcription factor (SREBP-2) with proliferation. miR33 could also be a key link between metabolism and proliferative responses in other organs where miR33 has been identified. (Fig. 1)



**Figure 1.** miR33 arrests cell cycle progression at G<sub>1</sub> phase by inhibiting expression of cyclin-dependent kinase 6 (CDK6) and cyclin D1 (CCND1).

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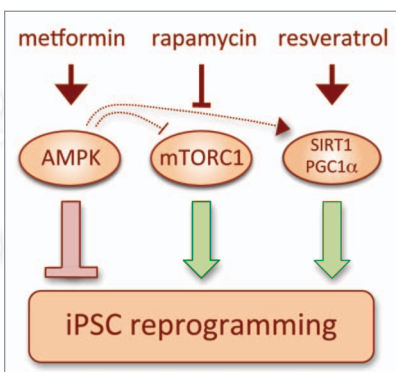
## Metformin and reprogramming into iPSCs

Comment on: Cirera-Salinas D, et al. *Cell Cycle* 2012; 11:922–33; PMID:22157090; <http://dx.doi.org/10.4161/cc.11.5.19450>

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The current paper by Javier Menendez and collaborators<sup>1</sup> adds a new piece to the puzzle of reprogramming of differentiated cells into induced pluripotent stem cells (iPSCs). This work reports that activation of AMPK, either indirectly using the mitochondrial poison metformin, or directly using the small compound A-769662, severely impairs reprogramming using the so-called “Yamanaka factors” (OCT4, KLF4, SOX2, cMYC). In particular, the presence of metformin or A-769662 during the reprogramming process of mouse or human fibroblasts profoundly decreased the formation of iPSCs. Moreover, despite the fact that p53-deficient fibroblasts are more efficiently reprogrammed than their wild-type counterparts, metformin or A-769662 reduced the reprogramming of p53-deficient cells to the same residual levels as in wild-type cells.<sup>1</sup>

**A conundrum.** The Ser/Thr-kinase AMPK is a main metabolic sensor that detects the presence of abnormally high levels of AMP within the cell.<sup>2</sup> Elevated levels of AMP are indicative of a negative energetic balance, and activation of AMPK triggers an adaptive response aimed to shut off anabolic processes and to turn on ATP production. These two important metabolic adaptations are achieved through multiple downstream effectors of AMPK, being among the best-studied ones, the inhibition of mTORC1 (which shuts off anabolic processes) and the activation of the SIRT1/PGC1 $\alpha$  axis (which turns on mitochondrial ATP production).<sup>2</sup> This brings up an interesting conundrum, because none of



**Figure 1.** AMPK and reprogramming. Activation of AMPK with metformin inhibits reprogramming. This is opposite to the effect of two other compounds that recapitulate selective effects of AMPK, namely, rapamycin and resveratrol. The negative effect of AMPK on reprogramming must occur independently of mTORC1 and SIRT1/PGC1 $\alpha$ .

these AMPK mediators recapitulates the effects of AMPK activation on iPSC reprogramming. On the contrary, rapamycin (which mimics the inhibitory effect of AMPK on mTORC1) and resveratrol (which mimics the stimulatory effect of AMPK on SIRT1/PGC1 $\alpha$ ) enhance, rather than inhibit, iPSC reprogramming.<sup>3</sup> The emerging picture from these observations is that AMPK negatively regulates reprogramming through mechanisms unrelated to mTORC1 or SIRT1/PGC1 $\alpha$  (Fig. 1).

**A new lead.** The authors of the current work provide an intriguing new lead, namely,

that AMPK represses the transcription of the pluripotency master gene *OCT4*. In particular, they report that metformin selectively impairs the expression of *OCT4* but not of the other reprogramming factors.<sup>1</sup> Suggestively, a number of previous circumstantial evidences also point in this direction. In particular, activation of AMPK with metformin decreases *OCT4* expression in breast cancer cells<sup>4</sup> and in pancreatic cancer cells.<sup>5</sup> The mechanistic details about how metformin affects *OCT4* mRNA levels are, at present, unknown. Based on their data,<sup>1</sup> the authors of the current work favor a post-transcriptional mechanism mediated by the upregulation of microRNAs (miRNAs). Indeed, metformin upregulates the levels of a number of miRNAs (including let-7)<sup>5-7</sup> that could conceivably downregulate *OCT4* mRNA levels. The fact that metformin upregulates the transcription of miRNA genes is not surprising given the multiple effects of AMPK on important transcriptional regulators, such as FOXO or CREB.<sup>2</sup> Finally, it is worth mentioning that activation of AMPK (with AICAR) in embryonic stem cells does not repress *OCT4* mRNA levels.<sup>8,9</sup> This is an important reminder of the general fact that the effects of AMPK may depend on the cellular context and, therefore, may differ between cells that are undergoing reprogramming and cells that are already fully pluripotent. Following the inroads made by the current report,<sup>1</sup> future work will undoubtedly dissect the pathways by which AMPK regulates the acquisition of pluripotency.

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## Reverse Warburg: Straight to cancer

Comment on: Witkiewicz AK, et al. *Cell Cycle* 2012; 11: In this issue; PMID:22313602; <http://dx.doi.org/10.4161/cc.11.6.19530>

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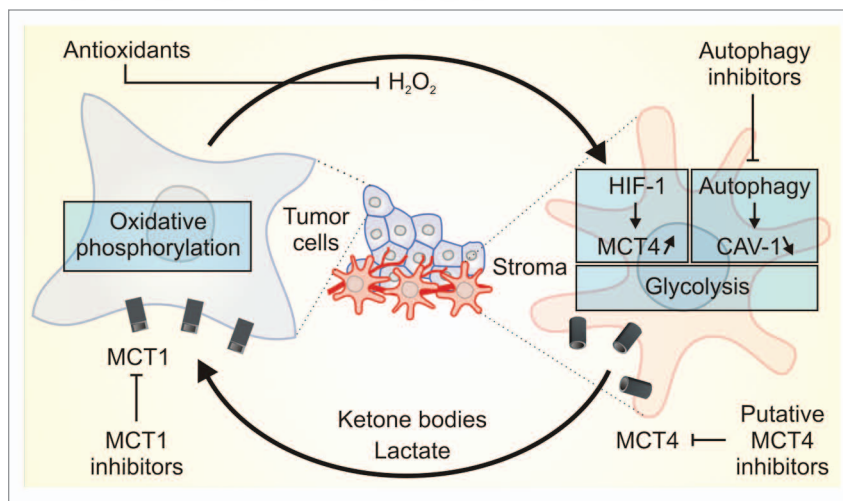
For a long time, cancer has been viewed as a “self-governing” disease, in that oncogenesis and tumor progression were mostly, if not entirely, ascribed to cancer cell-intrinsic defects. One biochemical alteration of cancer cells that was recognized as early as in the 1920s is their ability to sustain high levels of glycolysis even in the presence of normal oxygen levels, the so-called “Warburg effect.” Aerobic glycolysis is highly prominent across a wide range of human tumors, so much that it is routinely being exploited in the clinic for tumor imaging upon the administration of a radioactive analog of 2-fluoro-2-deoxy-*D*-glucose.<sup>1</sup>

However, it has now become clear that the tumor microenvironment plays a critical role not only in early oncogenesis, but also in tumor progression as well as in the response of cancer cells to therapy. In the last decade, great efforts have indeed been dedicated to the characterization of the molecular and cellular interactions between cancer cells and their stroma, encompassing immune, vascular and structural components. This intense wave of research led to the elucidation of multiple mechanisms whereby stromal cells interact with their malignant neighbors, including pro- and anti-neoplastic pathways.<sup>1</sup> For instance, cancer-associated fibroblasts can secrete pro-tumorigenic cytokines and promote the establishment of an immunosuppressive microenvironment, while natural killer cells and CD8+ lymphocytes reportedly ensure antitumor immunosurveillance and, in some instances, can mediate therapeutic antitumor responses.<sup>2</sup> Recently, Pavlides et al.

demonstrated that cancer cells and their stroma also are intimately connected at the level of bioenergetic metabolism. In such a scenario, stromal cells are subjected to oxidative stress and switch to a glycolysis-based metabolism. This leads to the generation of high levels of lactate and ketone bodies, which are avidly taken up by cancer cells for fueling

oxidative phosphorylation. This two-compartment metabolic circuitry, which closely resembles the well-known lactate shuttle bridging neurons and astrocytes, has been named “reverse Warburg effect” (Fig. 1).<sup>3</sup>

The reverse Warburg effect is based on the co-existence of metabolic alterations in both cancer and stromal cells. On one hand,



**Figure 1.** The reverse Warburg effect. Cancer cells are known to secrete high levels of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), leading to the establishment of a local oxidative microenvironment. Stromal cells, including cancer-associated fibroblasts, react to these oxidative conditions by increasing their autophagic flux and by activating the hypoxia-inducible factor 1 (HIF-1). Enhanced autophagy underlies the degradation of caveolin 1 (Cav-1), a signal transduction regulator implicated in various aspects of tumorigenesis. HIF-1 transactivates several genes whose products are involved in glycolysis, including the monocarboxylate transporter 4 (MCT4). As a result of these biochemical alterations, stromal cells switch to a glycolysis-based metabolism, concomitant with the release (via MCT4) of large amounts of lactate and ketone bodies. These energy substrates are avidly taken up by cancer cells—via MCT1—to fuel oxidative phosphorylation. This two-compartment metabolic crosstalk has been named “reverse Warburg effect” and provides multiple targets for the development of novel anticancer strategies.

tumor cells secrete hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), which promotes the establishment of an oxidative microenvironment, and upregulate the monocarboxylate transporter 1 (MCT1), which mediates lactate uptake.<sup>4</sup> On the other hand, stromal cells react to oxidative stress by elevating the autophagic flux and by activating hypoxia-inducible factor 1 (HIF-1), with at least two levels of consequences. First, autophagy underlies the degradation of caveolin 1 (Cav-1), a negative regulator of multiple signal transduction pathways involved in tumor progression and metastasis.<sup>5</sup> Second, HIF-1 transactivates genes that encode enzymes involved in glycolysis, including MCT4, the major transporter responsible for the efflux of lactate from glycolytic cells.<sup>6</sup>

The loss of Cav-1 in stromal cells has been shown to correlate with early tumor recurrence, metastasis, resistance to therapy and decreased overall survival in melanoma<sup>7</sup> and breast cancer patients, independent of the status of the estrogen receptor (ER), progesterone receptor (PR) and HER2.<sup>8</sup> In a previous issue of *Cell Cycle*, Witkiewicz and colleagues demonstrate, in a cohort of 181 ER-PR-HER2<sup>+</sup> (triple

negative) cancer patients, that the expression levels of stromal MCT4 and stromal Cav-1 inversely correlate.<sup>9</sup> Moreover, stromal MCT4 levels predicted poor overall survival, and they could be used in combination with the stromal Cav-1 status to precisely stratify intermediate-risk patients into a high- and a low-risk group.<sup>9</sup> Based on this model, high-risk patients might benefit from various interventions, including antioxidants, which would block the establishment of oxidative stress in the tumor stroma; autophagy inhibitors, which would prevent the degradation of Cav-1; MCT4-targeting agents, which would inhibit lactate release from glycolytic stromal cells, as well as MCT1 inhibitors, which would block lactate uptake by cancer cells. While MCT4-targeting compounds are not yet available, some autophagy and MCT1 inhibitors (e.g., AR-C155858, AR-C117977 and AZD-3965) are currently being evaluated in phase I/II clinical trials.

The results by Witkiewicz et al. have prominent conceptual and therapeutic implications. First, they strengthen the notion that cancer is not a cell-autonomous disease, as they unravel that alterations of the tumor stroma may

constitute clinically useful biomarkers. Second, they provide deep insights into a metabolic crosstalk between tumor cells and their stroma that may be targeted by a new class of anticancer agents.

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## MiR-33 connects cholesterol to the cell cycle

Comment on: Cirera-Salinas D, et al. *Cell Cycle* 2012; 11:922-33; PMID:22333591; <http://dx.doi.org/10.4161/cc.11.5.19421>

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Cell cycle progression and cell proliferation are tightly controlled processes that are critical for normal development and organogenesis, and deregulation of these processes may result in cancer. The cholesterol synthesis pathway is known to affect cell proliferation and cell cycle progression.<sup>1,2</sup> Cholesterol is an essential component of cell membranes and organelles, and its synthesis is thereby tightly regulated by the sterol regulatory element-binding protein (SREBP) family of transcription factors.<sup>3</sup> Three SREBP family members are known in humans, and they coordinate the expression of fatty acid metabolism and cholesterol metabolism-related genes.<sup>3</sup> Additionally, SREBPs have been implicated in cell cycle regulation and have gained attention as the link between lipid synthesis, proliferation and cell growth.<sup>4</sup> Whether the contribution of cholesterol in cell cycle progression is of a regulatory nature or a

side-effect of its structural requirement is not known.

Recent studies have uncovered a partner for SREBPs in regulating lipid metabolism—the miR-33 family microRNAs (miRNAs).<sup>5-8</sup> MiRNAs comprise a class of small non-coding RNAs that regulate genes post-transcriptionally by base pairing with sequences in the 3' untranslated regions (3' UTRs) of target genes. Because a single miRNA species can target the expression of multiple genes, miRNAs are thought to act as master coordinators of cellular processes. The *mir-33* genes are found in the intronic regions of *Srebp* genes and are co-transcribed with their host genes. Research by multiple groups has shown that miR-33 family miRNAs regulate cholesterol and fatty acid metabolism in mammalian systems, corresponding with the function of their host genes.<sup>5-8</sup> Adding to the repertoire of miR-33-SREBP co-regulated processes, in a recent issue of *Cell Cycle*,

Cirera-Salinas and colleagues reported a role for miR-33 in regulating cell proliferation and cell cycle progression.<sup>9</sup>

In Cirera-Salinas et al., researchers first found that miR-33's potential targets include genes involved in cell proliferation and cell cycle, such as cyclin-dependent kinase 6 (*Cdk6*) and cyclin D1 (*Cnd1*), and they further investigated these putative regulatory interactions. They found that transfection of miR-33 in human cell culture significantly inhibited both mRNA and protein levels of these cell cycle genes in addition to that of *Abca1*, a previously identified miR-33 target.<sup>5-8</sup> The opposite result was obtained when miR-33 was inhibited using anti-miR-33 oligonucleotides. Luciferase reporter assays of 3' UTR sequences of these cell cycle genes containing miR-33 target sites provided strong evidence for the direct interaction of miR-33 with these sequences.

The authors next addressed whether miR-33 affects cell proliferation and cell cycle progression. They showed that cell growth was inhibited when miR-33 was overexpressed, whereas cell proliferation was increased when miR-33 was inhibited. Transfection of miR-33 in synchronized cells resulted in cell cycle arrest in G<sub>1</sub> phase. These effects on cell cycle and cell proliferation seem to be mediated by CDK6 and CCND1: their expression inversely correlated with that of miR-33 during the cell cycle, and they could be reduced by miR-33 transfection, even following mitogenic stimuli, which usually induces their expression.

The role of miR-33 in cellular proliferation was further investigated in vivo by examining mouse liver regeneration following partial hepatectomy. Consistent with findings in cell culture, the authors observed an inverse correlation between the expression of miR-33 and those of CDK6 and CCND1 as well as with the proliferative status of liver cells. Anti-miR-33

treatment increased proliferative marker expression and accelerated liver regeneration as determined by changes in liver-to-body mass ratio. Through the regulation of CCND1 and CDK6, miR-33 appears to be an important regulator of liver regeneration and may be a good target for liver disease treatment.

MiR-33 is currently being targeted as a therapeutic for atherosclerosis based on its inhibition of lipid metabolism-related genes, while this new work reveals its promise as a good target for liver regeneration. We must, though, take heed that therapies affecting cell cycle modulation may also cause undesirable consequences, like cancer. In this important work, Cirera-Salinas et al. have filled in another piece of the puzzle, linking lipid synthesis, cell cycle, SREBPs and miR-33 with new findings hinting at a regulatory role for cholesterol in cell cycle progression.<sup>9</sup> Since we do not yet fully understand the impact of modulating miR-33, further research is needed to elucidate

the reach of the SREBP/miR-33-mediated regulatory network and its therapeutic potential.

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