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AKT-ing via microRNA

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MicroRNAs are involved in almost every aspect of a mammalian cell's functionality, from stem cell differentiation to aging and pathogenesis; however, their role in immediate cell signaling is less defined. This has been recently demonstrated by the rapid increase or decrease of miR-21's abundance within minutes of activation or inhibition of the AKT pathway, respectively, which mediates its regulation of Fas ligand (FasL) and phosphatase and tensin homolog deleted on chromosome 10 (PTEN) expression, among other targets. Conversely, AKT induces rapid downregulation of miR-199a-5p to effect upregulation of hypoxia-inducible factor 1α (Hif-1α) and sirtuin 1 (Sirt1). This suggests that posttranscriptional mechanisms regulate miRNAs' processing and/or stability to induce the rapid fluctuation in their levels. In support, a growing number of studies are showing specific posttranscriptional regulation of miRNAs. The data potentially explain how AKT, and plausibly other signaling pathways, can specifically and promptly modulate a gene's translation while circumventing the need for transcription during transient signaling events. In this article we present our views regarding cell signaling via miRNAs.

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The level of a gene's translational output can be adjusted by either transcriptional or posttranscriptional mechanisms. The difference is that posttranscriptional regulation can provide a more rapid change when required, via circumventing the need for DNA remodeling and transcription. A classic example is the increase of the Hif-1α protein within minutes of exposure of a cell to hypoxia.[1] The promptness of the response here is vital as it is necessary for preconditioning the cell to hypoxia and, thereby, minimizing the damage. Thus, a priori, none of the steps involved in this type of rapid regulation require gene transcription. In concordance, Hif-1α protein, but not its mRNA, rapidly increases. This led to the thinking that during normoxia Hif-1α mRNA is continuously translated but then the protein is rapidly degraded through the function of a prolyl hydroxylase,[2] which labels it for ubiquitination by von Hippel-Lindau and, subsequently, proteasomal degradation.[3] This process is inactivated during hypoxia, thus, permitting rapid accumulation of Hif-1α. Later, we discovered that, in conjunction, miR-199a-5p can directly target and inhibit the translation of Hif-1α mRNA during normoxia.[4] This, theoretically, provides a tighter, two-tiered mode of regulation and challenges the idea that Hif-1α is continuously translated only to be rapidly degraded during normoxia. Accordingly, rapid downregulation of miR-199a-5p upon exposure to hypoxia is required for upregulation of Hif-1α. This is associated with an increase in Sirt1, which we show is involved in degradation of prolyl hydroxylase 1, thereby, increasing the stability of Hif-1α. Meanwhile, the premature miR-199a-5p continues to accumulate and is detectable at later time points, suggesting inhibition of pre-miR-199a-5p processing but not transcription.

The response of a cell to hypoxia is biphasic. Brief exposures to hypoxia elicit an adaptive response that involves activation of the AKT pathway, which protects the cells against protracted periods of hypoxia that may immediately

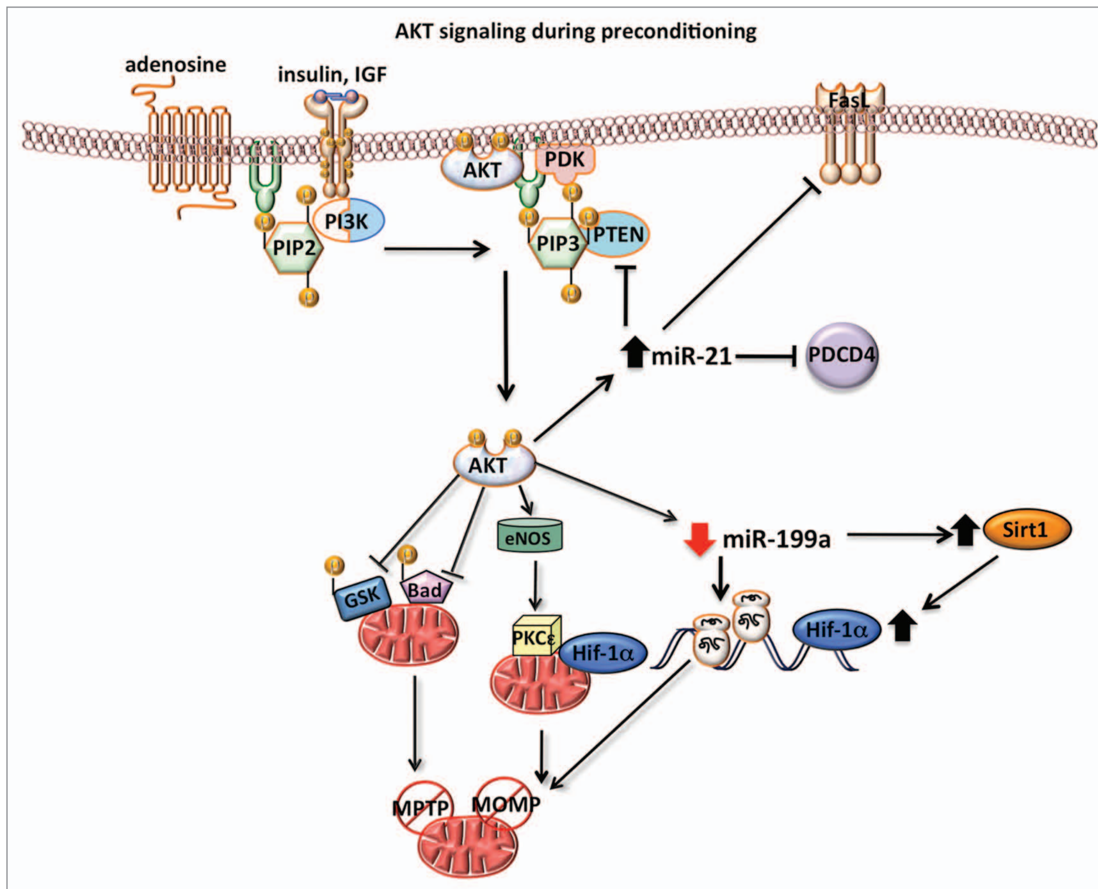

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Figure 1. The AKT pathway mediates ischemia preconditioning. Exposure of the cells to brief intermittent episodes of hypoxia or ischemia elicits an adaptive preconditioning effect. One of the main signaling pathways that mediate this effect is the AKT pathway, which in this context is activated by adenosine, a byproduct of ATP hydrolysis. Stimulation of the cells with insulin can have a similar preconditioning effect. Activation of AKT triggers immediate signaling through posttranscriptional modifications that are responsible for early preconditioning. These include phosphorylation and inhibition of Bad and glycogen synthase kinase 3β GSK3β induction of enodothelial nitric oxide synthase (eNOS), and activation of protein kinase C epsilon (PKCε). In addition, AKT induces rapid upregulation of miR-21, which targets and inhibits Fas ligand (FasL), phosphatase and tensin homologue deleted on chromosome 10 (PTEN), and programmed cell death 4 (PDCD4) that are induced during protracted hypoxia. Conversely, AKT induces prompt downregulation of miR-199a-5p, thus, derepressing its targets, hypoxia-inducible factor 1alpha (Hif-1α) and Sirtuin 1 (Sirt1), where Sirt1 is required of Hif-1α stability. Finally, These signaling events coordinate to protect mitochondrial damage by inhibiting the formation of mitochondrial outer membrane pores (MOMP) and leakiness of mitochondrial permeability transition pores (MPTP).

follow. This is known as early hypoxia preconditioning (HPC) or ischemia preconditioning (IPC) if it occurs in an organ in vivo,[5] and involves posttranscriptional modifications and de novo protein but not mRNA synthesis[6] (**Fig. 1**). Conversely, prolonged periods of hypoxia or ischemia are damaging and induce cell apoptosis and necrosis. We have shown that this is associated with dephosphorylation of AKT in parallel with an increase in PTEN and FasL.[7] Central to the preconditioning effect is the protection of mitochondria against hypoxic damage, which is a well established function of the AKT pathway.[8] In this context, it has been shown that some of AKT's major effects are mediated by its phosphorylation and inhibition of Bad and glycogen synthase kinase 3β, induction of enodothelial nitric oxide synthase, and activation of protein kinase C epsilon. However, other critical effects of AKT that are not always acknowledged are its role in regulating the expression of Fas ligand (FasL) and Hif-1α. Indeed, there have been several studies in cancer,[9,10] T lymphocytes,[11] and smooth muscle cells[12,13] that show that inhibition of AKT induces upregulation of FasL. A couple of these studies have suggested that this occurs via forkhead-induced transcriptional activation of the FasL gene.[9,13] Likewise, in our recent report we found that inhibition of AKT during prolonged exposure of myocytes to hypoxia coincided with upregulation of FasL, which we were able to reverse by a constitutively active mutant of AKT.[7] In concordance, inhibition of AKT by wortmannin or a dominant negative mutant was also sufficient for inducing upregulation of FasL. On the other hand, we found that miR-21, which is similarly reduced during prolonged hypoxia, directly targets and inhibits FasL. Accordingly, resupplying the cells with exogenous miR-21 inhibited hypoxia-induced FasL. This led us to speculate and subsequently prove that AKT regulates FasL via regulating miR-21 abundance in cardiac myocytes. In **Figure 2A** we further examined this

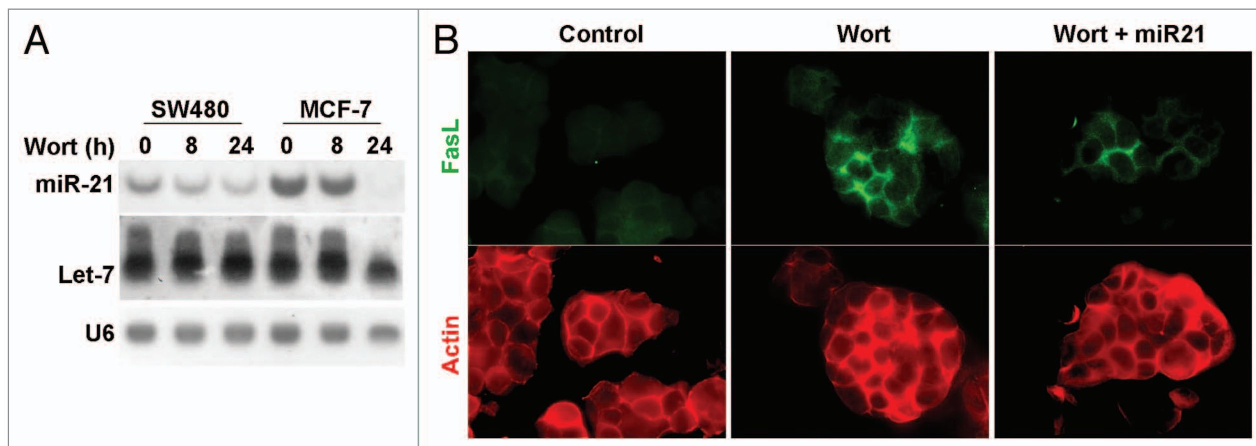

Figure 2. Inhibition of AKT by wortmannin downregulates miR-21 in SW480 colon cancer cells and MCF-7 breast cancer cells. (A) Cultured SW480 or MCF-7 cells were treated with 5 μM wortmannin (Wort) for the indicated time periods, after which total RNA was extracted and analyzed by northern blotting for miR-21 levels (n = 3). Let-7 and U6 were used as internal controls. The Let-7 signal that is observed is that of the pre-Let-7 as determined by it size (~70–100 nt). (B) MCF-7 cells were cultured in glass chamber slides and were then treated with wortmannin for 16 h in the absence or presence of an adenoviral-delivered pri-miR-21 construct (Ad.miR-21). Cells were then fixed and florescently stained with anti-FasL (green) and phalloidin (red) (n = 2).

relation in SW480 colon cancer cells and MCF-7 breast cancer cells, where we show that treatment with wortmannin reduced miR-21 to almost undetectable levels. This was also associated with upregulation of FasL, which was partially reversed by overexpressing miR-21 in MCF-7 cells (**Fig. 2B**). This also resulted in rapid death and detachment of the cells.

It should be noted, though, that one of the characteristics of miRNAs is their ability to simultaneously target and inhibit multiple genes that are plausibly involved in co-regulating a given function. A good example is miR-21 and its role in enhancing cell survival by targeting a plethora of proapoptotic and tumor suppressor genes such as tropomyosin 1,[14] PTEN,[15-17] programmed cell death 4 (Pdcd4),[18,19] TAp63 isoform of p53 family, LRRFIP1, an inhibitor of NFκB signaling,[20] and FasL.[7,21] Among these, PTEN is a well characterized inhibitor of AKT activity, functioning via dephosphorylating phosphatidylinositol 3,4,5-trisphosphate (PIP3), which is necessary for recruiting the Akt-activating protein kinase-D1 (PDK1).[22] Thus, miR-21 suppresses PTEN, which inhibits AKT that would, in turn, result in downregulation of miR-21, thus, forming a double-negative feedback loop often seen between miRNAs and their targets, such as miR-200 family and ZEB1,[23] and let-7 and lin-28.[24]

While AKT induces upregulation of miR-21, which inhibits hypoxia-induced upregulation of FasL, it also induces downregulation of miR-199a-5p, which is required for induction of Hif-1α and Sirt1.[4,25] Thus, on the one hand, AKT suppresses proapoptotic FasL and PTEN and on the other, it enhances prosurvival genes such as Hif-1α and Sirt1, both through miRNA-dependent mechanisms. These complementary effects could explain why it is a major antiapoptotic pathway in ischemia preconditioning, where our studies are the first to demonstrate this aspect of its function in cardiac myocytes and the heart. We have indeed confirmed that miR-21 is upregulated, while miR-199a-5p is downregulated, during ischemia preconditioning of porcine hearts, induced by 2 x 10 min cycles of ischemia/reperfusion (**Fig. 3**). Since ischemia preconditioning does not require transcriptional activity,[6] this suggests that the mechanisms involved in regulating the abundance of these miRNAs are posttranscriptional vs. transcriptional; however, direct evidence is pending. These results demonstrate for the first time the utility of miRNAs in cellular signaling via the AKT pathway.

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While our results demonstrate that some miRNAs can function as downstream effectors of AKT, it is worth noting that there is many more that function as upstream regulators of AKT activation, including miR-21 through its inhibition of PTEN (**Fig. 4**). Other miRNAs that also target PTEN and activate AKT include, miR-221/222 in lung and liver cancer,[26] miR-216a/217 in response to TGFβ in mesangial cells,[27] and miR-486 in myocytes.[28] One explanation of why there are multiple miRNA regulators of PTEN, is that they may function in a cell type- and/or condition-specific fashion. Moreover, miR-155 in hematopoietic cells[29,30] and miR-205 in epithelial cells[31] target Src homology-2 domain-containing inositol 5' phosphatase 1 and 2, respectively, which are also known PIP3 phosphatases that deactivate AKT. Furthermore, activators of the AKT pathway are also subject to regulation by miRNAs; PDK1 is targeted by miR-375 in gastric carcinoma cells,[32] while the p85 subunit of phosphatidylinositol 3 kinase is targeted by miR-126 in colon cancer[33] and miR-320 in adipocytes;[34] however, the mechanism of regulation of these regulators is not known yet. This illustrates that the AKT pathway is subject to regulation at every level and that the miRNAs involved may be differentially employed by the various cell types under different conditions.

MiRNAs can alter the translational output of genes through fluctuations in their own concentration, which is widely observed throughout development and all diseases examined to-date. For a miRNA

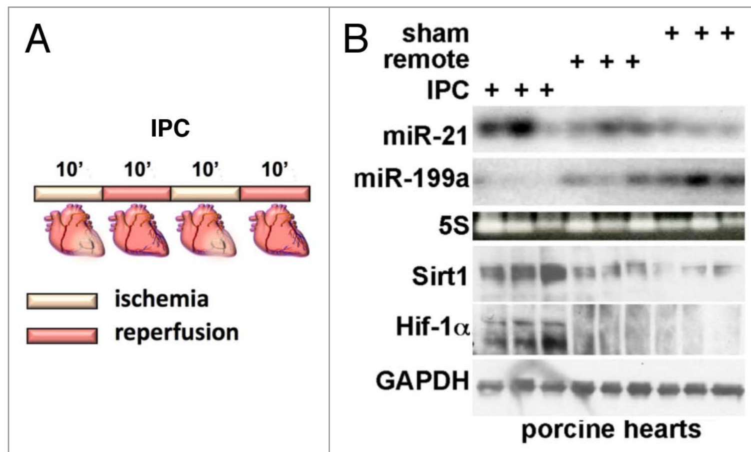

Figure 3. MiR-21 is upregulated and miR-199a-5p is downregulated during ischemia preconditioning of a porcine heart. (A) Ischemia preconditioning (IPC) was elicited in porcine hearts by 2 x 10 ischemia/reperfusion cycles (n = 3).[4] (B) The IPC area of the left ventricle, remote zone and sham-operated ventricles, were immediately dissected (early/first window IPC) and analyzed by northern and western blotting. The top 2 parts are the results of a northern blot detecting miR-21 and miR-199a-5p. While miR-199a-5p was downregulated in 3/3 IPC hearts, only 2/3 hearts exhibited upregulation of miR-21. This can be explained by the fact that miR-21 is initially upregulated but is then downregulated if ischemia is prolonged any further. Thus, any slight prolongation in the timing of these I/R episodes might have led to the latter effect. The lower 3 parts are the result of western blotting showing that the miR-199a-5p targets Hif-1α and Sirt1 are also upregulated during this period, also confirming successful IPC of the region.

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to regulate a function that requires a timely response or is transient, as observed during developmental timing, hypoxia preconditioning or immune response, one would predict that the miRNA itself is posttranscriptionally regulated. Indeed, more studies are emerging regarding this mode of regulation of miRNA levels. For example, Michlewski et al. discovered that hnRNP A1 specifically binds to the terminal loop region of miR-18a and regulates its processing by Drosha.[35] Since little conservation was previously noted in the terminal loop sequences of miRNAs, it was believed that they are not functionally relevant. However, upon closer examination they found that 14% of pri-miRNAs have highly conserved terminal loop sequences, suggesting that they may have a more significant role during processing. In support, targeting the loop sequences by antisense oligonucleotides inhibited the processing of miRNA that harbored conserved (e.g., miR-18a, miR-101, let-7, miR-379, miR-31) but not non-conserved (e.g., mmiR-16-1 and miR-27a) loops. Interestingly, pri-miR-21 is among the 14% that have a conserved loop sequence, supporting the idea that its processing may also be subject to posttranscriptional regulatory mechanisms. In agreement, it has been shown that miR-21, as well as, miR-199a-5p are posttrascriptionally regulated by SMAD1, 3 and 5 via its interaction with the p68 RNA helicase subunit of the nuclear microprocessor complex, which results in enhancing the processing of the primary constructs upon stimulation of smooth muscle cells with transforming growth factor-beta.[36] A second protein, the KH-type splicing regulatory protein (KSRP), also binds to the loops of select miRNAs, e.g., Let-7a, miR-21, miR-206, miR-1, in a sequence-specific manner, and regulates the processing of their primary transcripts.[37] This protein itself is subject to regulation by various stimuli, such as lipopolysaccharides, which was observed to enhance its binding to the miR-155 loop and rapidly induce its maturation in macrophages.[38] In addition to modulating miRNAs abundance via the specific regulation of the processing of their primary transcripts, the stability of the mature form is a target of regulation by posttranscriptional editing in the form

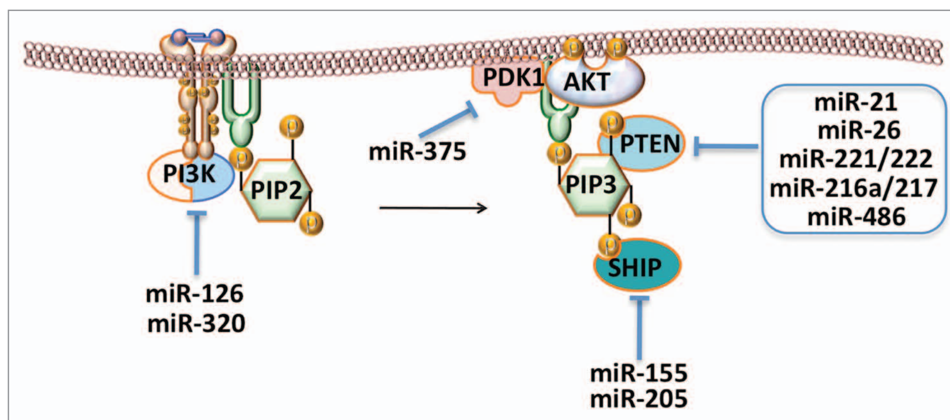

Figure 4. MiRNAs regulating AKT activity. MiRNAs that target and inhibit phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and, thus, activate AKT include miR-21, miR-26, miR-221/222, miR-216a/217 and miR-486. On the other hand, miR-155 and miR-205 target Src homology-2 domain-containing inositol 5' phosphatase 1 and 2 (SHIP), respectively, which are also known PIP3 phosphatases that deactivate AKT. Activators of the AKT pathway are also subject to regulation by miRNAs; PDK1 is targeted by miR-375, while the p85 subunit of phosphatidylinositol 3 kinase (PI3K) is targeted by miR-126, however, the mechanism of regulation of these regulators is not known yet.

of 3'-terminal adenylation, which is for example known to regulate the abundance of miR-122.[39] The recognition of such posttranscriptional mechanisms that specifically regulate miRNA abundance can potentially explain how miRNAs, such as miR-21 and miR-1995-p, are upregulated or downregulated within minutes of inducing hypoxia/ischemia preconditioning[4,40-42] (**Fig. 3**).

Concluding Remarks

Until now, the prevailing idea was that miRNAs are end transcriptional targets of signaling pathways, as little is known about the specific regulation of their post-transcriptional processing. However, the recent emergence of more studies that identify these mechanisms help explain how a miRNA's level can rapidly change in response to an incoming signal and, accordingly, promptly mediate the signal's effect on a gene's abundance without involving transcriptional events. This provides a mechanism of how short-lived cell signals may induce transient changes in protein abundance.

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