

CURRENT PERSPECTIVE ESSAY

A Renaissance of Metabolite Sensing and Signaling: From Modular Domains to Riboswitches

The ability of an organism to sense cellular, extracellular, or environmentally derived signals, to integrate that information, and to respond appropriately is broadly termed signal transduction and is fundamental to the survival of that organism. In our first biochemistry course, most of us were exposed to specific metabolites, but likely only in terms of being intermediates or cofactors of a metabolic pathway and as allosteric activators or inhibitors of key regulatory enzymes. This view of metabolites is rapidly changing as recent work across a broad spectrum of organisms has shown certain metabolites to be signaling molecules that coregulate and integrate metabolic status with other fundamental cellular events, such as transcription, translation, covalent modification of signal transduction proteins, and membrane channel function. This essay will highlight some of these discoveries using the best-characterized examples from a selection of organisms, ultimately comparing these to higher plants and examining what might be gleaned from comparative genomics of metabolite-mediated signal transduction.

AMPK, SNF1, AND SnRK1

All organisms have the remarkable ability to maintain a nearly constant, nonequilibrium ratio of ATP:ADP. This suggests that cells have very sophisticated mechanisms to maintain and monitor this balance. In eukaryotes, the key player in this system is a heterotrimeric protein kinase, which in mammals is referred to as the AMP-activated protein kinase (AMPK). The catalytic α and the regulatory β and γ subunits of AMPK are present as multiple isoforms and are found in the genomes of all eukaryotes sequenced to date, including plants and the primitive eukaryote *Giardia lamblia* (Hardie, 2003; Hardie et al., 2003). The yeast and plant homologs of AMPK are sucrose non-fermenting-1 (SNF1) and

SNF1-related kinase-1 (SnRK1), respectively (Hardie et al., 2003; Halford et al., 2004). This high degree of conservation across eukaryotes indicates an ancient origin and supports the idea that metabolite sensing and signaling evolved very early in life.

All eukaryotic cells have a very active adenylate kinase that catalyzes $2\text{ADP} \leftrightarrow \text{ATP} + \text{AMP}$ near to equilibrium. The consequence of this activity is that the ratio of AMP:ATP varies as the approximate square of the ADP:ATP ratio. Therefore, a small decrease in cellular ATP level results in a large increase in AMP, making the latter a sensitive indicator and, therefore, a good signaling molecule of energy status. AMP was recognized many years ago as a key metabolite to indicate cellular energy status because of its ability to allosterically regulate many enzymes of intermediary metabolism (for instance, liver glycogen phosphorylase, the first demonstration of an allosteric effector, bacterial glutamine synthetase, and phosphofructokinase-1). AMP is also a direct allosteric activator of mammalian AMPK, as the name suggests. Most protein kinases are activated by phosphorylation of the their T-loops, and it has been clearly demonstrated that AMP bound to AMPK holds the enzyme in a conformation that allows enhanced phosphorylation by its upstream protein kinase, LKB (Hardie, 2003; Hawley et al., 2003). The association of AMP with AMPK also hinders dephosphorylation by its target protein phosphatase, PP2C. This results in a very sensitive (de)activation system in response to a small change in cellular ATP. High ATP antagonizes the activating effect of AMP; thus, the system really responds to the AMP:ATP ratio.

Early work showed that the recombinant human AMPK α subunit (catalytic) alone was not responsive to AMP, indicating that one of the other subunits bound AMP

allosterically. It was proposed that the CBS domain found in the mammalian γ subunit performs this role, and Scott et al. (2004) formally demonstrated that γ can bind both AMP and ATP. The CBS domain is an ~ 60 -amino acid module found in proteins across all domains of life. They exist as tandem pairs, and two sets of pairs are found in all AMPK γ subunits, suggesting that all AMPK homologs respond to the cellular AMP:ATP ratio. Direct evidence that AMP allosterically activates plant and yeast AMPK homologs is lacking, but the plant system does respond to AMP. That is, the ability of the upstream kinase to activate the enzyme and the protein phosphatase to deactivate it is controlled by AMP:ATP (Halford et al., 2004). Conditions that activate yeast SNF1 also cause a large increase in AMP.

It is likely that the primary function of AMP:ATP binding to the γ subunit is to control activation by the upstream protein kinase. In support of this hypothesis, various human α , β , and γ subunit isoform combinations are known to exist, and the allosteric AMP activation of some combinations is as high as fivefold, whereas the $\alpha 1, \gamma 3$ combination is only activated 0.5-fold (Hardie, 2003). Therefore, it is likely that if the AMPK catalytic subunit is not phosphorylated in the T-loop by the upstream kinase, it is essentially inactive no matter what concentration of AMP is present. Intriguingly, plants have a subunit designated $\beta\gamma$ because of the presence of a portion of the classic β subunit and the CBS domains of a γ subunit (Hardie, 2003). Other work published this last year also demonstrated a property of the AMPK β subunit that was initially revealed through bioinformatics; that is, the β subunit in all species has a highly conserved carbohydrate binding domain. This domain of the mammalian β formally has been shown to bind glycogen (Hudson et al., 2003), and

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a population of AMPK molecules localizes to glycogen particles in vivo (Polekhina et al., 2003). It has been proposed that the targeting of AMPK to mammalian glycogen particles localizes the protein kinase to one of its substrates (glycogen synthase), but an attractive proposal is that AMPK resides here to monitor glycogen reserves (Hudson et al., 2003). This immediately makes us ponder what may be the target of the plant β subunit carbohydrate binding domain. The overall effect of AMPK activation can be best described as turning on energy generating metabolic pathways and switching off energy consuming anabolic pathways, and we refer readers to several reviews (Hardie, 2003; Hardie et al., 2003; Carling, 2004).

TOR AND GCN2 SIGNALING: SENSING IN THE CYTOSOL

Rapamycin was purified from an Easter Island soil bacterium and was initially characterized as a potent antifungal agent. Its cellular target is the peptidyl-prolyl *cis-trans* isomerase FKBP12, and when complexed with rapamycin, they bind to and block the function of a protein kinase designated target of rapamycin (TOR). TOR belongs to the PI3K-related kinase family of protein kinases (which includes ATM, ATR, and DNA-PK) and phosphorylates its substrates on Ser or Thr residues (Harris and Lawrence, 2003; Fingar and Blenis, 2004). It is highly conserved in eukaryotes and even with a size of ~289 kD, the human protein is still >95% identical to mouse and rat TOR, 38% identical to Arabidopsis TOR, and 42 and 45% identical to yeast (*Saccharomyces cerevisiae*) TOR1 and TOR 2, respectively. TOR is composed of a series of conserved modular domains, all of which are present in plant TOR, including multiple N-terminal HEAT repeats. Consistent with HEAT repeats being protein-protein interaction modules, mammalian TOR displays a mass of >2 mD during gel filtration chromatography, suggesting multiple interacting partners.

TOR is considered an integrator of nutrient (amino acid and energy) and, in metazoans, growth factor signaling that

couples cell growth and proliferation with regulation of the cellular protein synthesis machinery (Harris and Lawrence, 2003; Fingar and Blenis, 2004). This is consistent with observations that TOR mutants or cells treated with rapamycin across a broad spectrum of organisms display a starvation phenotype and upregulated autophagy (an additional marker of starvation). In yeast, disruption of TOR causes an inhibition of translation initiation, cell cycle arrest at G₁, glycogen accumulation, and a reprogramming of transcription that includes a down-regulation of rRNA, tRNA, and ribosomal protein genes and an upregulation of genes of the TCA cycle and those involved in assimilation of alternative nitrogen sources.

Recent data indicate that in yeast, the TOR pathway senses and responds to the amino acid Gln (Crespo et al., 2002). In cultured mammalian cells, the removal of glucose or amino acids from the growth media causes a rapid dephosphorylation of the best-characterized substrates of TOR—the protein translation regulators S6 protein kinase-1 (S6K1) and 4EBP1—which control ribosomal protein translation and biogenesis and cap-dependent mRNA translation, respectively. The readdition of nutrients to starved cells causes a rapid phosphorylation and activation of S6K1 and 4EBP1 in a TOR-dependent manner (Harris and Lawrence, 2003). In mammals, the key amino acid indicator appears not to be Gln, but Leu. An excess of Leu causes an increase in mammalian TOR activity, but the actual sensor of the amino acid Leu may be one of the highly conserved TOR binding proteins, known as raptor (Harris and Lawrence, 2003; Fingar and Blenis, 2004).

TOR pull-down experiments in mammalian and yeast cells have identified raptor/KOG and LST8 as TOR interacting proteins. Raptor consists of a conserved N-terminal domain, three HEAT repeats, and seven WD-40 domains, whereas LST8 is comprised almost entirely of WD-40 domains. This domain structure is consistent with the data that TOR resides in a large protein complex. Like HEAT repeats, WD-40 domains are believed to function in protein-protein interactions, and it is likely that other proteins target to TOR as well

(Harris and Lawrence, 2003). Both raptor/KOG and LST8 are highly conserved in eukaryotic genomes, and the Arabidopsis raptor and LST8 proteins are 39 and 52% identical, respectively, to the human proteins. In mammals, raptor appears to function as an adaptor to target S6K1 and 4EBP1 to the TOR complex (for phosphorylation) through a 5-amino acid domain found on both substrate proteins that is designated the TOS motif (Schalm and Blenis, 2002). This motif is not present in the two plant S6K enzymes and plants also lack a 4EBP1 protein. Because of the high degree of conservation of raptor and its key role in TOR signaling, it is natural to predict that other TOR substrates target to the complex with a TOS motif, including the as yet unknown plant targets.

Decreasing cellular ATP levels inhibit the TOR-dependent phosphorylation of S6K1 and 4EBP1 in mammalian cells. It is thought that mammalian TOR can function as an ATP sensor because of its high K_m for ATP (~1 mM; most protein kinases have a K_m for ATP in the 10 to 50 μ M range); thus, TOR can only signal when energy levels are high, although this concept has been debated in the literature (Harris and Lawrence, 2003). More recent work in mammalian cells has placed the GTPase activating protein complex TSC1/TSC2 and its target, the GTPase Rheb, upstream of TOR. It appears that AMPK phosphorylation of TSC2 increases the ability of TSC2 to block TOR signaling (Pan et al., 2004), thus integrating AMPK function with TOR. This is consistent with a role of AMPK to shut down energy consuming processes, like protein translation, when cells are stressed. To date, there is no link between plant SnRKs and TOR signaling.

Disruption of the single Arabidopsis TOR gene results in early arrest of endosperm and embryo development (Menand et al., 2002). GUS reporter experiments demonstrated that plant TOR is expressed in developing endosperm and embryo and primary meristems but not in differentiated cells. This expression pattern corresponds with the function of TOR in other organisms where it is thought that TOR controls the synthesis of cytosolic components necessary for cell division. This then poses the

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question, how do differentiated plant cells perceive nutrient status in the cytosol? Of course TOR is likely one component of a network that monitors and signals cytosolic amino acid and energy status in plant cells. For instance, during amino acid starvation in yeast, the accumulation of uncharged tRNAs results in the activation of the protein kinase GCN2 (general control non-depressible). GCN2 has a domain like a histidyl-tRNA synthetase that binds uncharged tRNAs, causing the release of a pseudosubstrate from the kinase domain and, therefore, enzyme activation. The kinase target of GCN2 is eIF2 α , phosphorylation of which causes inhibition of the entire eIF2 complex, leading to a general reduction in protein synthesis by preventing further initiation of translation (Wilson and Roach, 2002). This general reduction in protein synthesis is directly linked to increased translation of the transcriptional activator GCN4, which in yeast increases transcription of 539 genes, including amino acid biosynthetic pathway genes (Halford et al., 2004). GCN2 appears to be present and highly conserved in all eukaryotes, including Arabidopsis. The presence of GCN4 in plants is under debate (Halford et al., 2004), and our BLAST results fail to find a GCN4 protein in Arabidopsis. Recent work in yeast suggests that TOR influences GCN2 activity and provides an intriguing link between cytosolic amino acid sensing mechanisms (Cherkasova and Hinnebusch, 2003).

PII SIGNALING: SENSING IN BACTERIA AND THE CHLOROPLAST

The PII protein was discovered more than 35 years ago in *Escherichia coli* and has been found in nearly every bacterial and archaeal genome examined. The PII network was one of the first signal transduction pathways elucidated and represents one of the classic as well as most ancient signal transduction cascades (Arcondeguy et al., 2001; Moorhead and Smith, 2003; Forchhammer, 2004). In *E. coli*, this small homotrimeric protein is regarded as the central processing unit at the heart of the integration of energy, carbon, and nitrogen metabolism

(Arcondeguy et al., 2001), ultimately controlling the activity of Gln synthetase and the transcription of a multitude of genes. Energy and carbon status are allosterically sensed through ATP and 2-ketoglutarate. 2-Ketoglutarate is the carbon skeleton of nitrogen assimilation/amino acid biosynthesis, and the binding of ATP and 2-ketoglutarate to PII is mutually dependent with ATP interacting first. Nitrogen status is interpreted by covalent modification of PII (Tyr uridylylation in proteobacteria). (De)uridylylation of PII is performed by a bifunctional uridylyltransferase/uridylyl-removing enzyme. Gln, the nitrogen status molecule of *E. coli*, inhibits the transferase activity and activates the removing activity of this enzyme, allowing Gln levels to control the covalent modification state of PII and, thus, its ability to regulate target proteins.

Similar to *E. coli* PII, cyanobacterial PII binds ATP and 2-ketoglutarate, but in cases where covalent modification occurs, it appears to be Ser phosphorylation instead of Tyr uridylylation. In the cyanobacteria *Synechococcus elongatus*, the protein kinase that phosphorylates PII could only be detected during in vitro assays if both ATP and 2-ketoglutarate were present (as effectors) (Forchhammer and Tandeau de Marsac, 1995). A type 2C phosphatase was identified as the PII protein phosphatase, and its ability to dephosphorylate PII is also regulated by ATP and 2-ketoglutarate, but in a reciprocal manner to the PII protein kinase (Irmeler et al., 1997). This property of the 2C phosphatase was not observed if nonphysiological substrates (phosphoproteins other than PII) were employed, illustrating that these metabolites maintain PII in a conformation that controls (de)phosphorylation.

This series of elegant experiments by the Forchhammer group, and those described above for the mammalian AMPK, exemplify key examples of metabolite-controlled protein conformation that regulates covalent modification and, therefore, signaling events. Other examples of metabolite-mediated phosphorylation events include the activation of type 2A protein phosphatases by xylulose-5-phosphate or Glu to dephosphorylate bifunctional fructose-

6-phosphate 2-kinase/phosphatase and acetyl-CoA carboxylase, respectively (Nishimura et al., 1994; Gaussin et al., 1996). Most enzymatic assays for covalent modification (for instance a protein kinase or phosphatase) of a substrate do not examine the potential effect of metabolites, and it is likely that many important effects of metabolites on signaling cascades have been missed and may, in some cases, warrant reexamination.

PII was recently discovered in plants (Hsieh et al., 1998; Smith et al., 2002; Moorhead and Smith, 2003) and, consistent with an ancient origin, is localized to the chloroplast where much of the carbon, nitrogen, and energy metabolism of plants occurs. The plant PII protein is highly conserved (50 and 54% amino acid identity compared with *E. coli* and *S. elongatus* PII, respectively) and, like its bacterial counterpart, readily binds ATP and 2-ketoglutarate (Smith et al., 2003). The Arabidopsis PII does not appear to be regulated by covalent modification (Smith et al., 2004). To date, a plant PII target protein has not been identified. We believe PII will be a fundamental player in integrating signals from these key metabolites and controlling aspects of chloroplast metabolism through this signaling cascade. One of the key questions concerning PII function is how the chloroplast and cytosol communicate information regarding metabolite status.

The importance of sensing and signaling 2-ketoglutarate levels is further illustrated by several examples, the most noteworthy being the cyanobacterial transcription factor NtcA. NtcA is referred to as the global nitrogen regulator of cyanobacteria and controls expression of numerous genes necessary for nitrogen assimilation, including Gln synthetase. NtcA belongs to the catabolite activator protein family of transcription factors, which have classic helix-turn-helix DNA binding domains in their C-terminal and N-terminal regulatory modules. Two groups have shown that 2-ketoglutarate binding to NtcA is necessary for NtcA to bind DNA and initiate transcription (Tanigawa et al., 2002; Vazquez-Bermudez et al., 2002). This signal ensures that the carbon skeleton necessary for nitrogen assimilation into amino acids is

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present before investing in transcription and then translation of the assimilatory enzymes.

SENSING REDOX STATUS

NAD⁺ was detected 100 years ago as a low molecular weight compound necessary for sugar fermentation in yeast extracts (Berger et al., 2004). NAD⁺/NADH and its close analog NADP⁺/NADPH are the soluble carriers of electrons in cells, coupling the oxidation or reduction of a substrate to these electron carriers. In most cell types, the ratio of NAD⁺ to NADH is very high (ranging from 100 to 1000:1) (Bedalov and Simon, 2003), reflecting the general role of NAD⁺ as an electron acceptor in the oxidation of reduced substrates. On the other hand, the ratio of NADP⁺ to NADPH is generally low, reflecting the use of NADPH in biosynthetic processes. To date, more than 200 enzymatic reactions are known that are linked to the oxidation or reduction of these coenzymes. During our introduction to metabolism, we also learn that these molecules can function as allosteric regulators of key enzymes to control pathway flux, reflecting the cellular metabolic state. NAD⁺ is also a substrate for poly ADP-ribose polymerase and the NAD⁺-dependent histone deacetylase (HDAC) during covalent modification of target proteins and also serves as precursor for the calcium mobilizing agents cyclic ADP-ribose and NADP⁺ (Berger et al., 2004). The NAD⁺-dependent HDAC Sir2 gained notoriety when found to function in transcriptional silencing and longevity (Berger et al., 2004).

HDACs were first characterized as proteins that deacetylate histones, causing local chromatin condensation and repressed transcription. Additional HDAC substrates are now being uncovered (Berger et al., 2004). It is thought that the NAD⁺ dependence of the enzymatic activity of the Sir2 deacetylase provides a sensor for NAD⁺/NADH levels and links the redox state to transcriptional silencing. This concept was recently supported by work in skeletal muscle cells where Sir2 was shown to control muscle cell differentiation dependent upon the cellular redox state

(Fulco et al., 2003). Several other examples directly link the NAD⁺/NADH ratio to transcriptional regulation. For example, the mammalian, bacterial, and fungal transcriptional (co)repressors CtBP, REX, and NmrA contain a classic pyridine nucleotide binding module (Rossmann fold), and the binding of NAD⁺/NADH (and NADP⁺ in the case of NmrA) is thought to directly couple cellular redox status with gene transcription (Brekasis and Paget, 2003; Fjeld et al., 2003; Lamb et al., 2003). In the case of REX, cofactor binding was shown to alter DNA binding activity. To date, redox sensing transcription factors have not been described in plants, but the ability to recognize binding modules (like DNA binding domains and Rossmann folds) should provide insights from genomic data.

RIBOSWITCHES: RNA TAKES CONTROL

The first discovered means of metabolite-mediated control of gene expression directly at the mRNA level uses protein factors as a detection mechanism. An excellent example of this is the Trp RNA binding attenuation protein (TRAP) in *Bacillus subtilis*, which is responsible for both transcriptional attenuation and translational control of Trp synthetic pathway genes (Babitzke and Gollnick, 2001). The enzymes necessary for the synthesis of Trp from chorismate in *B. subtilis* are coded by the trpEDCFBA operon. TRAP binds Trp molecules when at a sufficient concentration, causing it to bind to the Trp operon mRNA. This can have two effects. First, binding of TRAP leads to the formation of a terminator hairpin, stopping transcription in the sequence before the trpE gene, a process known as transcriptional attenuation. Second, binding of TRAP also causes the formation of a sequestering hairpin (one that covers the ribosome binding site) that prevents translation when TRAP is bound.

Riboswitches are a method of controlling gene expression by direct binding of metabolites to RNA. Although originally characterized in bacteria, riboswitches recently have been found in a variety of eukaryotic species as well (Kubodera et al.,

2003; Sudarsan et al., 2003), including *Arabidopsis thaliana*. Essentially, a riboswitch is a sequence of RNA that, through its secondary and tertiary structure, selectively binds a specific metabolite. When the metabolite is bound, the secondary structure of the mRNA changes, affecting transcription and translation in prokaryotes and possibly mRNA processing in eukaryotes. Changes in mRNA secondary structure upon metabolite binding are best documented in bacteria. Metabolite-dependent mRNA structural changes include the formation of terminator hairpins (RNA structures that stop transcription) and sequesters (RNA structures that hide the ribosome binding site or the start codon). Some of the characterized riboswitches, and the metabolites that bind to them, include the thi-box (thiamine pyrophosphate), RFN-element (flavin mononucleotide), B₁₂ element (vitamin B₁₂), S-box (S-adenosylmethionine), G-box (purines [guanine or adenine depending upon the G-box variant]), L-box (Lys), glmS-element (glucosamine-6-phosphate), and the gcvT-element (Gly) (Barrick et al., 2004; Mandal and Breaker, 2004; Vitreschak et al., 2004). Consistent with the concept that a regulatory element must function in a milieu of many different molecules, all riboswitches characterized to date bind their target metabolites with high affinity and exceptional specificity (Mandal and Breaker, 2004; Vitreschak et al., 2004).

The thi-box is a conserved sequence/secondary structure found in the 5' untranslated region (UTR) of genes involved in biosynthesis of thiamine pyrophosphate (TPP) in bacteria. TPP is the coenzyme required for the decarboxylation of α -keto acids within the cell and thus is required for the function of several enzymes, for example α -ketoglutarate dehydrogenase and pyruvate decarboxylase. The thi-box itself was discovered in 1999 as a conserved motif in thiamine synthesis genes (Miranda-Rios et al., 2001), but it was not until 2002 that thiamine pyrophosphate was found to bind specifically to the thi-box itself. Because unstructured RNA is much more likely to undergo spontaneous cleavage than structured RNA, cleavage patterns with and without TPP were used to

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determine the difference between bound and unbound structure. In the unbound state, the ribosome binding site was unpaired and so could be recognized by the ribosome; however, once TPP was bound, the secondary structure of the RNA changed so that the ribosome binding site was paired with another segment of RNA, acting as a sequester. This bound structure prevents translation of the genes that follow the 5'UTR, in this case genes involved in the synthesis of thiamine (Winkler et al., 2002).

The thi-box has also been identified in several eukaryotes, including *Arabidopsis* and *Oryza sativa* (Sudarsan et al., 2003), with only one major difference: location. All riboswitches found in prokaryotes have been found in the 5' UTR, but the thi-box in *Arabidopsis* and rice is located in the 3' UTR, and other eukaryotes have it within introns. The working hypothesis about the action of these riboswitches is that they are involved in mRNA processing, either in the splicing of introns (for those contained within introns) or polyadenylation of mRNA (for those in the 3' UTR) (Sudarsan et al., 2003). In some eukaryotes, the thi-box is found specifically on an exon found in the 3' UTR, which, based on cDNA evidence, can be spliced out of the mature mRNA. This indicates that the cell can produce two splice variants of the mRNA, one that is regulated in some way by TPP and one that is not, adding a further dimension of control.

CONCLUSIONS

We have tried to illustrate the signaling function of metabolites with a series of diverse examples and point out where the signaling system is conserved across kingdoms. Undoubtedly, metabolites play a strategic role in signaling metabolic conditions and interfacing them with various cellular processes. There are many other excellent examples that we have not described, for instance, sugar sensing and signaling through glucose, sucrose, and trehalose-6-phosphate (Rolland et al., 2002) and modulation of potassium channel function by ATP and NADP⁺ (Trauner and Kramer, 2004), and we encourage

readers to seek them out. The recent discovery of riboswitches in bacteria and their presence in eukaryotes ushers in another level of metabolite regulation that will have implications on cellular regulation, about which, we can only speculate at this time. In the postgenomic age, we are particularly reminded of one of Arthur Kornberg's ten commandments of enzymology, "trust the universality of biochemistry" (Kornberg, 2003), but perhaps we should also remind ourselves to look closely for the differences.

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