More writing: mTORC1 promotes m6A mRNA methylation

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Abstract
Cho et al. (2021) and Villa et al. (2021) demonstrate that mTORC1 stimulates m6A mRNA methylation via WTAP expression and SAM synthesis. Increased mRNA methylation in turn promotes cell growth by enhancing mRNA degradation or translation.

Target of Rapamycin Complex 1 (TORC1) is an evolutionarily conserved serine/threonine kinase that regulates cell growth and metabolism in response to nutrients and growth factors (Gonzalez and Hall, 2017). Mammalian TORC1 (mTORC1) activity is altered in various diseases including hyperactivation in cancer (Saxton and Sabatini, 2017). mTORC1 promotes cell growth at least in part by enhancing RNA metabolism, including nucleotide synthesis, transcription, splicing, ribosome biogenesis, and translation (Tahmasebi et al., 2018). In this issue, Cho et al. (2021) and Villa et al. (2021) add an interesting new dimension to the regulation of RNA by mTORC1 - the stimulation of mRNA methylation (Cho et al., 2021; Villa et al., 2021).

Methylation of RNA at N6 of the adenosine base (N6-methyladenosine, m6A) is one of the most common mRNA modifications. It impacts mRNA splicing, degradation, and translation (He and He, 2021). This methylation is carried out co-transcriptionally by the so-called 'writer complex' comprising the methyltransferases METTL3, METTL14, and the accessory proteins WTAP, VIRMA, ZC3H13, and RBM15/15B (Zaccara et al., 2019). Changes in mRNA m6A have been reported in various contexts including pluripotency, cancer, and development. However, the underlying mechanism regulating such changes in mRNA methylation was not known - until now. The two studies in this issue and a concurrent study in another journal (Tang et al., 2021) report that mTORC1 promotes m6A modification of mRNA.

Cho et al. (2021) show that mTORC1 promotes m6A on several mRNAs by enhancing expression of the writer complex subunit WTAP. mTORC1, via its effector S6K, activates eIF4F to stimulate translation of *WTAP* mRNA. Increased WTAP promotes methylation of several mRNAs including mRNA encoding MXD2, a suppressor of cMYC. Villa et al. (2021) also observed an increase in mRNA m6A upon activation of mTORC1. However, they account for the increase in m6A RNA modification by proposing enhanced WTAP and an additional mechanism. They demonstrate that mTORC1, via cMYC, stimulates transcription of MAT2A which in turn promotes synthesis of S-adenosyl methionine (SAM). Since SAM is the methyl donor in mRNA methylation, elevated SAM levels further enhance m6A mRNA modification. Thus, mTORC1 stimulates mRNA methylation by activating the writer complex and by boosting the levels of an essential methylation co-factor.

The current two studies also provide insight on how mTORC1-mediated stimulation of m6A controls mRNA metabolism and ultimately cell growth. Cho et al. (2021)

show that m6A in *MXD2* mRNA targets the transcript for degradation. In other words, removal of the methylation site in the 3'UTR of *MXD2* stabilized the mRNA. Thus, m6A promotes cell growth by reducing MXD2 expression and thereby enhancing cMYC activity. Further studies will reveal how the m6A modification targets *MXD2* mRNA for degradation. Villa et al. (2021) propose that m6A stimulates translation. mTORC1 promotes translation by multiple mechanisms such as inhibition of eIF4E-binding proteins (eIF4BPs), activation of the eIF4F and eIF3 complexes and inhibition of eEF2K. mTORC1-mediated activation of global translation via m6A is novel. However, the extent to which m6A contributes to mTORC1-mediated upregulation of translation and the underlying mechanism require further study. Investigation of a possible correlation between ribosome foot-prints and m6A may reveal that the mechanism of translation stimulation is direct, although others have not seen such a correlation albeit in a different context (Meyer et al., 2015).

mTORC1 regulates various metabolic pathways in addition to protein synthesis, such as glucose catabolism and lipid and nucleotide synthesis. Villa et al. (2021) now show that mTORC1 also promotes SAM synthesis. SAM is the most important methyl group donor for various methyltransferases that modify DNA, rRNA, tRNA, proteins and lipids, in addition to mRNA. Thus, mTORC1-stimulated SAM synthesis may support cell growth in many ways. SAM synthesis is also coupled to central one-carbon metabolism (also called the folate cycle) (Shetty and Varshney, 2020). The folate cycle provides various one-carbon donor intermediates for the synthesis of methionine, purines, and thymidine. The folate cycle is also crucial for cancer cell growth; indeed, antifolates are one of the earliest chemotherapeutic agents. Further studies on how mTORC1 regulates one-carbon flux in normal physiology and in cancer cells will be of interest.

Both studies show that mTORC1 enhances m6A writer activity upon insulin stimulation. mTORC1 is also activated by nutrients such as amino acids. Whether writer complex activity responds to nutrient levels, in yeast or mammalian cells, remains to be determined. Furthermore, whereas Villa et al. (2021) demonstrated that mTORC1 controls SAM synthesis, the inverse has also been shown - SAM controls mTORC1 (Gu et al., 2017). Mammalian cells possess a SAM sensor (SAMTOR) that coordinates mTORC1 activity with the levels of methionine and SAM (Gu et al., 2017). SAMTOR inhibits the RAG GTPase via GATOR1 to repress mTORC1 in the absence of SAM. Interestingly, Villa et al. (2021) observed that depletion of SAMTOR did not perturb mTORC1 signaling in TSC2 null cells. Thus, the tumor suppressor and mTORC1 inhibitor TSC (a TSC1-TSC2 complex) might be required for the silencing of mTORC1 upon SAM depletion. This is consistent with Demetriades et al. (2014) who demonstrated that 'inactive' RAGs recruit TSC to inhibit mTORC1 (Demetriades et al., 2014). Future studies will reveal the logic of having SAM both upstream and downstream of mTORC1.

cMYC is a well-known oncoprotein reported to be both upstream and downstream of mTORC1. The two current studies support a role of cMYC downstream of mTORC1. Cho et al. (2021) propose an mTORC1-WTAP-cMYC axis to promote cell growth whereas Villa et al. (2021) claim an mTORC1-cMYC-MAT2A-SAM axis to promote translation. It will be interesting to determine whether these axes are parallel or a linear mTORC1-WTAP-cMYC-MAT2A-SAM pathway.

A major question in the m6A mRNA modification field is how the writer complex finds its nascent mRNA substrates (He and He, 2021). One model is that writer complex encounters its substrates via transcription factors. Cho et al. (2021) found that activation of mTORC1 increases overall m6A modification. However, m6A mRNA modification negatively correlated with expression of the modified transcripts, suggesting that mTORC1 induced transcription is not a determinant of methylation. Another model is that chromatin marks such as trimethylation of lysine 36 in histone H3 (H3K36m3) guide the writer complex to nascent mRNA. However, Villa et al. (2021) did not observe major global changes in epigenetic marks, including H3K36m3, upon alteration in SAM levels or mTORC1 activity. Thus, like any good study, the current studies raise new questions while revealing new findings in m6A biology. mTORC1-mediated enhancement of m6A mRNA modification has created new leads on the mechanism of m6A deposition and its role in mRNA metabolism.

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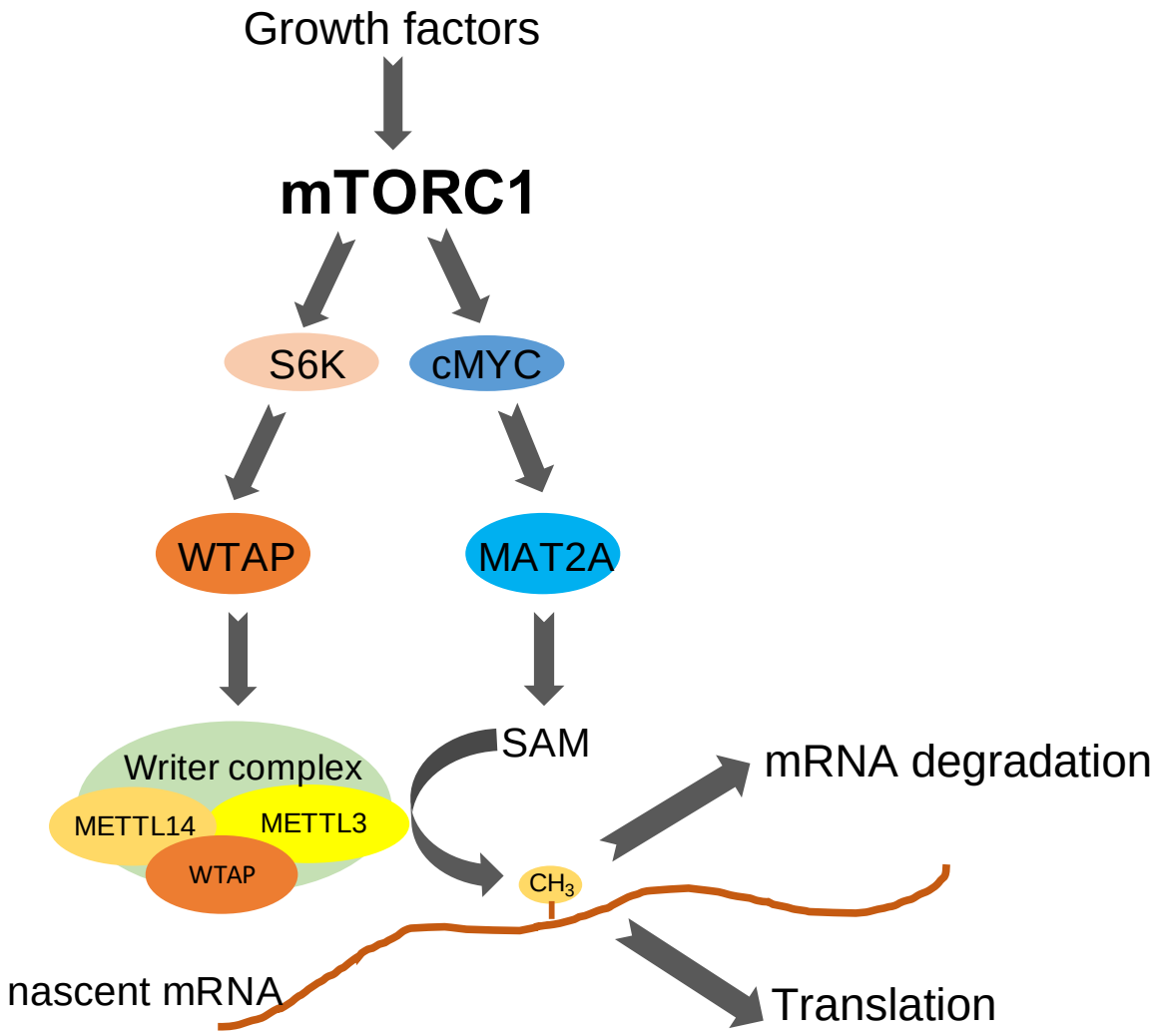

Figure legend
Figure 1. mTORC1 enhances mRNA methylation (m6A) via WTAP and SAM to promote mRNA degradation or translation.