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mTOR goes to the nucleus:

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Mammalian target of rapamycin (mTOR) is protein ser/thr kinase that plays a central role in cell growth and metabolism.[1] For many years, mTOR has been viewed as a cytoplasmic kinase, whose function is engaged in many cellular activities outside of nucleus, such as translation, autophagy and protein degradation. Even its role in transcription regulation appears to be fulfilled by controlling the cytoplasm to nucleus translocation of transcription factors. In accordance with its cytoplasmic activities, mTOR is found on membrane structures distributed in the cytoplasm, such as endosomes, ER, Golgi and mitochondria. Recently, however, an increasing body of evidence indicates that mTOR is also presented in the nucleus. In HEK293 cells, a commonly used cell line for mTOR study, mTOR was found to distribute predominantly in the cytoplasm under normal condition but accumulate in the nucleus when the nuclear export receptor Crm1 was blocked by leptomycin B,[2] which suggests an active shuttling of mTOR between the cytoplasm and the nucleus. In addition, mTOR was also found in the nucleus of many types of cancer cells.[3] These observations contradict the view of mTOR being merely a cytoplasmic kinase and beg the question—what does mTOR do in the nucleus? In their paper published in this issue of *Cell Cycle*, Tsang et al. demonstrate that the nuclear localized mTOR is involved in RNA polymerase I (Pol I) and III (Pol III)-mediated transcription of ribosomal DNA (rDNA) and transfer RNA (tRNA) genes.[4]

Transcription of rDNA and tRNA genes by Pol I and Pol III is a major transcriptional event in the nucleus, which dictates the rate of ribosome biogenesis, and consequently, the capacity for protein synthesis.[5] The transcriptional activity of Pol I and Pol III is tightly regulated by growth factor and nutrient conditions. However, the underlying mechanism is poorly defined. Tsang et al. find that mTOR is associated with the promoters of 45S rDNA and genes of 5S rDNA and tRNAs.[4] This association hence imparts an element into the transcriptional machinery, allowing growth factors and nutrient conditions control Pol I and Pol III activity through mTOR. In support of this view, Tsang et al. show that the association of mTOR with the rDNA promoters is dependent on the availability of growth factors and nutrient.[4] This observation is also consistent with previous studies in yeast from the same group showing that the yeast Tor1 protein is associated with the promoter of 35S DNA in a nutrient-dependent and rapamycin sensitive manner.[6] Hence the direct role of TOR in Pol I and Pol III-mediated transcription appears to be a conserved mechanism.

How does mTOR regulate Pol I and Pol III-mediated transcription? In yeast, the TOR complex 1 (TORC1) has been shown to control the Pol III repressor Maf1 by modulating its phosphorylation and binding to Pol III-transcribed genes.[7] In mammalian cells, mTOR is

implicated in phosphorylation of TIF1A and UBF, two transcription initiation factors of Pol I.[8] It is thus likely that mTOR controls Pol I and Pol III activity through phosphorylation of factors involved in their regulation. In this regard, the mechanism of mTOR in Pol I and Pol III regulation is similar to its action in Pol II regulation, which is dependent on its kinase activity. However, while the role of mTOR in Pol II-dependent transcription is achieved by regulating the cytoplasm to nucleus translocation of transcriptional factors, its function in Pol I and Pol III regulation requires its direct presence in the nucleus and association with rDNAs.

The presence of mTOR in the nucleus also raises an issue concerning how the nuclear mTOR is regulated by growth factor and nutrient conditions. After all, the growth factors and nutrient conditions are normally sensed at the cell surface or inside the cytoplasm and many known regulators of mTOR, such as Rheb and Rag GTPases, are localized outside of the nucleus.[9] It is possible that mTOR is activated in the cytoplasm before being translocated into the nucleus. Alternatively, the nuclear mTOR is regulated by mechanisms independent of Rheb and Rag GTPases. In either case, a cytoplasm to nucleus signaling mechanism is needed to convey environmental signals for the function of mTOR in the nucleus. In this regard, the finding that mTOR controls Pol I and Pol III-mediated transcription not only reveals a novel function of mTOR but also indicates a new aspect in mTOR regulation.

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