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STRESS RESPONSES

SIRT1 puts an embargo on mRNA export

> “the SIRT1–PABP1 translation regulatory network … modulates energy expenditure under stress”

When under stress, cells switch to an energy-preserving, non-proliferative state, one hallmark of which is translation inhibition. Wang and colleagues now show that translation repression in these conditions involves the retention of polyadenylated mRNAs in the nucleus and that the protein deacetylase sirtuin 1 (SIRT1) has a key role in this process.

In mammalian cell cultures, energy (glucose) deprivation led to nuclear accumulation of polyadenylated mRNAs, suggesting that starvation-induced repression of translation is mediated, at least in part, by nuclear mRNA retention. SIRT1 is a known nutrient sensor and a regulator of cellular metabolic status, and its expression is increased during fasting. Thus, the authors speculated that SIRT1 may restrict nuclear export of polyadenylated mRNAs in starved cells. Indeed, *SIRT1* knockout or knockdown reduced the nuclear accumulation of polyadenylated mRNAs in starved cells, whereas its overexpression or activation induced nuclear retention of these mRNAs.

Translation of mRNAs is regulated by polyadenylate-binding proteins (PABPs). PABP1 is one of seven human PABPs, which in normal growth conditions shuttles between the nucleus and the cytoplasm and promotes translation. In response to stress, PABP1 accumulates in the nucleus, which is associated with nuclear accumulation of polyadenylated mRNAs and inhibition of translation. The authors demonstrated that SIRT1 directly interacts with PABP1 and deacetylates it at Lys95. PABP1 deacetylation led to PABP1 being retained in the nucleus, and at the same time reduced its ability to interact with polyadenylated mRNAs, leading to downregulation of protein synthesis. Importantly, SIRT1-dependent deacetylation was necessary and sufficient for PABP1 to promote nuclear retention of polyadenylated mRNAs. Thus, SIRT1-mediated PABP1 deacetylation sequesters PABP1 in the nucleus and suppresses nuclear export of polyadenylated mRNAs, thereby repressing translation.

SIRT1-dependent PABP1 deacetylation and its nuclear accumulation were promoted by cell starvation, and notably, they were accompanied by reduced ATP consumption. Previous studies showed that SIRT1 is phosphorylated by 5′ AMP-activated protein kinase (AMPK) — a major regulator of cellular energy homeostasis. AMPK-mediated phosphorylation of PABP1 promoted SIRT1–PABP1 interaction, and AMPK activity was important for nuclear accumulation of both PABP1 and polyadenylated mRNAs in starved cells. Thus, the SIRT1–PABP1 translation regulatory network responds to energy deprivation through the activity of AMPK and modulates energy expenditure under stress.

In summary, SIRT1-mediated deacetylation of PABP1 inhibits translation by sequestering polyadenylated mRNAs in the nucleus. This mechanism seems to be part of an adaptive cellular response to energy deprivation that is integrated into cellular pathways regulating energy homeostasis. As nuclear retention of polyadenylated mRNAs has also been observed in response to stresses other than starvation, it is possible that suppression of nuclear export of polyadenylated mRNAs mediated by SIRT1–PABP1 (and/or other mechanisms) is more generally implicated in translation regulation in the event of stress.

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