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Title: PGC-1α SENSES THE CBC OF PRE-MRNA TO DICTATE THE FATE OF PROMOTER-PROXIMALLY PAUSED RNAPII

Abstract:
PPARɣ coactivator (PGC)-1α is well-established as a transcriptional coactivator for the metabolic adaptation of mammalian cells, but its molecular dynamics during early steps of gene transcription are incompletely understood. We previously defined a cap-binding protein (CBP)80-binding motif (CBM) within PGC 1α that mediates association with the 5'-cap of nascent transcripts deriving from PGC 1α-responsive genes. Here, we report that PGC 1α serves as a DNA–RNA conduit between promoter-bound estrogen-related receptor (ERR)α and nascent transcript-bound CBP80 to overcome promoter-proximal pausing of RNAPII at stress-response genes by competing against the premature transcription termination complex Integrator and by recruiting the positive transcription elongation factor (P-TEF)b. Using mice homozygous for five amino-acid changes in PGC 1α that destroy CBM function, we show that efficient differentiation of primary myoblasts to myofibers, and effective skeletal-muscle regeneration after injury, requires PGC 1α binding to CBP80. Our findings reveal how PGC-1α activates stress-response gene transcription in a previously unanticipated pre-mRNA quality-control pathway.