New Roles for AMP-activated Protein Kinase in Gene Transcription and DNA Repair

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Abstract
AMP-activated protein kinase (AMPK) constitutes a major metabolic switch which is involved in many cellular activities. We are utilizing the powerful genetic tools of the simple model eukaryote *S. cerevisiae* to study the mechanisms of action of AMPK. *S. cerevisiae* cells lacking AMPK are unable to utilize galactose and to repair double-strand breaks in DNA (DSBs), reflecting the regulatory role that AMPK plays in the transcriptional activation of the glucose-repressed genes and in the DNA Damage Response (DDR). Our results indicate that AMPK directs conditional protein degradation to regulate both gene transcription and the DDR. In gene transcription, AMPK acts via components of Mediator and in the repair of DSBs, AMPK acts via the metabolic enzyme fumarase. Mediator is required for the transcription of nearly all RNA Polymerase II-dependent genes, and we have shown that Mediator causes the transcriptional activation of glucose-repressed genes via the conditional protein degradation of transcriptional repressors. Fumarase, which was shown previously to be involved in the DDR, is a tumor suppressor linked to Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC). Recently, metabolic reprogramming has been recognized as a hallmark of cancer and many examples have emerged where specific alterations in the cellular energy and intermediary metabolism contribute directly to cancer development. Mutations in the tricarboxylic acid (TCA) cycle enzymes succinate dehydrogenase and fumarase, for example, are directly involved in the development of specific tumors, and it has been suggested that this is due to accumulation of the TCA cycle metabolite succinate. Our preliminary results indicate that fumarase interacts directly with proteins whose conditional degradation is part of the DDR. We propose that the protein interaction with fumarase results in the succinylation and degradation of the targeted proteins.

Selected Publications