Rpd3 helps put yeast cells to bed

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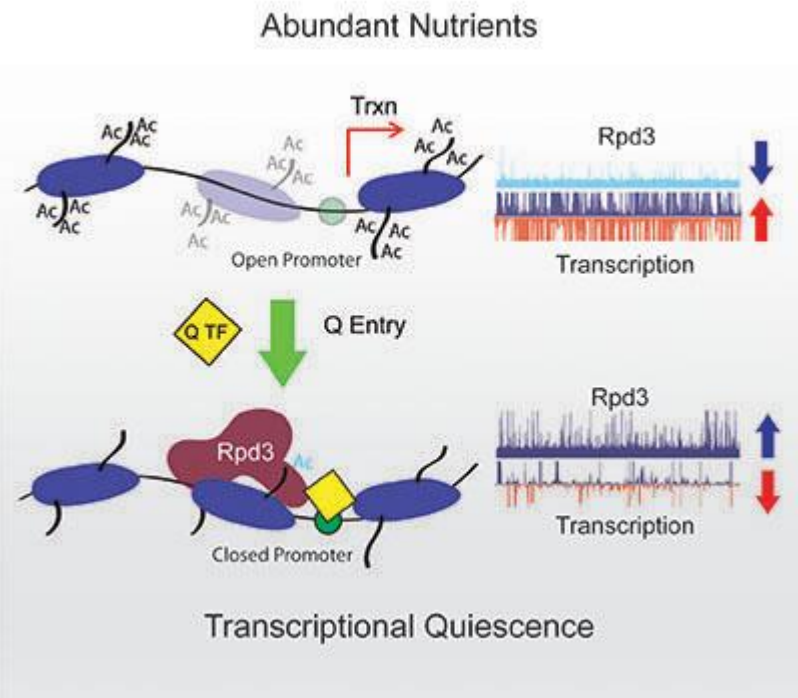

In the presence of abundant nutrients, Rpd3 binds mainly to gene bodies, allowing promoter histones to be highly acetylated. Upon nutrient consumption, quiescence-specific TFs recruit Rpd3 to promoters to deacetylate histones and globally repress transcription.

Image provided by Dr. Jeffrey McKnight.

Quiescence is a state of reduced cellular activity, characterized by cell cycle arrest, increased longevity and stress resistance, as well as decreased transcription, protein synthesis, and metabolic activity. However, the molecular details of the establishment of quiescence, particularly how transcription is globally repressed, are still unclear. To better understand this transcriptional shutoff, postdoctoral fellow Dr. Jeffrey McKnight in the laboratory of Dr. Toshio Tsukiyama and colleagues in the laboratory of Dr. Linda Breeden (Basic Sciences Division) analyzed chromatin structure during the transition from growth to quiescence in budding yeast. "We were fascinated by the programmed ability of budding yeast to survive for so many weeks in water without any nutritional supplements. This was a beautiful system for trying to identify conserved regulators and mechanisms of stress tolerance and longevity during quiescence," said Dr. McKnight. "We found Rpd3, a conserved histone deacetylase with minimal known contributions in nutrient-rich conditions, was essential for quiescence entry and survival."

The authors first analyzed gene expression in cells growing in rich medium (log), cells growing until glucose was exhausted from medium (diauxic shift, DS), and quiescent (Q) cells. Q cells showed a

30-fold decrease in overall mRNA levels compared to log cells and a 15-fold decrease in mRNA versus DS cells. Further analysis revealed decreased binding of RNA polymerase II and the transcription pre-initiation complex to the genome, suggesting that the global transcriptional shutoff occurs at the level of transcriptional initiation.

Hypothesizing that chromatin might play a role in the Q transcriptional shutoff, the authors compared chromatin structure between log and Q cells. Q cells displayed increased nucleosome occupancy at promoters, indicating the establishment of a repressive chromatin architecture. Q cells also displayed a global decrease in histone acetylation, which is generally associated with transcriptional activation. These chromatin alterations were strongly correlated with transcriptional shutoff, suggesting that chromatin is indeed the means by which Q cells repress transcription.

Many of the observed chromatin shifts were associated with binding sites for transcription factors (TFs) proposed to function through the lysine deacetylase Rpd3, and so the authors next investigated the potential function of this protein in Q cells. Cultures of cells lacking Rpd3 displayed a lower fraction of Q cells following nutrient exhaustion, likely due to reduced viability, and also had a shortened lifespan. Rpd3 is present in two distinct complexes, Rpd3S and Rpd3L, and genetic analysis suggested that the promoter-associated Rpd3L complex, but not Rpd3S, is involved for the establishment of the Q state. Indeed, cells lacking Rpd3 were impaired in the establishment of the repressive chromatin architecture in Q cells.

The authors next profiled the genome-wide binding of Rpd3 in log and Q cells. In log cells, relatively few Rpd3 binding sites were identified, and most Rpd3 signal was observed in in gene bodies. However, in Q cells, a large-scale redistribution of Rpd3 to promoters occurred. Furthermore, several hundred of these peaks were dependent on the quiescence-specific Stb3 and Xbp1 TFs.

These results convincingly demonstrate that establishment of repressive chromatin by Rpd3 is critical for entry into quiescence by yeast cells. Of note, understanding the role of Rpd3 in establishing quiescence may have implications for the treatment of disease. "These findings are particularly interesting, since targeted inhibition of the human Rpd3 orthologs is effective in treating drug-resistant leukemias and latent HIV infections. Our mechanistic investigation of transcriptional quiescence in yeast may therefore shed light on the mechanisms of drug resistance of quiescent cancers," said Dr. McKnight.

McKnight JN, Boerma JW, Breeden LL, Tsukiyama T. 2015. Global Promoter Targeting of a Conserved Lysine Deacetylase for Transcriptional Shutoff during Quiescence Entri. *Mol Cell* 59(5):732-743.

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