H3K36 Methylation Promotes Longevity by Enhancing Transcriptional Fidelity

Epigenetic mechanisms, including histone post-translational modifications, control longevity in diverse organisms. Relatedly, loss of proper transcriptional regulation on a global scale is an emerging phenomenon of shortened life span, but the specific mechanisms linking these observations remain to be uncovered. Here, we describe a life span screen in *Saccharomyces cerevisiae* that is designed to identify amino acid residues of histones that regulate yeast replicative aging. Our results reveal that lack of sustained histone H3K36 methylation is commensurate with increased cryptic transcription in a subset of genes in old cells and with shorter life span. In contrast, deletion of the K36m2/3 demethylase Rph1 increases H3K36me3 within these genes, suppresses cryptic transcript initiation, and extends life span. We show that this aging phenomenon is conserved, as cryptic transcription also increases in old worms. We propose that epigenetic misregulation in aging cells leads to loss of transcriptional precision that is detrimental to life span, and importantly, this acceleration in aging can be reversed by restoring transcriptional fidelity.