The Role of SUPT4H in Neurogenesis, Fear Memory, and Repeat Expansion Disorders

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SUPT4H (named as Spt4 in yeast) is a transcription elongation factor that, in complex with SUPT5H, facilitates RNA polymerase II processivity during transcription elongation. While traditionally regarded as a general elongation factor, emerging evidence suggests that SUPT4H plays a crucial role in the transcription of genes with substantial genomic length, high GC content, and expanded nucleotide repeats.

Our previous studies demonstrated that SUPT4H is essential for the expression of genes containing highly expanded nucleotide repeats, such as CAG repeats in Huntington's disease (HD) and GGGCC repeats in C9orf72-mediated amyotrophic lateral sclerosis (ALS). Consistently, we showed that pharmacological disruption of the SUPT4H-SUPT5H interaction reduces mutant gene expression in various HD cell models and mitigates photoreceptor neuron degeneration in a Drosophila melanogaster HD model. More recently, conditional knockout of SUPT4H revealed its critical role in regulating mRNA synthesis from a subset of long genes in the amygdala, thereby influencing amygdala-dependent associative memory formation in adult mice. Additionally, during embryonic development, SUPT4H plays a pivotal role in directing neural progenitor cells to differentiate into neurons responsible for inspiratory rhythm generation. These findings challenge the canonical view of SUPT4H as a general transcription elongation factor, highlighting its indispensable role in select physiological and pathological contexts where gene length and nucleotide sequence composition are key determinants.