Ctk1 regulates replicative lifespan by controlling the expression of ribosomal proteins

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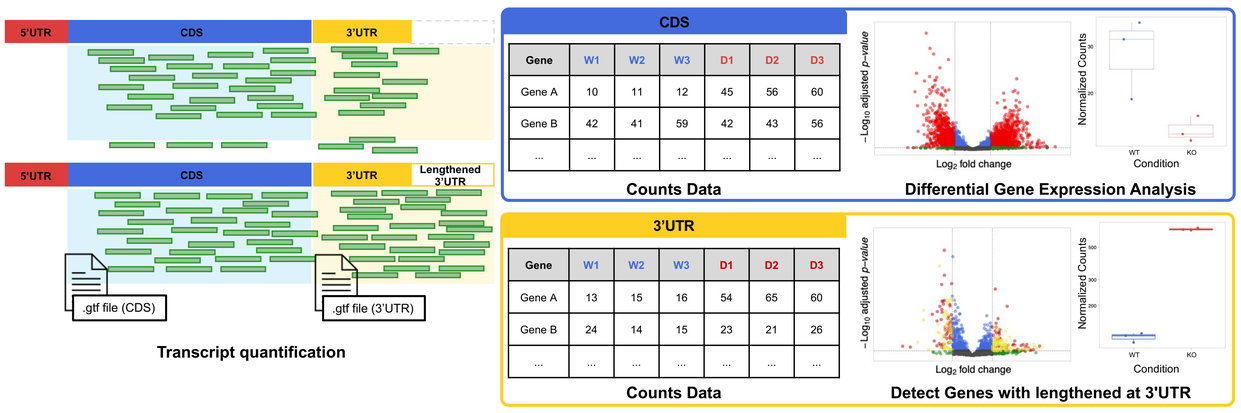
Introduction

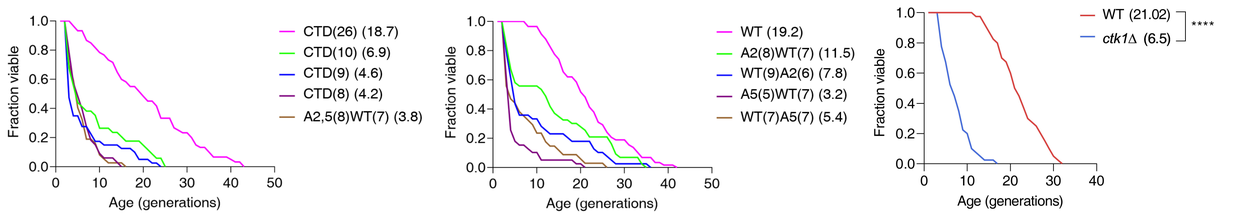
In Saccharomyces cerevisiae, CTK1 primarily serves as a coordinator for pre-mRNA 3' end processing, cellular proliferation, and transcriptional elongation. The biggest RNA polymerase II (RNAP II) subunit's C-terminal domain (CTD), known as CTK1, is made up of several repeats of the heptameric sequence (YSPTSPS). During transcription, this domain experiences dynamic phosphorylation at Ser2 (S2P) or Ser5 (S5P). Notably, RNA Pol I transcription depends on the catalytic component of CTD kinase I (Ctk1)-mediated CTD S2P. Here, we demonstrate that in partly truncated CTD mutants, the replicative lifespan (RLS) is dramatically reduced. Implementing bulk RNA-sequencing, we examined the significant differences in gene expression between *ctk1Δ* mutants and WT. We have found similarities between the transcriptomes of *ctk1Δ* mutants and aging cells. We have found an intriguing downregulation of cytoplasmic translation by Ctk1 loss. Surprisingly, multiple ribosomal proteins overexpressed can reverse the growth abnormalities in *ctk1Δ* mutants which supports that Ctk1 and aging are tightly connected.

Study Design

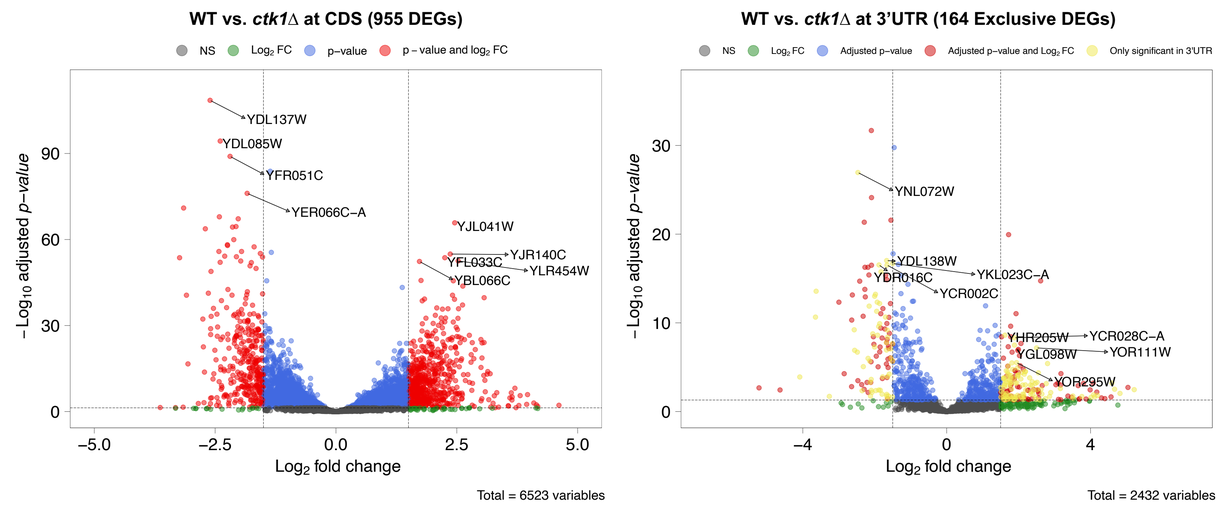


Results

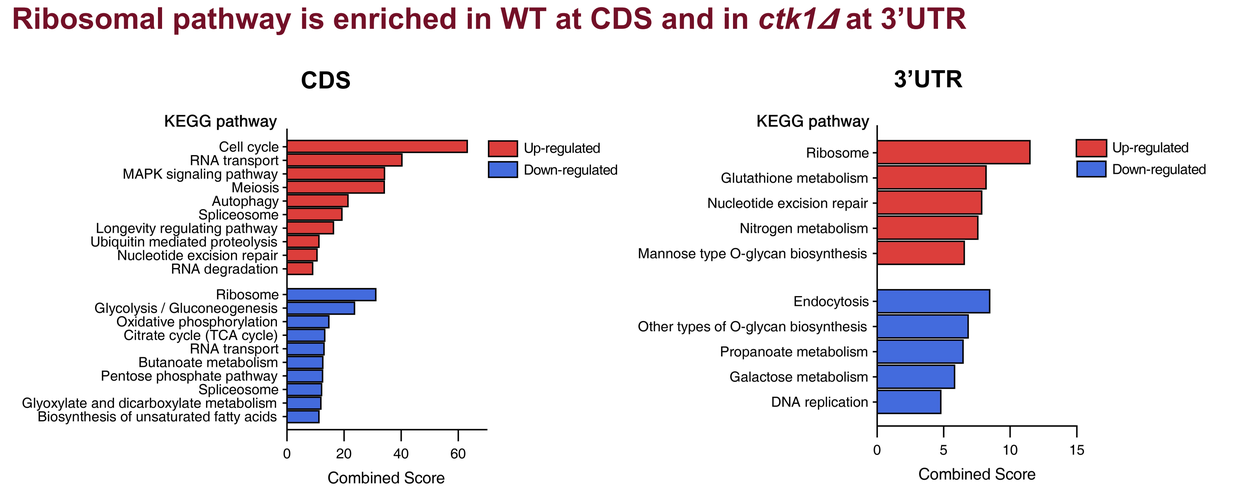
RLS is dramatically decreased in partially truncated *ctk1Δ*



955 DEGs at CDS and 164 DEGs which are exclusively significant at 3'UTR were discovered



Ribosomal pathway is enriched in WT at CDS and in *ctk1Δ* at 3'UTR

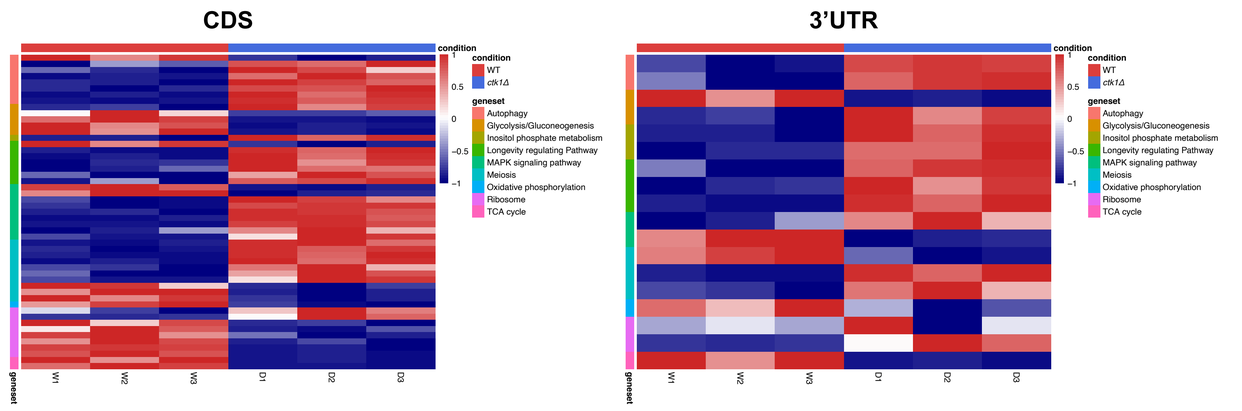


We quantified yeast transcriptome at CDS and 3'UTR separately and identified DEGs. 955 DEGs at CDS and 164 DEGs which are exclusively significant in 3'UTR were discovered with following criteria, $|\text{Log}_2 \text{ fold change}| > 1.5$ and adjusted p-value < 0.05.

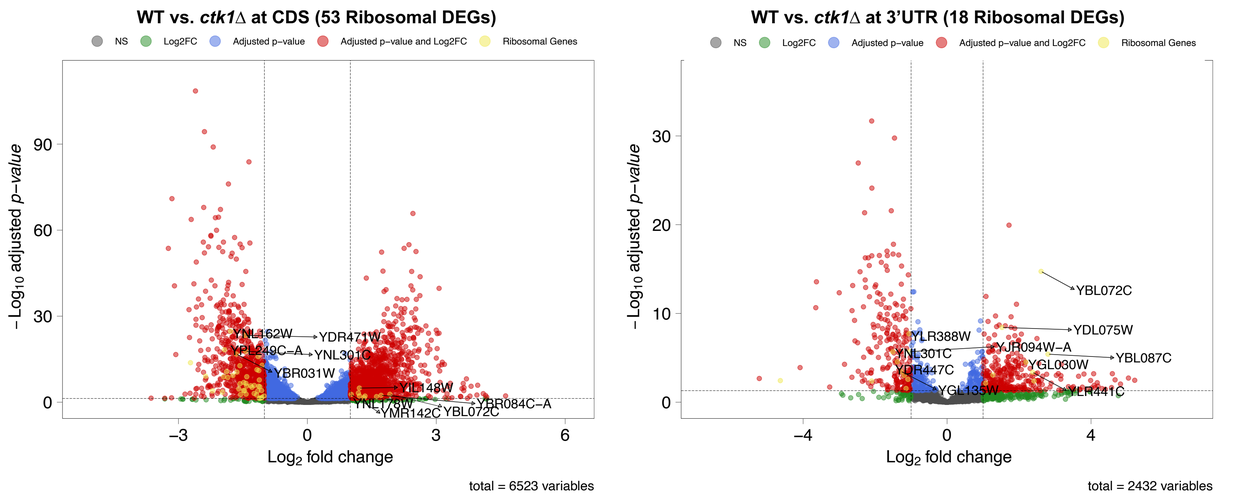
Ribosome and Glycolysis / Gluconeogenesis pathways are enriched in WT and cell cycle and RNA transport pathways are enriched in ctk1Δ at CDS. On the other hand, the ribosome pathway is enriched in *ctk1Δ* at 3'UTR. This supports that ribosomal genes are downregulated cytoplasmic translation due to the lengthened 3'UTR.

Results

The expression level of ribosomal genes is higher in WT compared to *ctk1Δ* and aging-related genes show higher expression in *ctk1Δ* compared to WT at CDS

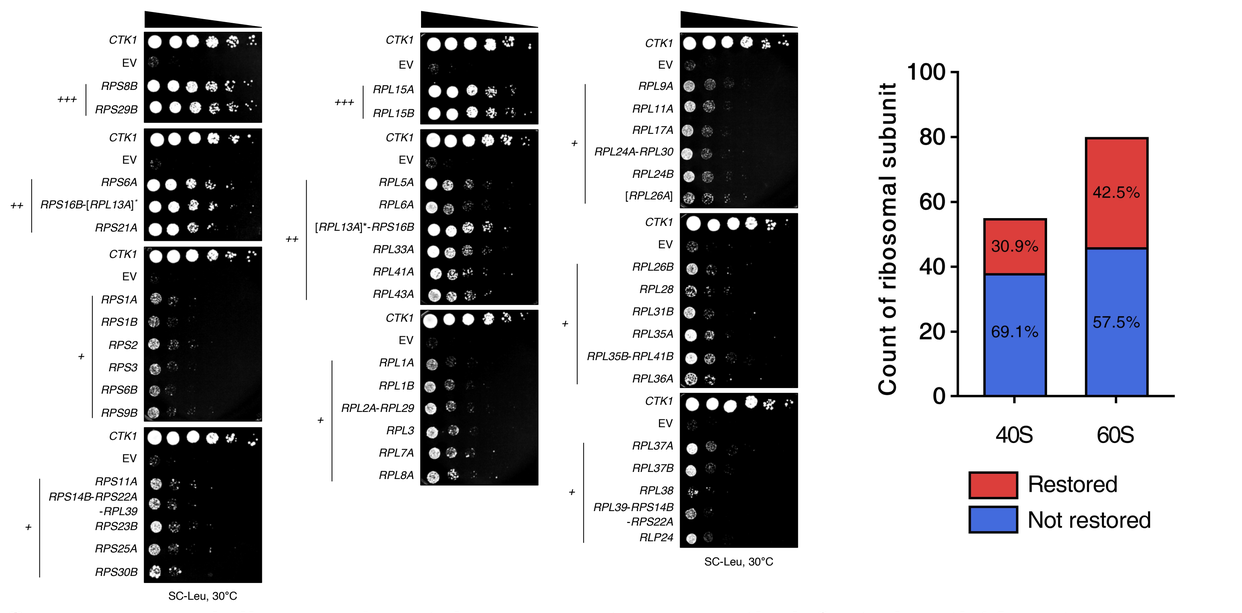


Most of the ribosomal genes that are significantly differentially expressed showed higher expression in WT than *ctk1Δ* at CDS

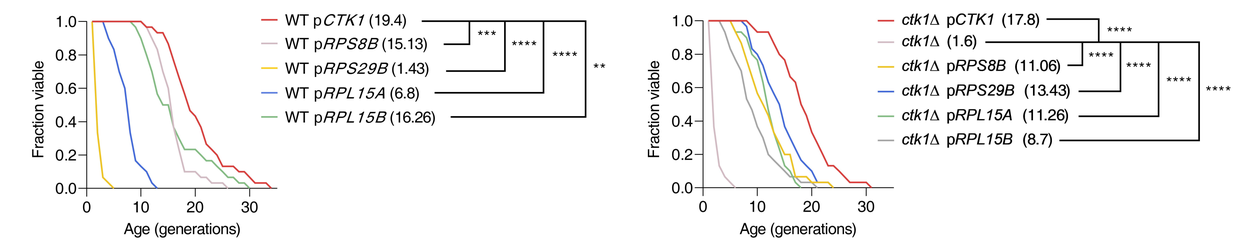


The expression level of ribosomal genes is significantly higher in WT compared to *ctk1Δ* at CDS and the expression level of aging-related genes is higher in *ctk1Δ*. Also, ribosomal genes are more lengthened in *ctk1Δ* at 3'UTR which might hinder the cytoplasmic translation.

Expression of ribosomal proteins level decreased in partially truncated *ctk1Δ*



Overexpressed ribosomal proteins can restore growth defects in *ctk1Δ* mutants



At a protein expression level, ribosomal proteins' expression level decreased as an expression of Ctk1 decreased. With the expression of ribosomal proteins, longer RLS could be observed both from WT and *ctk1Δ* samples.

Conclusion

Ctk1 is required for normal growth of Saccharomyces cerevisiae. As a result, Ctk1 deletion is extremely lethal to cell growth. Additionally, the loss of Ctk1 causes a downregulation of cytoplasmic translation, which is a characteristic of aging cells. Some RP genes in the yeast tiling collection rescue the *ctk1Δ* strains' growth problem. RPS2 is a well-known target of Ctk1 phosphorylation, which improves translational precision. However, our hypothesis is that CTK1 interacts with other undisclosed RP genes. We think that ribosomal proteins and Ctk1 may control aging.