Roles of Rrp6/EXOSC10-targeted lncRNAs in anti-cancer drug toxicity and cell wall architecture

EB-04-3

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Saccharomyces cerevisiae is a versatile model organism that has been used extensively to study mitotic cell growth and division in the presence of numerous toxic compounds, including chemotherapeutical agents and toxic molecules that affect cell wall formation and maintenance. The widely used anti-cancer drug 5-fluorouracil (5-FU) was initially identified as a DNA replication inhibitor but was later found to also inhibit the conserved 3′-5′ exoribonuclease Rrp6/EXOSC10, a catalytic subunit of the nuclear RNA exosome. The protein plays a role in degradation and processing of protein-coding and non-coding transcripts and its absence renders cells hypersensitive to 5-FU. Transcriptome analysis of 5-FU treated yeast cells revealed a negative effect on the expression of the transcriptional activators Swi5 and Ace2 that induce cell cycle regulated genes involved in mitotic cell division. Moreover, we observed that different types of non-coding RNAs (ncRNA) accumulated in 5-FU treated cells, which are typically present at high levels in a strain lacking Rrp6/EXOSC10. Interestingly, comparison of transcriptome data from wild type and rrp6 mutant strains showed altered expression levels both of genes that encode proteins crucial for cell wall integrity and lncRNAs that either overlap their promoters or that are in a sense/antisense configuration. Consistently, a yeast strain lacking Rrp6 is more sensitive than the wild-type to cell wall stressing compounds. Our data offer interesting leads for the discovery of novel protein-coding and non-coding RNAs that may be involved in 5-FU toxicity and cell wall defects caused by cell wall stressing compounds. These results are potentially important for improving antifungal therapies and 5-FU based chemotherapies.