The Anti-Cancer Drug Zeocin Affects TORC1 pathway, mitochondrial function and autophagy, in *S. cerevisiae*.

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ABSTRACT

The radiomimetic drug Zeocin is widely used as DNA damaging agent, antitumor drug and antibiotic due to its wide range of toxicity. Specifically, its genotoxicity is caused, mostly, by the reduction and removal of the chelated Cu^{2+} when the drug enters the cells. Our research group revealed that, Zeocin affects distinct biological processes in the cells in addition to inducing DNA damage response.

Exploring the transcriptional profile of *S. cerevisiae*, in several DNA damaging conditions (Zeocin, UV, 4NQO) we found that Zeocin specifically affects the conserved signaling pathway TORC1, revealed by the downregulation of ribosome biogenesis genes. The transcription of these genes is induced by the Sfp1 transcription factor, which is regulated via TORC1-dependent phosphorylation pathway. In the presence of Zeocin, the upregulation of genes vital for mitochondrial functions was also observed. This finding is in agreement with increased oxygen consumption in the presence of Zeocin measured by a Clark electrode, as well as, survival of yeast cells under those conditions, in glycerol-based medium, which induces mitochondrial function, compared to the glycolysis dextrose-based medium. Finally, autophagy appeared up-regulated in the presence of the drug, as it was indicated by the Zeocin-specific transcriptome and confirmed by fluorescence microscopy in the presence of specific molecular indicators[1].

Overall, the presence of Zeocin appeared to result in a switch of metabolism towards catabolism. Our results so far, indicate that Zeocin possibly induces metabolic reprogramming in the *S. cerevisiae* cell, through the TORC1 protein complex function. This finding has potential promising biomedical applications: metabolism of some cancer cells has similarities with yeast, displaying decreased respiration along with enhanced lactate production and dependence mainly on fermentative metabolism for ATP production (Warburg effect)[2]. Zeocin treatment indicates potential metabolic reversal of cancer cells as it is suggested in several studies to target cancer cell metabolism as a potential cure[3,4].

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