The Anti-Cancer Drug Zeocin Affects Copper/ Iron-Regulated Transcription and Causes Metabolic Reprogramming in *Saccharomyces cerevisiae*

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ABSTRACT

Our research group is interested in the mechanisms of gene regulation, in response to environmental changes, through specific transcription factors and chromatin regulators. In particular, we focus on the regulation of Metal-binding Activator (Mac1), whose functionality is affected primarily by the availability of copper ions in the cell.

We have, recently, identified a specific link between, the widely used anticancer, radiomimetic and antibiotic drug Zeocin and the copper/iron homeostasis in yeast. Our findings suggest that, Zeocin causes functional deregulation of Mac1 transcription factor, apart from inducing DNA damage. Specifically, we have evidence for a functional interference of the drug with Mac1's DNA binding ability to target promoters.

Exploring the transcriptional profile of S. cerevisiae, we found that the total number of Mac1-regulated genes were down-regulated, exclusively in the presence of Zeocin, compared to other DNA damaging sources. We also found a Zeocin-specific negative effect on the conserved signaling pathway TORC1, revealed by the downregulation of ribosome biogenesis genes, upregulation of genes vital for mitochondrial functions, as well as, autophagy-related genes. Overall, the presence of Zeocin appeared to result in a switch of metabolism towards catabolism. In agreement with these findings, we have demonstrated experimentally that the drug affects a specific, TORCI-associated, kinase that phosphorylates Mac1 transcriptional activator at its DNA binding domain, important for its function.

Our results so far, establish a functional link between the copper-dependent Mac1-regulated transcription and the TORC1 signaling pathway. Moreover, they indicate two new effects of the drug Zeocin apart from its role in DNA damage induction. First, Zeocin disturbs copper/iron-regulated homeostasis by inhibiting the DNA binding function, of Mac1 transcription factor. Second, Zeocin possibly induces metabolic reprogramming in the *S. cerevisiae* cell, through the TORC1 protein complex function, an observation with potential promising biomedical applications.