Transcriptional regulation of arsenic stress response in yeast: functional characterization of a novel player

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Duration: 10-12 months
Number of students: 1

Project Summary

Arsenic is a naturally occurring and highly toxic metalloid, responsible for a variety of adverse health effects, including carcinogenesis [1]. The molecular mechanisms involved in arsenic toxicity and detoxification are not yet fully understood. Arsenic has been shown to interfere with multiple cellular mechanisms due to its ability to induce oxidative stress, inhibit enzyme activity and impair DNA repair, among others [2]. Paradoxically, arsenic cytotoxic effects sustain the use of arsenic trioxide in the treatment of diseases such as acute promyelocytic leukemia, this compound being nowadays considered as promising in the treatment of other cancers [3].

The yeast *Saccharomyces cerevisiae* has proven to be an invaluable model organism to study metal and metalloid homeostasis in higher eukaryotes, as a consequence of conservations across species of several of the key players involved in those processes [4]. In *S. cerevisiae,* arsenic detoxification is largely mediated by the activity of the transcription factors Yap1 and Yap8, two members of the Yap (Yeast AP-1 like) family [5]. Yap8 specifically controls arsenic extrusion from the cell [6], whereas Yap1 avoids arsenic-induced oxidative damages [7]. Accordingly, yeast cells lacking both Yap1 and Yap8 are more sensitive to arsenate than cells lacking each regulator individually.

Growing evidences suggest, however, that the involvement of the Yap family in the arsenic stress response is not restricted to the activity of Yap1 and Yap8. Yap3, another member of the family should as well fulfill a role in this process, as (i) cells lacking this transcription factor are hypersensitive to arsenite [8] and (ii) Yap3 expression is strongly induced after arsenate stress [9].

Using a combined genetic and biochemical approach, the main objectives of this project are:

- To understand how Yap3 senses arsenic stress,
- To evaluate if Yap3 acts synergistically with other Yap members,
- To identify the arsenic detoxification pathway regulated by Yap3.

References

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