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SHORT COMMUNICATION

Histone H3 N-terminal tail provides tolerance to tartrazine induced stress in *Saccharomyces cerevisiae*

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Abstract

Tartrazine (TZN) is used in a wide variety of foods, medicines and cosmetics. Studies have associated TZN exposure with several side effects such as asthma, nausea, bronchitis, rhinitis, bronchospasm, etc. in humans. However, the mode of action of this molecule is not properly understood. In this study, we used budding yeast to decipher the mechanism of TZN toxicity. Our data revealed that the deletion of H3 N-terminal tail H3-Δ(1–16), H3-Δ(1–20), H3-Δ(1–24), H3-Δ(1–28) lead to hypersensitivity for TZN indicating that the tail region mediates intracellular signaling for survivability upon TZN exposure. Next, we performed computational study to characterize TZN-interactome by STITCH tool. Our analysis revealed that TZN have only two interacting partner (CTT1 and CTA1) and both of them are involved in oxidative stress pathways. This data was validated by the rescue of TZN toxicity by supplementation of antioxidant. Altogether, our data indicate that TZN causes oxidative stress in budding yeast cells and the intracellular response to alleviate such stress requires N-terminal tail of histone H3.

Keywords Histone H3 · Tartrazine · H3 N-terminal tail · Epigenetics · Budding yeast

Abbreviations

GO	Gene Ontology
H2O2	Hydrogen Peroxide
KEGG	Kyoto Encyclopedia of Genes and Genomes
NAC	N-acetyl Cysteine
OD	Optical Density
OD600	Optical density at 600 nm wavelength light
PANTHER	Protein ANalysis THrough Evolutionary Relationships
STITCH	Search Tool for Interactions of CHemicals
TZN	Tartrazine
YPD	Yeast Extract, Peptone, Dextrose
YPDA	Yeast Extract, Peptone, Dextrose, Agar
S. cerevisiae	*Saccharomyces cerevisiae*

Introduction

Food additive are used to enhance the smell, texture and looks of the dietary items. Many synthetic dyes have been created for this purpose that includes food colorizing agents. One of the most extensively used food colorant in the food industry is tartrazine (TZN) (Kamal and Fawzia 2018). TZN is a trisodium salt of tartrazine acid having azo dye properties. TZN is found in a wide variety of foods, including desserts and candies, soft drinks, condiments, and breakfast cereals (EFSA Panel 2010). TZN is also used in medicines (cough drops, capsule, lotion, and gel) and cosmetics (soaps, sanitizer, moisturizers and lotions). TZN has been extensively studied by toxicologists and allergists because it has been associated with several side effects such as asthma, nausea, eczema, and bronchitis, rhinitis, bronchospasm, headache (Gičević et al. 2020; Mizutani 2009; Nasri and Pohjanvirta 2021). However, molecular targets of TZN are largely unexplored.

Unicellular organisms has simple life cycle and conserved intracellular processes with eukaryotic cells enable them to be used as model organisms for studying fundamental processes. One such popular organism is budding yeast

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(*Saccharomyces cerevisiae)* that have a simple nutritional requirements and can be easily cultured in standard lab conditions (Burgess et al. 2017; Duina et al. 2014; He et al. 2018). The genetic material of eukaryotic cells is densely packed within the nucleus, but they remain dynamically accessible for transcription and replication processes. The fundamental unit of packaging of eukaryotic genome is initiated by the formation of nucleosomes. The nucleosome is an octameric protein structure that contains two copies each of four core histone protein H3, H4, H2A and H2B (Cutter and Hayes 2015; Luger 2001). Each of the core histones has at least two distinct structural domains, a flexible amino-terminal domain 'histone tail' rich in basic amino acids and accounting for 20–30% of proteins, and a more structured globular domain (Kouzarides 2007; Morales et al. 2001; Taylor and Young 2021). While the N-terminal tails of the four core histones protrude from the core particle of the nucleosome. The unique structure of nucleosomes acts as connecting link between the environmental signal and chromatin. Different cellular signaling causes change of modifications in histone proteins that affect the stability of nucleosomes and recruitment of chromatin modifiers leading to transcriptional activation or repression. Subsequently, the differential gene expression occurs to maintain the cellular homeostasis and cell survivability. Therefore, it is important to understand the effect of any molecule such as dietary compound on chromatin structure to understand its mode of action.

This study aimed to understand the molecular targets of TZN using budding yeast as model organism. The results obtained from our study showed that the alleviation of TZN induced stress requires histone H3 N-terminal tail. Furthermore, TZN causes oxidative stress and such effect can be reversed by antioxidant supplementation. Altogether, for the first time the link of histone and TZN has been established.

Materials and methods

Chemicals and yeast strains

The catalogue number of reagents used in this manuscript are yeast extract powder (Himedia, Cat. No. RC1239), Peptone (Himedia, Cat. No. RM667), Dextrose (Himedia, Cat. No. GRM016), Agar (Himedia, Cat. No. RC1011), Tartrazine (Himedia, Cat. No. GRM431), N-acetyl-cysteine (Himedia, Cat. No. RM3142). All yeast strains including the synthetic H3 mutant strains used in this study were received as gift from Dr. R.S. Tomar lab, IISER Bhopal, India (mutants were purchased from Dharmacon, Cat No. YSC5106, Lafayette, CO, USA). These mutants were developed by Dr. Jef Boeke at Johns Hopkins University (Dai et al. 2008). *S. cerevisiae* strains used in this study are H3 wild-type and Histone H3 N terminal tail mutants that includes H3-Δ(1–4), H3-Δ(1–8), H3-Δ(1–12), H3-Δ(1–16), H3-Δ(1–20), H3-(Δ1–24) and H3-Δ(1–28). The Genotype of H3 wild type used in this work is MATa his3Δ200 leu2Δ0 lys2Δ0 trp1Δ63 ura3Δ0 met15Δ0 can1::MFA1pr-HIS3 hht1-hhf1::NatMX4. The different tail truncations mutants were generated in this H3 wild-type background. The mutants used in this manuscript has been previously used in various studies (Dai et al. 2008; Singh et al. 2021; Thakre et al. 2019). *Sod1*Δ cells used in this study were generated in BY4741 background (MATa his3Δ1 leu2Δ0 met15Δ0 ura3Δ0).

Preparation of yeast media for culture

LIQUID MEDIA: For preparation of YPD liquid media, 1% yeast extract powder, 2% peptone, 2% dextrose were taken in distilled water. 3 mL of above solution was transferred in test tubes. It was then autoclaved at 121°C for 20 min and then stored at room temperature.

SOLID MEDIA: For solid media preparation 1% Yeast extract, 2% Peptone, 2% Dextrose and 2% Agar were taken in distilled water and mixed well by shaking the solution. It was then autoclaved at 121°C for 20 min.

Spot test assays

A colony of yeast cells was inoculated in autoclaved liquid media from revived yeast strain plate. The cells were then incubated at 30°C overnight and next day the experiments were performed on those cells. Spot test assay was performed after preparing the serial dilution of yeast cells as described earlier (Golla et al. 2013; Singh et al. 2014). Cell density of inoculated cell was checked using spectrophotometry after 24 h of inoculation at OD600 (Optical density at 600 nm wavelength light). We took 1mL cells (OD-1.0) in eppendroff, followed by preparation of serial dilution in distilled water. The 10 times serial dilution was prepared (1, 1:10, 1:100, 1:1000 and 1:10000). From these serially diluted samples, approximately 3 µL cells were spotted on YPD agar plates. These plates were kept for growth at 30°C and the data was recorded by taking photographs at 48 h.

ROS scavenging assay by supplementation of N-acetylcysteine (NAC)

NAC is a synthetic precursor of intracellular cysteine and GSH and has been widely used as free radical scavenger in budding yeast (Arita et al. 2020; Bankapalli et al. 2015; Zafarullah et al. 2003). Here, we used N-acetyl-cysteine (Cat. No. RM3142) for scavenging ROS generated by exposure of yeast cells to H2O2 (positive control) and TZN.

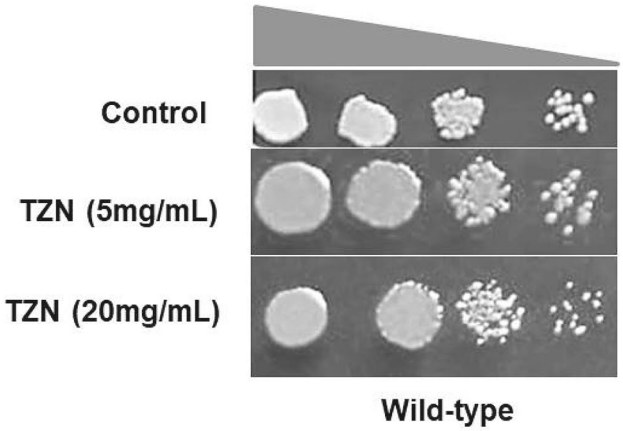


Fig. 1 TZN inhibits growth of yeast cell in dose dependent manner. 3 µL of 10-fold serially diluted culture was spotted onto control YPDA plates, YPDA plates containing control, 5 and 20 mg/mL TZN. All plates were incubated at 30 °C for 2 days and photographed

Briefly, 3 µL of each undiluted and 10-fold serially diluted culture was spotted onto control YPDA, NAC (5mM) only, TZN (20 mg/mL) only, TZN (20 mg/mL) supplemented with NAC (5mM), H2O2 only, H2O2 supplemented with NAC (5mM) plates. All plates were incubated at 30°C for 2 days and photographed.

Drug-protein interactome analysis

To study the targets of TZN, STITCH online tool ('search tool for interactions of chemicals') (Kuhn et al. 2008) was used. For creating the protein-protein network, we set the interaction score at medium confidence level (0.400) with no more than 50 interactors in the first shell. These settings are available at the STITCTH webserver and users can change them according to their experimental need.

Results

TZN reduces growth of S. cerevisiae in a dose dependent manner

To conduct experiment with TZN, we first identified the growth inhibitory dose of this molecule. The wild-type yeast cells were exposed to increasing concentration of TZN and the growth assay was performed by spot test assay as described in methods section. Our data revealed that TZN is toxic to the yeast cells and we observed inhibition of yeast growth at 20 mg/mL (Fig. 1). Therefore, we selected 20 mg/mL dose of TZN for subsequent experiments in this manuscript.

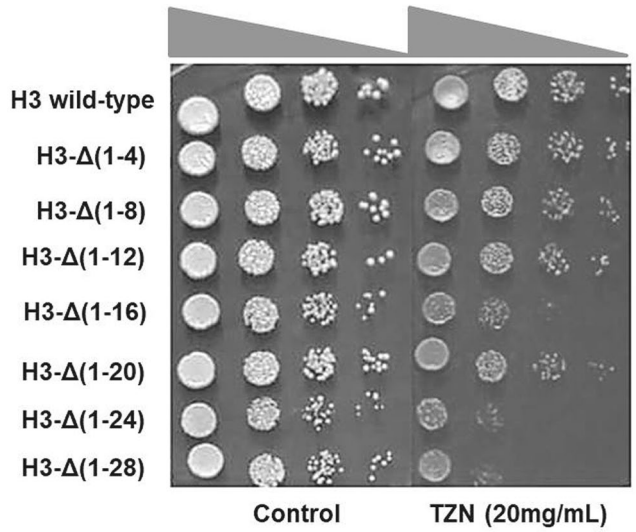


Fig. 2 The deletion of histone H3 tail enhances growth inhibitory effect of TZN A) Wild-type and different H3 tail truncation mutants were grown up to log phase. 3 µL of each undiluted and 10-fold serially diluted culture was spotted onto control YPDA plates, YPDA plates containing 20 mg/mL TZN. All plates were incubated at 30°C for 2 days and photographed

Deletion of H3 N-terminal tail confers sensitivity for TZN

To understand the underlying mechanism through which TZN shows its effect on budding yeast cells, we took yeast strains harboring mutations in the histone tails, including strains with amino acid deletions in the N-terminal tail of H3. Wild-type and truncation mutants (Fig. 2) grew to saturation in regular YPD medium. The spot test assay was performed to check the sensitivity of different histone tail truncation mutant yeast strain onto control YPD plates and plates containing 20 mg/mL of TZN. Interestingly, as compared to the wild-type control, growth patterns of the different H3 tail truncation mutations were significantly reduced. We observed that till (1–12) deletion of H3 N-terminal tail, yeast cells were able to grow but truncation of more than 12 residues lead to drastic loss of cell viability (Fig. 2). Truncation mutant H3-Δ(1–16), H3-Δ(1–20), H3-(Δ1–24) and H3-Δ(1–28) were hypersensitive for TZN (Fig. 2) indicating that H3 N-terminal tail residues are required for survivability of yeast cells.

TZN-protein interactome identifies enrichment of oxidative stress related pathways

In order to identify the mechanism of action of TZN, we used in silico approach to study the molecular targets of this molecule. Here, we used STITCH webserver to analyse the drug-protein interactions. The TZN- protein interactome

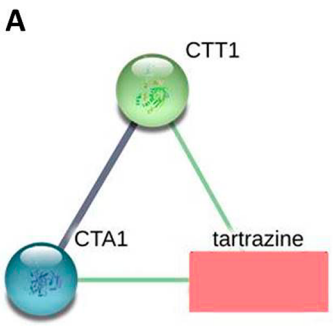
data obtained from STITCH database revealed two interacting partners CTT1 and CTA1 (Fig. 3A) that regulates oxidative stress response. Subsequently, we performed the GO annotation enrichment by STITCH tool powered by PANTHER (Protein ANalysis THrough Evolutionary Relationships). The top 2 GO biological process were related to response to hydrogen peroxide and reactive oxygen species (Fig. 3B) indicating that TZN is causing oxidative stress in yeast cells. The GO-molecular function enrichment indicates heme binding because both CTT1 and CTA1 possess such activity (Fig. 3C). The KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways analysis shows enrichment of metabolic pathways including the tryptophan, glyoxylate, dicarboxylate and peroxisomes pathways (Fig. 3D). Moreover, the two interacting molecules of TZN, CTT1 and CTA1 are catalases that induce breakdown of hydrogen peroxide into dioxygen (O2) and water molecules (Lushchak and Gospodaryov 2005). CTT1 encodes cytosolic catalase T while, CTA1 encodes catalase A that localizes in peroxisomal and mitochondrial matrices (Petrova et al. 2004). Both CTT1 and CAT1 enzymes are involved in hydrogen peroxide detoxification and their activity is important during the oxidative stress response and in protecting proteins against oxidative inactivation. Furthermore, CTT1 and CTA1 expression is also reported to increase under osmotic stress (Ramos-Moreno et al. 2019). Altogether, our data show that TZN binds to these two enzymes and therefore, may affect oxidative and osmotic stress response in yeast cells.

Antioxidant supplementation rescues TZN induced toxicity in budding yeast

We performed rescue experiments to validate our in silico observation. The rescue experiment was performed by supplementing TZN containing media with antioxidant N-acetly-L-cysteine (NAC). We prepared YPD media with TZN (20 mg/mL), NAC supplemented (TZN-20 mg/mL + 5mM NAC) plates. As a control we also prepared YPD media with NAC (5mM) only plates. We performed spot test assay with wild type and TZN sensitive mutants that includes H3-Δ(1–16), H3-Δ(1–20), H3-(Δ1–24) and H3-Δ(1–28). Our data show that NAC supplementation led to rescue of TZN induced growth inhibition in wild-type and TZN sensitive H3 tail truncation mutants H3-Δ(1–16), H3-Δ(1–20), H3-(Δ1–24) and H3-Δ(1–28) as shown in Fig. 4A. Finally, we analysed the sensitivity of *Sod1*Δ cells for TZN. Our data revealed that *Sod1* deletion enhances the sensitivity for TZN and H2O2 (positive control) and this enhanced growth inhibition can be rescued by supplementation of NAC (Fig. 4B). Altogether, this data strongly indicates that TZN exposure induces oxidative stress in budding yeast cells.

Discussion

Yeast has been used as popular model organism to study molecular targets of drugs (Nielsen 2019). Here, in this study we used budding yeast to understand the mechanism of action of TZN. TZN is one of the most popular food



B

#pathway ID	GO-Biological Process pathway description	observed gene count	false discovery rate
GO.0042744	hydrogen peroxide catabolic process	2	0.0019
GO.0000302	response to reactive oxygen species	2	0.0474

C

#pathway ID	GO-Molecular Function pathway description	observed gene count	false discovery rate
GO.0020037	heme binding	2	0.0325

D

#pathway ID	KEGG pathway description	observed gene count	false discovery rate
380	Tryptophan metabolism	2	0.00165
630	Glyoxylate and dicarboxylate metabolism	2	0.00165
4146	Peroxisome	2	0.00267
1120	Microbial metabolism in diverse environments	2	0.0449

Fig. 3 TZN-protein interactome and GO enrichment analysis. (**A**) The drug-protein interactome was obtained by STITCH tool. Stronger associations are represented by thicker lines. Protein-protein interactions are shown in grey and chemical-protein interactions in green. (**B**) The GO annotation showing the terms related to 'biological processes' that were enriched in TZN-protein interactome dataset. (**C**) The GO annotation showing the terms related to 'molecular function' that was enriched in TZN-protein interactome dataset. C) The KEGG analysis showing the cellular pathways enriched in TZN-protein interactome dataset

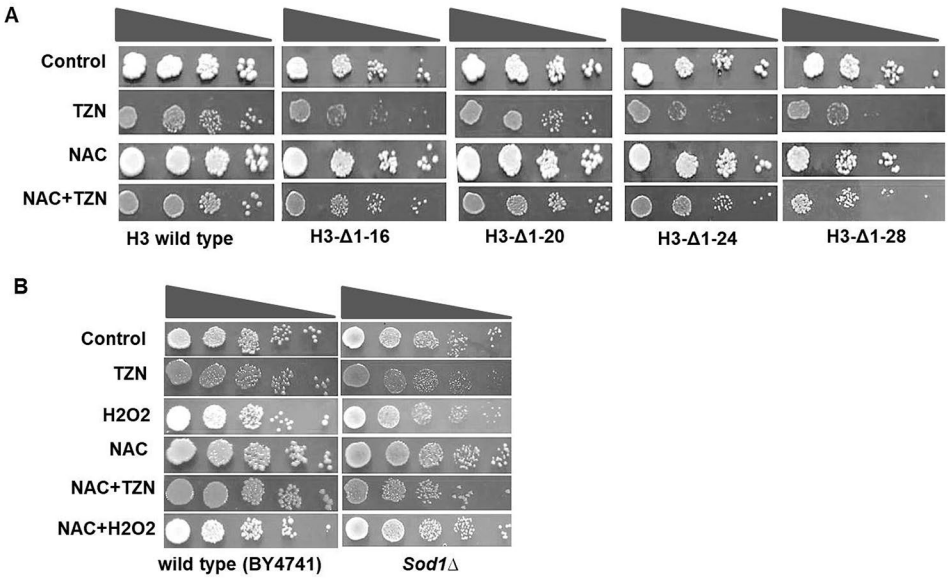


Fig. 4 Analysis of effect of NAC supplementation on growth of yeast cells. (**A**) 3 µL of each undiluted and 10-fold serially diluted culture was spotted onto control YPDA, NAC (5mM) only, TZN (20 mg/mL) only, TZN (20 mg/mL) supplemented with NAC (5mM) plates. All plates were incubated at 30°C for 2 days and photographed. (**B**) 3 µL of each undiluted and 10-fold serially diluted culture of wild-type (BY4741) and Sod1Δ cells were spotted onto control YPDA, NAC (5mM) only, TZN (20 mg/mL) only, H2O2 only (3mM), TZN (20 mg/mL) supplemented with NAC (5mM) plates and H2O2 (3mM) supplemented with NAC (5mM) plates. All plates were incubated at 30°C for 2 days and photographed

colorant used in the food processing industries. However, its effect of biological systems is not properly known till date. Interestingly, our data revealed that TZN has growth inhibitory effect on budding yeast cells. Subsequently, we observed that TZN growth inhibition was enhanced in histone tail truncation mutants indicating the direct link of TZN and epigenetics. The epigenetics includes the interplay of histone post-translational modifications, which regulates the gene expression in response to different environmental conditions including exposure of drugs or chemicals (Cheng et al. 2023). Most of these histone post-translational modifications occurs on the histone H3 N-terminal tails (Klose and Zhang 2007); Kouzarides 2007), which facilitates DNA dependent processes including, replication, transcription and DNA repair (Masumoto et al. 2005); Ye et al. 2005); Van Leeuwen et al. 2002). Therefore, using the H3 tail deletion mutants provides the direct role of epigenetics in stress signaling.

Here, in this study we have observed hypersensitivity of H3 tail deletion mutant for TZN indicating that this molecule is an epigenetic modulator. Our data further revealed that some of the H3 N-terminal tail truncation mutants were hypersensitive for TZN includes H3-Δ(1–16), H3-Δ(1–20), H3-(Δ1–24) and H3-Δ(1–28). The deletion of the first few amino acids has no effect on yeast growth; however, when the H3 tail was progressively deleted further, we started to observe the enhanced growth inhibitory effect of TZN. We also used *in silico* tools to identify TZN-protein interactome network that was mainly constituted by the proteins related to oxidative and osmotic stress. CTT1 and CTA1 proteins were found to be two interacting partners of TZN as observed by our *in silico* TZN-interactome analysis. Interestingly, CTT1 and CTA1 regulate oxidative stress response (Lushchak and Gospodaryov 2005; Petrova et al. 2004; Ramos-Moreno et al. 2019). Furthermore, GO biological process enriched in TZN interactome were related to response to hydrogen peroxide and reactive oxygen species. Moreover, the two interacting molecules of TZN, CTT1 and CTA1 are catalases that induce breakdown of hydrogen peroxide into dioxygen (O2) and water molecules (Jamieson 1998). Furthermore, CTT1 and CTA1 expression is also reported to increase under oxidative stress(Ramos-Moreno et al. 2019). These in silico observations were validated by the successful rescue of TZN growth inhibition by supplementation of antioxidant to the growth media. Furthermore, our data revealed that *Sod1* deletion enhances the sensitivity for TZN and H2O2 (positive control) and this enhanced growth inhibition can be rescued by antioxidant supplementation (Fig. 4B).

Altogether, the data presented here strongly suggests that the TZN exposure to budding yeast cells cause oxidative and osmotic stress and the intracellular response to alleviate such stress requires N-terminal tail of histone H3.

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Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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