661: Purine Nucleoside Phosphorylase as a target for the treatment of Interstitial Cystitis/Bladder Pain Syndrome with and without Hunner's Lesions

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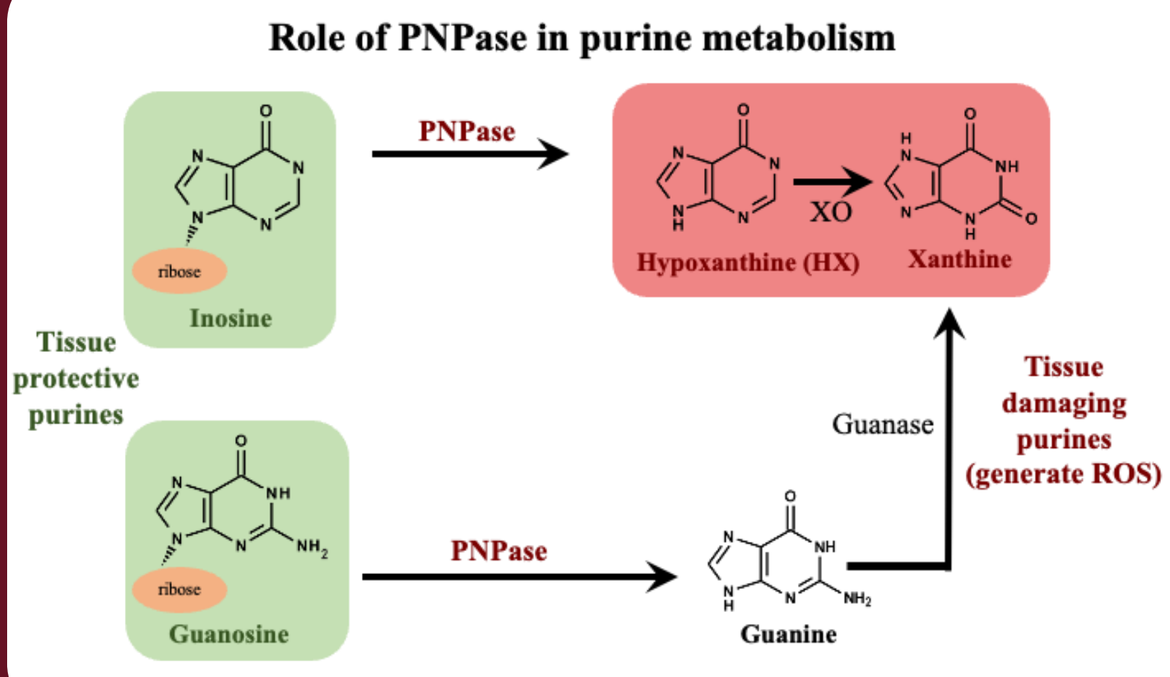
Introduction

Chronic visceral pain disorders, such as interstitial cystitis/bladder pain syndrome (IC/BPS), are difficult to diagnose and have no compelling therapeutic targets. Nonetheless, patients with IC/BPS express biomarkers linked to increased oxidative stress which trigger responses that can exacerbate generalized pain syndromes. Emerging evidence suggests that alterations in the enzyme purine nucleoside phosphorylase (PNPase) may participate in oxidative injury and cellular damage. Preclinical findings in our lab in a rodent model of IC/BPS demonstrate that inhibition of PNPase results in uro-protective effects on bladder function and biomarkers of oxidative stress[1]. PNPase transforms the uro-protective purine metabolite inosine to the uro-damaging metabolite hypoxanthine (a source of free radicals). This suggests that PNPase may be a target for treatment of IC/PBS using a non-opioid based PNPase inhibitor. Because there are no satisfactory treatments for IC/BPS, our research program is dedicated to validating PNPase as a target for treatment of IC/BPS.



Hypothesis

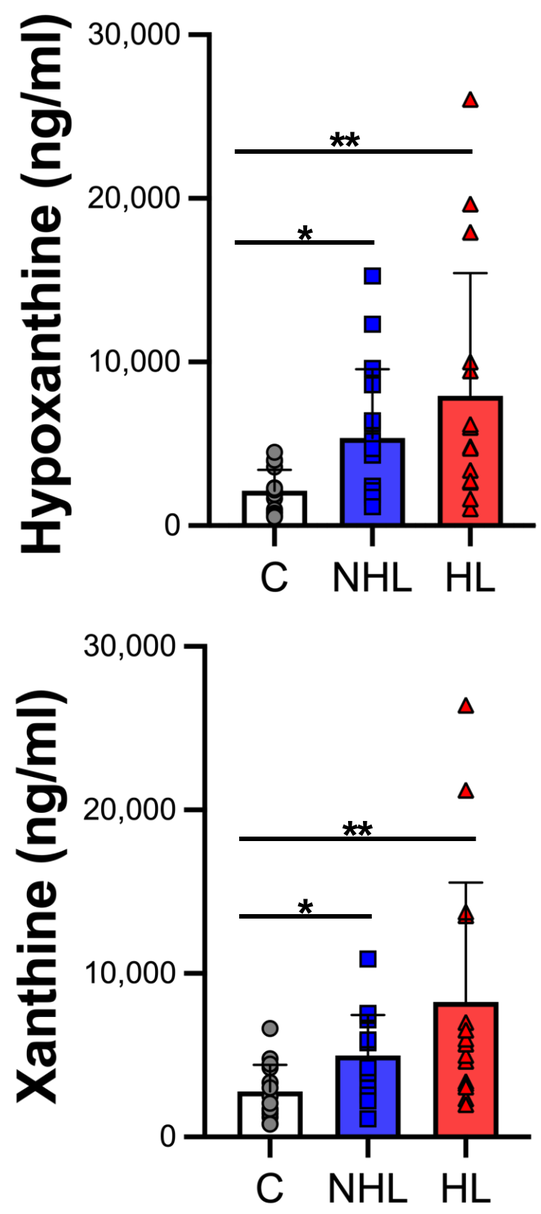
- Patients living with IC/BPS without or with Hunner lesions exhibit purine dysregulation, with higher levels of tissue-damaging purine metabolites.

Methods

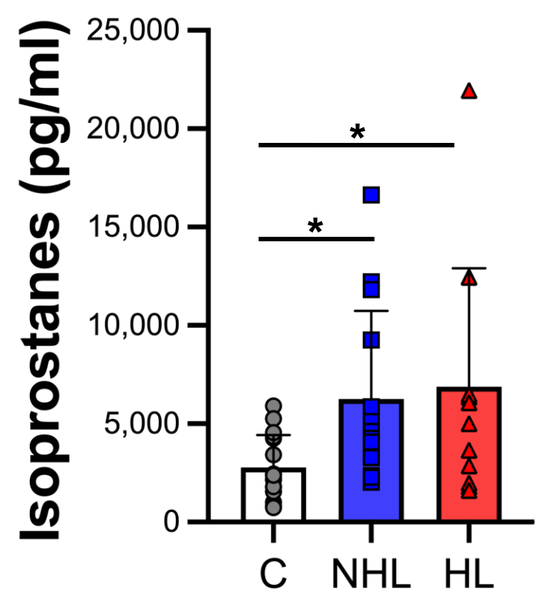
De-identified human urine samples were obtained (with IRB approval and informed consent) from control subjects and patients diagnosed with IC/BPS with or without Hunner's lesions. We measured the urinary purine metabolome by high-performance liquid chromatography-tandem mass spectrometry, following assays developed in our lab. Urinary isoprostanes were measured by colorimetric assay kit from Enzo Life Sciences (ADI-900-010) following manufacturer instructions. Samples for patient control (C, n=16, mean age 42+/-4.6), non-Hunner's lesions (NHL, n=16, mean age 52+/-4.0), and Hunner's lesions patients (HL, n=15, mean age 61+/-3.2) were analyzed and compared. Data between groups were analyzed by Kruskal-Wallis one-way analysis of variance followed by Dunn's multiple comparison's post-hoc test. Data are presented as mean +/- standard deviation. $p<0.05$ was considered significant.

Results

- Urinary purine metabolites were assessed in patients with non-Hunner's lesions (NHL) and Hunner's lesions (HL).
- Significant increases in **'urodamaging' (hypoxanthine/xanthine)** purine metabolites are found in both patient subtypes relative to controls.



Urinary levels of isoprostanes, a biomarker for oxidative stress, are significantly increased in patient urines.



Conclusions

- **Levels of urotoxic purine metabolites (hypoxanthine and xanthine) in IC/BPS patients with and without Hunner lesions are elevated related to healthy controls - suggesting there may be pathophysiologic commonalities between patient groups.**
- **The accumulation of uroprotective purines and depletion of urodamaging purines by PNPase inhibition may be therapeutically effective in both groups of patients.[1,2]**

1 Wolf-Johnston A, et al. Purine nucleoside phosphorylase inhibition is an effective approach for the treatment of chemical hemorrhagic cystitis. JCI Insight. 9(5):e176103. 2024.
2 Birder LA, et. al. Purine nucleoside phosphorylase as a target for the treatment of interstitial cystitis/bladder pain syndrome with and without Hunner lesions. Scientific Reports. 14: 21898. 2024.