Hematuria Regulates Urothelial Response to UTI

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BACKGROUND
UTI is diagnosed by lower urinary symptoms and by urinary findings including bacteriuria, leukocyturia, and hematuria. Each component of the UTI diagnosis is likely to contribute to urothelial damage, sloughing and inflammation.

Our lab focuses on iron biology of bladder and kidney disease. In the setting of urinary infection, we defined a variety of defenses to bacteria, including Lipocalin-2 (Lcn2/NGAL). We find that Lcn2 is expressed by urothelial cells; Lcn2 is a narrow spectrum antimicrobial limiting the growth of bacteria by chelating catecholate siderophores bound iron.

Yet, bacteria express many types of molecules that acquire iron, in addition to the catecholate siderophores.

We developed a method to isolate cell specific time specific nascent RNA directly from urothelial cells, hence tracking gene expression. We document the nascent genes involved in response to bacteria and document heme metabolic genes.

RESULTS
1. NGAL (LCN2) is specifically expressed by superficial cells 4-12hrs after infection (Fig 1). Red= NGAL RNA. Many superficial cells have already shed at this 12 hr point.

2. Heme (500nM) is found in the urine at the 6hr point after infection (measurement by spectrophotometry). The presence of Heme can be detected by dipstick (Fig 2).

3. HMOX is specifically expressed by superficial cells 4-12 hrs after UTI. Red= HMOX RNA at 8hr point (Fig 3).

4. HMOX activity produces CO gas—indicating that heme enters the superficial cells and is metabolized. CO is detected with a Pd-based fluorescent probe synthesized by Don Landry, Columbia (Fig 4).

5. HMOX produces CO, Iron, Biliverdin and is protective. To test whether heme itself is protective we developed a technique to deliver heme to the bladder. The process resulted in 4000nM urine heme. Hematuria had little effect on bladder gene expression but in the setting of UTI, we identified preservation of superficial bladder cells even in the presence of bacterial infection (Fig 5). Superficial cells are represented by CK20 staining (Green); Bacterial Colonies (White).

CONCLUSION
The data demonstrate complex mechanisms associating iron biology and UTI. Since published data (and our own confirmations) identify iron and heme as bacterial growth factors via heme specific heme receptors, it would be expected that the presence of heme would worsen bladder pathology due to increased colony counts. In addition, the lipid mediated toxicity of heme would support the view that hematuria would enhance the destructive effect of UTI. The data indicate that rather than a toxin, heme mitigates the effect of UTI. Further work is focused on characterizing the protective effect. In sum, hematuria, a frightening complication of many urogenital diseases, is not necessarily a toxic component of UTI.

REFERENCES

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