Review Article

The Role of Tamm–Horsfall Protein in the Pathogenesis of Urinary Tract Infection

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Abstract: Although Tamm–Horsfall protein (THP) has been implicated in a variety of pathologic conditions, its physiologic function still remains unclear. Several studies have shown conclusively that bacteria expressing mannose-sensitive (MS) fimbriae bind to THP and to THP-coated exfoliated uroepithelial cells. Therefore it has been suggested that THP may prevent MS-fimbriated organisms from colonizing the epithelial surface of the urinary tract. Whereas older clinical studies were often inconclusive, recent studies using more sensitive assays demonstrated reduced THP levels in a geriatric population, in children with urinary tract infections and in elderly women with bacteriuria. Although additional studies are required, available data support a protective role for THP as a non-immune antibacterial host factor against uropathogens. The clinical importance of in vitro studies showing interference of THP with bacterial recognition by leukocytes and down-regulation of cell-mediated immune responses is presently unclear.

Keywords: Host defenses; Leukocytes; MS-fimbriated bacteria; Tamm–Horsfall protein; Urinary tract infection; Uroepithelial cells

Introduction

The presence of urinary slime or mucus has been known to nephrologists for many decades. In 1950, Tamm and Horsfall noted the potent inhibitory effect of urine on hemagglutination by influenza, mumps, and Newcastle disease viruses. They were able to isolate the inhibitory substance by simple salt precipitation in 0.58 M NaCl and determined its glycoprotein nature [1,2]. The physicochemical characteristics of this substance, commonly referred to as uromucoid or Tamm–Horsfall protein (THP), have since then become extensively characterized. THP is a fibrillar glycoprotein with an unusually high concentration of complex-type branched carbohydrate side chains [3]. It is present in urine as a highly aggregated macromolecule of several million Daltons, which can be seen as mucous strands on light microscopy. These THP aggregates are composed of subunits of approximately 80 kD which associate with each other only by hydrophobic interactions [4]. Recently the gene coding for THP has been sequenced [5].

THP is secreted exclusively by the cells of the ascending limb of the loop of Henle and adjacent convoluted tubules. Its presence in urine has been associated with a variety of renal conditions, including acute renal failure (especially in combination with IV-dyes [60]), promotion/inhibition of kidney stone formation [61], interstitial nephritis 2 to VUR [58] or immune-complex disease [62], interstitial cystitis [63], Balkan nephropathy [64], renal transplant rejection [65], marker for renal/extrarenal rhabdoid tumors [66], elevated autoantibodies to THP in patients with UTI and reflux nephropathy [52], coating of urinary catheters promoting adherence of E. coli and development of UTI [67], and renal tubular acidosis and autoimmune liver disease [41].

Table 1. Association of THP with renal pathology

| 1. Acute renal failure (especially in combination with IV-dyes [60]) |
| 2. Promotion/inhibition of kidney stone formation [61] |
| 3. Interstitial nephritis 2 to VUR [58] or immune-complex disease [62] |
| 4. Interstitial cystitis [63] |
| 5. Balkan nephropathy [64] |
| 6. Renal transplant rejection [65] |
| 7. Marker for renal/extrarenal rhabdoid tumors [66] |
| 8. Elevated autoantibodies to THP in patients with UTI and reflux nephropathy [52] |
| 9. Coating of urinary catheters promoting adherence of E. coli and development of UTI [67] |
| 10. Renal tubular acidosis and autoimmune liver disease [41] |
between mannose and concanavalin A [18]. The pre-
many aspects similar to the sugar-lectin association
pyelonephritis do not attach to THP to any significant
fimbriated
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sence of MS-fimbriae on
of MS-fimbriated organisms to this glycoprotein is in
alternate attachment sites [17]. Other researchers
proposed a role for THP as a host defense mechanism
inhibited by mannose and that this interaction was very
similar to the binding characteristics of MS-E.
col to various epithelial cell receptors [16]. They subsequently
proposed a role for THP as a host defense mechanism
against UTI, suggesting that it may prevent uropatho-
gens from binding to uroepithelial receptors by present-
ing alternate attachment sites [17]. Other researchers
have confirmed their findings and further characterized
the interaction between MS-E. coli and THP. Binding
of MS-fimbriated organisms to this glycoprotein is in
many aspects similar to the sugar–lectin association
between mannose and concanavalin A [18]. The pre-
ence of MS-fimbriae on E. coli is crucial for THP
binding; non-fimbriated organisms or bacteria switch-
ing off MS-fimbrial expression (phase variation) do not
attach to THP [19]. Mannose-containing side chains on
THP are potential receptor sites for MS-fimbriae. P-
fimbriated E. coli which have been found more fre-
frequently in upper urinary tract infections and cases of
pyelonephritis do not attach to THP to any significant
degree. In contrast, S-fimbriae were shown to adhere
to THP even more strongly than MS-fimbriae [18].
These organelles characteristically bind to sialic acid
residues, which have been shown to exist on THP. However, the significance of these findings is debatable
as S-fimbriated E. coli, in contrast to MS- and P-
fimbriated organisms, are rarely urinary tract patho-
gens.

Although these in-vitro studies seem to support the
concept of THP as a host defense against bacterial
colonization, clinical studies have failed to show a
definite relationship between urinary THP level and
risk of UTI. Israele and co-workers studied infants and
children using a sensitive ELISA technique for THP
quantitation. They found significantly lower urinary
THP concentrations in infants with UTI than in con-
trols, but – surprisingly – increased THP levels in
children with E. coli–UTI [20]. The latter group con-
stituted of only 8 patients, therefore the results were
considered only as preliminary by the authors. Lose et
al. studied THP excretion in a larger number of young
women with recurrent UTI who had no identifiable predis-
posing factors for recurrent infection. These researchers
were unable to find differences in urinary THP
levels between controls and patients [21]. Unfortu-
ately, they used a less sensitive assay for THP quantifi-
cation (radial and electroimmunoassay) which resulted in
widely scattered THP values in both patient and control
group. This may possibly have obscured existing differ-
ences and lead to a type II error. Sobel and Kaye
measured urinary THP semi-quantitatively in the elder-
ly. They found reduced amounts of THP in elderly
patients in comparison with younger controls, but no
difference in histochemical score between elderly bac-
terium and uninfected women [22].

In order to clarify whether methodologic problems
may have contributed to these confounding results, we
measured urinary THP levels in girls and young females
with a history of recurrent UTI and in elderly infected
and non-infected patients using a very sensitive ELISA
method [23–25]. No differences in urinary THP excre-
tion were found between healthy individuals and
patients with UTI or a documented history of recurrent
UTI in the past. Urinary THP levels are lower in
elderly patients than in young women, which may
explain the propensity for urinary tract infections in the
geriatric population. However, we were unable to show
any difference in THP excretion between infected and
uninfected elderly women [25]. These studies have
identified a second problem, namely the great intraindi-
vidual and day-to-day variability of urinary THP con-
centration, which makes it difficult to show significant
differences in excretion rates between individuals and
populations. The factors influencing THP production
and secretion are not yet well enough understood to
compensate for these physiologically occurring fluctua-
tions.

It should be noted that in all the published clinical
trials described above, THP was measured after total
disaggregation. None of these studies measured THP in
its native state. Likewise, qualitative differences in the
carbohydrate composition of THP known to occur
physiologically and in certain disease states may influ-