Trichomonas vaginalis origins, molecular pathobiology and clinical considerations

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Purpose of review
To integrate a selection of the most recent data on Trichomonas vaginalis origins, molecular cell biology and T. vaginalis interactions with the urogenital tract microbiota with trichomoniasis symptoms and clinical management.

Recent findings
Transcriptomics and proteomics datasets are accumulating, facilitating the identification and prioritization of key target genes to study T. vaginalis pathobiology. Proteins involved in host sensing and cytoskeletal plasticity during T. vaginalis amoeboid transformation were identified. T. vaginalis was shown to secrete exosomes and a macrophage migration inhibitory factor-like protein that both influence host–parasite interactions. T. vaginalis co-infections with Mycoplasma species and viruses were shown to modulate the inflammatory responses, whereas T. vaginalis interactions with various Lactobacillus species inhibit parasite interactions with human cells. T. vaginalis infections were also shown to be associated with bacterial vaginosis. A broader range of health sequelae is also becoming apparent. Diagnostics for both women and men based on the molecular approaches are being refined, in particular for men.

Summary
New developments in the molecular and cellular basis of T. vaginalis pathobiology combined with data on the urogenital tract microbiota and immunology have enriched our knowledge on human–microbe interactions that will contribute to increasing our capacity to prevent and treat T. vaginalis and other sexually transmitted infections.

Keywords
Lactobacillus, microbiota, Mycoplasma, omics data, Trichomonas virus

INTRODUCTION

Trichomonas vaginalis is the most common nonviral sexually transmitted infection (STI) worldwide. The World Health Organization estimated that in 2005, there were 248 million cases of T. vaginalis and this had increased by 11.2% to 276.4 million cases in 2008 [1]. There is significant regional variation with the highest rates in the Americas, with an incidence of 177.7 per 1000 women and 180.6 per 1000 men aged 15–44 and a prevalence of 22% in women and 2.2% in men. This contrasts with south-east Asia, where the incidence is estimated as 40.3 per 1000 women and 50.1 per 1000 men with a prevalence of 5.6 and 0.6%, respectively. Notably, T. vaginalis is affecting primarily woman of disadvantaged populations in both affluent and resource-limited countries, and is still very much a neglected disease despite the increasing awareness of its important health sequelae.

The availability, for one T. vaginalis strain, of a draft genome sequence and annotation [2] have stimulated numerous studies on the parasite population genetics and molecular basis of it pathobiology [3**,4]. These developments paralleled with the studies on the urogenital microbiota and immunology will eventually converge to improve our knowledge of T. vaginalis pathobiology and assist with the prevention and treatment protocols. Here, we present an initial integration of a selection of the most recent developments in basic research on the parasite molecular cell biology with its clinical symptoms and management.
T. vaginalis AS A BIRD-DERIVED ZOONOSIS?

A number of different molecular phylogenies have surprisingly supported a close relationship between T. vaginalis and parasites isolated from birds [5]. The two human parasites T. vaginalis and Trichomonas tenax (from the oral cavity) were thought for some time to be closely related to, and possibly derived from, each other [2,5]. Molecular phylogenies established that T. vaginalis and T. tenax are more closely related to the distinct species of Trichomonas isolated from birds than they are to each other (Fig. 1). This suggests two independent zoonotic origins from birds for these two human parasites. Hence, it will be of great interest to perform comparative studies of the genomes and host–parasite interactions between human and bird Trichomonas species to identify the molecular basis of their respective pathobiologies. Thus, T. vaginalis is likely to join the long list of human pathogens derived from birds [6]. These considerations further illustrate the importance of studying pathogens in an integrated way across the fields of medical and veterinary research [6].

FIGURE 1. Molecular phylogeny identify bird parasites as sister taxa to Trichomonas vaginalis. Molecular phylogeny based on an Rpb1 (the largest subunit of the RNA-polymerase II) protein alignment focusing on Trichomonadinae are consistent with phylogenies derived from other genes – see Maritz et al. [5] for details including accession number of sequences. Species isolated from humans are highlighted with arrows; all other species were isolated from birds (bird species and country are indicated). Note one sequence derived from a bird isolate that is highly similar to T. vaginalis sequences, which could represent a transfer from human to bird.
Sexually transmitted diseases

Table 1. *Trichomonas vaginalis* genome features compared with selected species

| Species                      | Predicted gene number (ORF) | Genome size (Mbp) | % of genome that is repetitive |
|------------------------------|------------------------------|-------------------|-----------------------------|
| *Trichomonas vaginalis*      | 59,681                      | 160               | 65                          |
| *Homo sapiens*               | 35,845                      | 2900              | 46                          |
| *Drosophila melanogaster*    | 13,679                      | 180               | 2                           |
| *Entamoeba histolytica*      | 9,938                       | 25                | 6                           |
| *Giardia lamblia*            | 9,649                       | 12                | ‡                           |

Subset of a table from Ref. [2].

*a*Microbial eukaryotes infecting mucosal surfaces.

Surprisingly large and highly repetitive genome for a microbial eukaryote (Table 1) [2,4]. These data represent an invaluable source of information to study the epidemiology and molecular cell biology of host–*T. vaginalis* interactions [3**]. Only a selection of the recent developments is discussed here and complementary reviews cover a broader range of issues [3**,4,7–9]. As a result of *T. vaginalis*’s vast potential protein-coding capacity (Table 1), transcriptomics and proteomics investigations are particularly pertinent to identify and prioritize the functional characterization of key *T. vaginalis* proteins enabling infections [3**,4].

Two recent studies have initiated the global profiling of *T. vaginalis* gene transcription in various in-vitro growth conditions for two distinct *T. vaginalis* strains using RNA-seq methodologies [10**,11**]. Approximately 30,000 genes were transcribed in the various tested conditions in each strain [10**,11**] and a core set of about 20,000 genes was identified across the 11 conditions considered in one study [10**]. Modulation of mRNA levels upon exposure to oxidative stress, binding to vaginal epithelial cells (VECs) or glucose restriction have identified hundreds of genes involved in responses to these environmental cues. These included genes mediating oxidant scavenging and cytoskeletal re-arrangements upon exposure to oxygen, binding to VECs or a combination of both [10**], or amino acid metabolism upon glucose restriction [11**]. Notably, the combined exposure of *T. vaginalis* to oxygen and VECs stimulated the broadest set of TvBspA genes upregulation [10**], consistent with the hypothesis that the largest gene family (911 genes) encoding candidate surface proteins are important in host–*T. vaginalis* interactions [12]. A selection of *TvBspA* genes are listed in Supplementary digital content 1 http://links.lww.com/COID/A10, illustrating the striking variation of transcription for some genes between the two studied strains, possibly underlying the antigenic variation [7,12]. The modulation of the actin-based cytoskeleton upon contact to VECs at the transcription level was also highlighted [10**]. *T. vaginalis* trophozoites binding to VECs rapidly differentiate into an amoeboid form maximizing the contact with host cells, a key step in the infection process (Fig. 2). The fimbrin protein (an actin bundling protein) was recently shown to dramatically change its cellular distribution from the cell periphery in trophozoites to focal points co-localizing with actin in the amoeboid form [13**].

With a highly repetitive genome possessing numerous transposable elements, it is important to highlight here the recent analyses of one family of transposable elements (class II Tc1/mariner) and their impact on gene transcription across 94 *T. vaginalis* isolates [14**]. Several insertions of transposable elements were demonstrated to reduce or abolish the transcription of neighbouring genes, suggesting that such transposable element-driven mutations could have functional implications and contribute to adaptive evolution of the parasite [14**]. Combining comparative genomics and transcriptomics across a number of strains will be required to assess the role of transposable elements in mediating *T. vaginalis* genetic and phenotypic diversity.

An annotated genome also facilitates proteomics investigations and a number of such datasets have been published [3**,7,9]. Here, we consider the most recent data on surface proteins and cargo proteins of the secreted exosomes.

**SURFACE AND SECRETED PROTEINS AND EXOSOMES**

Surface and secreted proteins from the parasite are at the forefront of host–parasite interactions; hence these proteins have attracted great interests [7–9]. Two recent insights into the molecular basis of host–parasite interactions are considered here.

Gene annotations identified a total of 11 *T. vaginalis* tetraspanin (TSP) proteins possessing the characteristic four transmembrane domain of TSPs and two strains transcribe slightly different set of
these genes (Supplementary digital content 1, http://links.lww.com/COID/A10). On the basis of the numerous role of TSP proteins in human and model systems in orchestrating cell adhesion, fusion, signalling, proliferation and migration and their status as markers of exosomes identified TvTSP as important target proteins to study host–T. vaginalis interactions [15,16]. Cell-surface proteomics confirmed three TvTSP proteins [15] and one TvTSP protein, TvTSP6, was functional investigated [16]. The TvTSP6 cellular re-distribution (from flagella to the main cellular body and large intracellular vesicles) upon T. vaginalis binding to VECs and its role in regulating T. vaginalis migration makes it a prime target to further investigate how T. vaginalis sense and orchestrate its binding to, and migration through, human tissues during infection [16]. The TvTSP6 and the fimbrin re-localization data [13*] illustrate the dramatic cellular changes taking place in T. vaginalis upon binding to host cells.

The secretion of exosomes by T. vaginalis was investigated through a combination of cellular and proteomics approaches and identified exosomes with cargo RNA and a total of 215 cargo proteins including TvTSP1 and TvBspA_TVAG_216280 [17**], the most and second most highly transcribed genes of these two gene families, respectively, in the recent RNA-Seq data (Supplementary digital content 1, http://links.lww.com/COID/A10). Remarkably, T. vaginalis exosomes were shown to bind to host cells, to modulate the T. vaginalis–T. vaginalis binding and T. vaginalis–VEC and T. vaginalis–prostate cells binding properties and to have immunomodulatory properties, making these microvesicles and their cargo proteins attractive targets to gain new insights into T. vaginalis pathobiology [17**]. These various data identify the two exosomal membrane proteins TvTSP1 and TvBspA_TVAG_216280 as potential antigens for vaccine developments [18].

Another secreted factor likely to be important in modulating host–T. vaginalis interactions is the T. vaginalis macrophase migration inhibitory factor (TvMIF_TVAG_219770) that was recently shown to be similar to human MIF and functionally investigated [19**]. Notably, the TvMIF gene is highly transcribed, whereas a related pseudogene is not (Supplementary digital content 1, http://links.lww.com/COID/A10). Functional characterization of the TvMIF protein demonstrated that it was active in inhibiting macrophase migration, stimulating host cell signalling, was interacting with the human CD47 MIF receptor and increased the growth and migration through matrigel of both benign and prostate cancer cells [19**]. The data also demonstrated an adaptive immune response to the TvMIF in T. vaginalis-positive patients, consistent with the protein being secreted during infections. Could different T. vaginalis strains express variant TvMIF genes in response to this host response? If so, this might rationalize the TvMIF pseudogene (Supplementary digital content 1, http://links.lww.com/COID/A10). Taken together, these data are consistent with TvMIF stimulating inflammation and host cell proliferation, and could be responsible for the underlying T. vaginalis association with aggressive prostate cancers [19**].

**T. vaginalis–MICROBE INTERACTIONS AND THEIR IMPACT ON HOST–T. vaginalis RELATIONS**

It is increasingly recognized that studying host–parasite–bacteria–virus complex interactions at mucosal surfaces represent an important new paradigm to comprehend the impact, positive and negative, of these interactions on human health and disease conditions, and T. vaginalis is no exception [20] (Fig. 2). Three recent developments are of interest in this context.

First, T. vaginalis interactions with *Mycoplasma hominis* have been shown *in vitro* to synergistically upregulate macrophage proinflammatory responses [21**]. The proinflammatory responses to the T. vaginalis–Mycoplasma consortium on immune, and possibly epithelial, cells might be clinically relevant by contributing to various health sequelae associated with T. vaginalis infections (see later sections). Notably, a recent metagenomics investigations of the vaginal microbiota led to the characterization of the genome sequence of a new species of *Mycoplasma* that is strongly associated with T. vaginalis infections [22*]. This suggests that different T. vaginalis–Mycoplasma consortia might exist. Could these lead to variations in inflammatory responses [21**] and variations in T. vaginalis gene transcription and protein synthesis profiles?

Second, endogenous T. vaginalis viruses (TVV) isolated as T. vaginalis–TVV consortium from symptomatic female patients were also shown *in vitro* to stimulate proinflammatory responses in human VECs [23]. Notably, metronidazole treatments amplified the in-vitro proinflammatory responses in TVV-positive parasites possibly because of the increase in TVV particles released from dying parasites. This phenomenon could explain the negative impact of drug treatments observed during pregnancy [23] (see later sections).

Finally, the effect of different Lactobacilli in *in-vitro* T. vaginalis–VEC interactions assay was investigated and demonstrated that the bacteria mostly associated with healthy vaginal microbiota inhibited these interactions, consistent with

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protective functions of Lactobacilli species, with the exception of *Lactobacillus pentosus*, which enhanced *T. vaginalis* adhesion to VECs [24]. These observations were shown to be Lactobacilli dose dependent [24]. Consistent with these data, *T. vaginalis* infections were shown to be associated with bacterial vaginosis, a dysbiosis characterized by the loss of protective Lactobacilli [25,26]. These different considerations suggest that diagnostics will be needed in the future to integrate *T. vaginalis*, bacteria (mutualists and pathogens) and viruses (from both *T. vaginalis* and humans) involved in the complex microbial ecology of the human urogenital tracts, possibly by adapting metagenomics approaches currently exploited to characterize the complex host–microbiota–pathogens interactions [22*]. So, for example, differentiating *T. vaginalis* infections from *T. vaginalis–TVV*, *T. vaginalis–Mycoplasma* or *T. vaginalis–TVV–Mycoplasma* co-infections could benefit patients by pointing to differential treatments, minimizing the inflammatory sequelae in those different contexts [23].

**IMPACT ON HUMAN HEALTH**

Previously regarded as a nuisance for women, it is now recognized that *T. vaginalis* has a number of presentations in both sexes, is a risk factor for HIV transmission and acquisition, as well as being associated with adverse pregnancy outcomes. *T. vaginalis* infects the squamous epithelium of the genital tract, often including the female urethra. The usual symptoms of *T. vaginalis* are vaginal discharge in women associated with vaginitis, cervicitis and urethritis, although it is recognized that up to one-third of women have no symptoms [27]. Recent studies have suggested an increased risk of acute endometritis in association with *T. vaginalis* [28]. In men, *T. vaginalis*...
is usually a transient infection and studies suggest up to 75% of men are asymptomatic, but it may be associated with urethritis, rarely with balanitis [29] and possibly prostatis [30]. A number of case reports suggest a widening of the pathologic spectrum of *T. vaginalis* in humans including vulval ulceration [31], adult conjunctivitis [32] and pulmonary infections in association with HIV [33], and there is discussion around the possible contribution of *T. vaginalis* to aggressive prostatic cancers [19**,34**].

*T. vaginalis* in pregnancy has been associated with low birth weight, premature rupture of membranes and preterm delivery [35,36]. However, some studies have failed to show that treatment of *T. vaginalis* improves pregnancy outcome and some have indicated that treatment of *T. vaginalis* infection in pregnancy may have a negative impact on the pregnancy [37,38] – possibly explained by TVV inducing strong proinflammatory response upon drug treatment discussed earlier [23]. Neonatal infection from vertical transmission with *T. vaginalis* is rare. It usually causes a urogenital infection and there are case reports of vulvitis and positive urine cultures in neonates. There are occasional reports of *T. vaginalis* causing neonates respiratory tract infection [39].

Multiple reports support an epidemiological association between HIV and *T. vaginalis*. There is growing evidence that *T. vaginalis* infection may enhance HIV transmission and acquisition, and there may be an increased risk of *T. vaginalis* infection in those who are HIV infected [40–42]. In women with vaginal *T. vaginalis* who are HIV positive, there is some evidence that *T. vaginalis* may be more difficult to treat. A randomized clinical trial found that a 2-g single oral dose of metronidazole was not as effective as 500 mg of metronidazole twice daily for 7 days for trichomoniasis amongst HIV-infected women [43].

**DIAGNOSTICS**

The choice of specimen, diagnostic test and testing strategy for the detection of *T. vaginalis* will depend on the patient population, clinical setting and the available laboratory facilities. In settings in which there is a high prevalence of STIs, nucleic acid amplification tests (NAATs) are now the test of choice where resources allow and have become the ‘gold standard’ offering the highest sensitivity for the detection of *T. vaginalis* [44,45**,46**,47]. In settings in which molecular testing is not available, the diagnosis of *T. vaginalis* infection remains problematic because wet mount microscopy alone performs poorly for the diagnosis of trichomoniasis in women. Wet mount microscopy and current rapid antigen detection tests are not suitable for the diagnosis of trichomoniasis in men.

A number of commercially available NAATs have sensitivities of 95–100% and the specificity is also 95–100% depending on the specimen and reference standard. The APTIMA *T. vaginalis* Assay (Hologic Gen-Probe, San Diego, California, USA) was cleared by the US Food and Drug Administration in 2011 for use with urine, endocervical and vaginal swabs, and endocervical specimens collected in the Hologic PreserveCyt solution (ThinPrep) from women only. The BD ProbeTec Trichomonas Vaginalis Qx Amplified DNA Assay (Becton Dickinson, Franklin Lakes, New Jersey, USA) launched in Europe (EU cleared) in 2012. The diagnosis of *T. vaginalis* in men has been challenging, given the low sensitivity of microscopy and lack of FDA clearance to date for any NAATs or point-of-care tests for use with male specimens. Some laboratories have verified the performance characteristics of NAATs through a validation process for male urine specimens or penile-meatal swabs [45**].

Culture, until recently, has been considered ‘the gold standard’, with specificity approaching 100%, but the sensitivity can be as low as 75% compared with molecular testing. Culture systems such as InPouch *T. vaginalis* (BioMed Diagnostics, San Jose, California, USA) allow for direct inoculation, culture and microscopic examination. Such systems are useful when immediate transportation of specimens to the laboratory is not available. The specimen should be inoculated within an hour of collection to maintain the viability of the parasite [46**].

A number of point-of-care tests that detect *T. vaginalis* antigens or nucleic acids have been recently developed that allow for extended time between specimen collection and testing, and more flexible sample storage temperatures. Commercially available tests include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, West Malling, UK) and the *T. vaginalis* latex agglutination test (Kalon Biological, Surrey, UK) and the Affirm VPIII (Becton Dickinson, Franklin Lakes, New Jersey, USA). The sensitivities of these tests are similar to culture and consistently higher than wet mount microscopy. The specificities range from 92 to 100%. All three tests are intended for use with vaginal swabs from symptomatic women. However, none has been evaluated for screening asymptomatic women or for the diagnosis of *T. vaginalis* in men.

Traditionally, the diagnosis of *T. vaginalis* has been made by the detection of the motile parasites on a wet mount preparation of vaginal or urethral secretions by light-field microscopy. Microscopy has the advantage that it is cheap and can be performed near to the patient in a clinic setting. The specificity
with trained personnel is high. However, specimens should be examined within 10 min, and the sensitivity is reported to be as low as 45–60% in women and even lower in men.

TREATMENT

Treatment for T. vaginalis is with nitroimidazoles. As T. vaginalis in women frequently infects the urethra and paraurethral glands and cure rates of around 50% with metronidazole intravaginal gel are reported, systemic treatment is required. A Cochrane review found a parasitological cure in more than 90% of cases of T. vaginalis, with almost any nitroimidazole drug given as a single oral dose or over a longer period [48]. Single-dose treatments are associated with more frequent side-effects than longer oral treatment. Standard treatments are a 5–7-day course of metronidazole 400–500 mg twice daily or 2 g of metronidazole or tinidazole as single dose [49,50].

Meta-analyses have concluded that there is no evidence of teratogenicity from the use of metronidazole in women during the first trimester of pregnancy [51]. Metronidazole can be used in all stages of pregnancy and during breastfeeding. Metronidazole enters breast milk and may affect its taste. The manufacturers recommend avoiding high doses if breastfeeding or, if using a single dose of metronidazole, breastfeeding should be discontinued for 12–24 h to reduce infant exposure. Tinidazole is pregnancy category C (animal studies have demonstrated an adverse event) and its safety in pregnant women has not been well evaluated.

Persistent or recurrent T. vaginalis may be because of inadequate therapy, re-infection or resistance [52]. Development of resistance against nitroimidazoles can be because of aerobic and anaerobic resistance. In the USA, it is estimated that 5% of clinical isolates of T. vaginalis exhibit some degree of metronidazole resistance, predominantly low level [53]. In-vitro resistance does not predict clinical response to treatment, as it may be relative rather than absolute, and may be overcome by high-dose metronidazole or tinidazole therapy. Clinical isolates resistant to metronidazole can be resistant to tinidazole, but usually with significantly lower minimal lethal concentrations to tinidazole than metronidazole [54,55].

CONCLUSION

Molecular cell investigations, greatly facilitated by the availability of the genome sequence, have brought important new insights into T. vaginalis pathobiology. These developments combined with investigations on the microbiota and immunology of the urogenital tract have started to draw a more precise picture of the complex interplay between pathogens, the microbiota and the immune system. It is imperative to integrate these different data to improve our knowledge on human–microbe interactions to eventually improve our capacity to avoid and treat STIs that affect hundreds of millions of people of all ages, in particular those living in resource-limited conditions.

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Conflicts of interest
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