NUTRIENT STARVATION IMPACTS PURINERGIC SIGNALING AND PATHOGENICITY OF THE HUMAN PARASITE *Trichomonas vaginalis*

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Trichomonas vaginalis (Tvag) is an extracellular parasite and the causative agent of trichomoniasis, the most common non-viral sexually transmitted infection worldwide. The parasite's primary energy source derives from glucose metabolism, and Tvag is auxotrophic for essential metabolites such as purines and pyrimidines, relying on salvage pathways for nucleotide synthesis. Tvag is routinely cultivated in Diamond's medium, which contains high levels of carbohydrates and is supplemented with serum as a source of purines. The parasite encounters variable levels of glucose and purines in the infection site due to its virulence that leads to cellular lysis. Here, we aimed to investigate the effects of glucose and serum limitation on purinergic signaling and pathogenicity traits (cytotoxicity and extracellular vesicles) of Tvag. Both starvation conditions increased NTPDase and E-5′-N enzymatic activities in all tested Tvag isolates. Interestingly, this effect was reversed by adenosine but not by glucose. When evaluating the final step of the purinergic cascade, we observed that starvation reduced adenosine deamination in Tvag isolates. Serum limitation enhanced Tvag-induced cytotoxicity against vaginal epithelial cells, an effect that was reversed by adenosine alone or in combination with erythro-9-(2-hydroxy-3-nonyl)adenine, an adenosine deaminase inhibitor. Considering the importance of adenosine, we investigated the expression levels of nucleoside transporters (ENTs). Interestingly, serum limitation and glucose restriction caused downregulation and upregulation of ENT expression in Tvag, respectively. Finally, we demonstrated that starvation modulates extracellular vesicles release from trophozoites, suggesting a potential role for nutrient sensing in mediating cellular responses. Our findings enhance the understanding of critical survival pathways in Tvag and highlight nucleoside transporters as potential targets for therapeutic interventions.

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