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A SHORT REVIEW ON *CRYPTOSPORIDIUM* AND COLONIC CANCER

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Abstract

Cryptosporidium is one of the major causes of parasitic diarrhea all over the world. Both animals and humans are impacted. The fecal-oral pathway encompasses the consumption of infected water or food, as well as the intake of oocysts following direct touch with infected humans or animals. There is a lack of treatment alternatives for cryptosporidiosis sufferers. Nitazoxanide is the only one that has been approved by the Food and Drug Administration (FDA) as a therapy for cryptosporidiosis. Colorectal cancers were linked to *Cryptosporidium* infections. Some diseases, including hematological malignancies and liver cancer were also be linked to infections with *Cryptosporidium* spp. Infection with *Cryptosporidium* leads to hyperproliferation, invasion, and resistance to apoptosis and immune responses, via influencing host cellular pathways. While the exact processes that lead to *Cryptosporidium*-induced intestinal neoplasia remain a mystery, it is evident that they are complex and involve both the parasite and the host. Cancer is the leading cause of death and disability is colon cancer.

Keywords: *Cryptosporidium*, Colon cancer, food contamination, water contamination.

Introduction

Cryptosporidium genus belongs to Apicomplexa phylum, Conoidasida class, and the Eucoccidiorida order of organisms. Molecular phylogenies showed that they were more closely related to gregarines, an early branch at the phylum base (Salomaki *et al,* 2021). It is an intestinal protozoan of the "*Cryptosporidium* genus" that can infect both animals and humans. More than twenty species of *Cryptosporidium* were recognized so far, the species causing human cryptosporidiosis are *C. hominis*, and *C. parvum* (Abouel-Nour *et al,* 2016).

Review and Discussion

Cryptosporidiosis is an infection triggered when *Cryptosporidium spp*., a type of parasite, penetrates the gastrointestinal and respiratory epithelium in numerous vertebrates, including man (Arias-Agudelo *et al,* 2020). The average illness prevalence was in severe poverty ranged from 2.98% to 25.9%, while in developed nations it is ranging from 0.1% to 9.1% (Crawford and Kol, 2021).

Asexual and sexual reproduction occurs at different points in *Cryptosporidium*'s biological life cycle. However, *Cryptosporidium* has a single-host life cycle in which both asexual and sexual processes occur in the infected hosts' intestine different from most apicomplexan parasites (Tandel *et al,* 2019). The final sexual reproduction stage in oocysts development is involved in the host ongoing infection and is crucial for its transmission (Amin *et al,* 2022). *Cryptosporidium* oocysts can develop into an instantly infectious form within the host by allowing existence of the infection and developmental cycle in the same host (Certad, 2022).

Sporulated oocysts with four sporozoites, are released from an infected host upon defecation, that resists the environment by durable wall; a complex protective barrier of inner and outer oocyst walls composed of a protein-lipid-carbohydrate matrix (Fayer, R, 2008). Infection begins when an appropriate host ingests at least ten oocysts where all developmental stages occur in a single host; *C. parvum* oocysts excyst in the gastrointestinal tract, releasing four motile, infective sporozoites (Guérin *et al,* 2021).

Cryptosporidium is one of the most common causes of diarrhea in man and animals worldwide (Pyzocha and Cuda, 2023). Infection can be trasamitted from person to person by feco-oral route or contaminated food

and/or, or oocysts by contact with infected humans or animals (Ryan *et al,* 2021). Children are at high risk, with the obvious sign of an infection is diarrhea, and in children, newborns, and toddlers, *Cryptosporidium* is the only known cause of severe diarrhea (Mansour *et al,* 2022). This was particularly true involved almost 20,000 children from Africa and Asia (Khalil *et al,* 2018). Besides, those received organ transplants, or on cancer chemotherapy or those with compromised immune systems are particularly vulnerable to the health risks caused by cryptosporidiosis a severe fatal illness was i characterized by persistent diarrhea, abnormalities in electrolyte and water balances, nutrient complication and defects in digestive absorption (Morsy *et al,* 2023).

The US/FDA has approved Nitazoxanide® for treating cryptosporidiosis, but it is more or less can alleviate diarrheal symptoms rather than stopping oocysts discharge (Caravedo and White 2023). Some malignancies such as liver and colorectal cancer were linked to cryptosporidiosis with cancer progression (Taghipour *et al,* 2022). In Egypt, up to 6.5% of all malignancies are colon cancers, shutting it the 6th commonest oncologic disorder (Hassan *et al,* 2021). Abd El-Latif *et al.* (2023) in Egypt found that higher incidence rates of colorectal cancer are more prevalent in men than women and that cryptosporidiosisis significantly higher among cancer colon patients reinforcing that it could be considered as a likely risk factor for the cancer colon development. Taghipour et al. (2022) reported that the risk factors were mainly the chronic cryptosporidiosis inflammatory disorders and the unhealthy lifestyle. Meanwhile, the epidemiological and experimental data recommended a possible association between chronic cryptosporidiosis infection and gastrointestinal malignancy (Sawant *et al,* 2020). The meta-analysis and systematic reviews on 3562 participants from 19 different studies found that cancer patients had a much higher incidence of *Cryptosporidium* infection than controls, and that infection was more or less linked to colorectal cancers (Kalantari *et al,* 2020). It was interesting that *C. muris* was unable to cause changes in the host epithelium. It was proposed that immunosuppression may not always be the cause of neoplasia development. In infected SCID mice, spontaneous thymic lymphomas have been reported, despite the extreme rarity of other tumor forms (Huang *et al,* 2011). However, the chronic cryptosporidiosis case of the biliary tract clinically mimicking a pancreatic cancer in an AIDS patient was also reported signs of adenocarcinoma in the ileocaecal area (Benamrouz *et al,* 2014). Again, there have been reports of neoplasia in other mouse models of cryptosporidiosis, as an example, animals lacking interferon-gamma (IFN-γ) and infected with *Cryptosporidium* showed signs of mild dysplasia in their bile duct tributaries. In NIH-III nu/nu mice, similar histologic abnormalities were associated with persistent *C. parvum* infection, additionally, infecting mice intestines with this parasite demonstrated its carcinogenicity (Baydoun *et al,* 2017).

The role of intracellular eukaryotic parasites in carcinogenesis, however, has received less attention up until now. *Plasmodium falciparum* was also proposed as a potential cofactor in Burkitt lymphoma progression, and experimental models have demonstrated that cell transformation may be induced by just two Apicomplexan genera: *Cryptosporidium* and *Theileria* (Cheeseman *et al,* 2016). Previously, *Trichomonas vaginalis* was suspected to be associated with cervical (Zhang *et al*, 1995) and prostate cancers (Stark *et al*, 2009), but *Toxoplasma gondii* was associated with ocular tumor, meningioma, leukemia and lymphomas (Khurana *et al.*, 2005), Generally, many helminthic infection cause cancer (Fried et al, 2011). As for examples; in Egypt, *Strongyloides stercoralis* causes malignancy together with human T-cell lymphotroppic virus-1 (HTLV-1), and/or directly carcinogenesis (Zaky *et al,* 2019). Also, Mohammad *et al.* (2023) corrected between the urinary schistosomiasis and bladder cancer.

A clear system for classifying the intricacies of malignant illness, referred to as the "hallmarks of cancer," was outlined. Some of these characteristics include the ability to activate invasion and metastasis, induce angiogenesis, resist cell death, enable replicative immortality, and sustain proliferative signals (Klöhn *et al,* 2021).

Cryptosporidium infection is characterized by excessive proliferation, infiltration, and resistance to apoptosis and immune responses. The infection is thought to be caused by the manipulation of pathways inside the host cell (Li *et al,* 2023). The parasite's virulence factors include proteins that aid in oocyst disencystment, motility, adhesion to host cells (including thrombospondin-like adhesive proteins and mucin-like glycoproteins), invasion of epithelial cells by sporozoites, formation of the parasitophorous vacuole (PV), multiplication within cells, and harm to host cells. Cellular damage has been attributed to several substances, including proteases, phospholipases, and hemolysin H4 (Bouzid *et al,* 2013).

There have been recent discoveries of miRNA applicants in *C. parvum* that target genes implicated in many pathways relevant to the pathogenesis, pathogenicity, and biology of the virus (Ahsan *et al,* 2021). Single nucleotide variations (SNV) in *C. parvum* isolates were found through comparative genomics, annotation, and sequencing of different isolates. These differences were discovered in numerous gene families, including mucins, cysteine proteases, transporters (ABC and ATPase3), that influence host-parasite interactions and parasite virulence. Also, many of these genes were connected to encoded membrane proteins, the secretory pathway, or the process of remodeling the cytoskeleton (Audebert *et al,* 2020). These findings corroborate the hypothesis that genes involved in the earliest phases of contact between host epithelial cells and *Cryptosporidium* oocysts and sporozoites are potential virulence factors for the parasite, in addition to genes convoluted in intracellular conservation and host cell destruction (Pinto and Vinayak, 2021). Also, *Cryptosporidium* manipulates host gene expression and disease through the use of long non-coding RNAs (lncRNA) that it delivers to the host cell (Li *et al,* 2021a).

The epithelial cells infected with *Cryptosporidium* undergo epigenetic histone methylations, which modulate the transcript of genes critical for cell multiplying, differentiation, and metabolic processes, indicated the nuclear transfer of parasite RNA transcriptions (Sawant *et al,* 2022). For example, several genes including LRP5, SLC7A8, and IL33 had their expression levels significantly altered after Cdg7_FLc_0990 was delivered into the intestinal epithelial cells by not clear transfer. Histone H3 lysine 9 (H3K9) methylation-mediated transcriptional repression proposed as a mechanism by genes regulate epithelial cell development and metabolism. For bacterial and viral infections, the epigenetic regulation of a host's transcriptional program associated with host defense genes has been shown, which aids in the pathogens' lifespan (Wang *et al,* 2017). Immunohistochemistry confirmed the aberrant location of p53 and other components of the Wnt signaling cascade. Despite extensive testing, high-throughput sequencing failed to detect any mutations in genes under animals investigation showed changed protein expression in their tissues, with less Apc and E-cadherin and more β-catenin in the cytoplasm of cancer cells, but no translocation to the nucleus, with an irregular staining of cytosolic p53 in the adenoma proliferating cells (Rauth *et al,* 2021). In the host, *Cryptosporidium* may cause change by hijacking signaling pathways. In the mice model, investigation of changes in genes or proteins elaborated in cell phase, differentiation, or migration, such as β-catenin, Adenomatous polyposis coli (Apc), E-cadherin, Kirsten rat sarcoma virus (Kras), and P_{53} following contamination of an animal model with *C. parvum* (Fang *et al,* 2024).

The *C. parvum*-induced malignancy trans-

formation and cell immigration of transformed cells to be facilitated by Wnt-transduction signaling pathway, namely the cytoskeleton linkage, as documented (Relat and O'Connor, 2020). Consistently, the experimental *C. parvum* infection demonstrated a significant down regulation of expression of occludin, claudin 4, & E-cadherin, three essential components of epithelial cell adherent junctions. Additionally, ZO1, an adapter protein that connects the actin cytoskeleton to the formation of epithelial tight junctions, was also markedly reduced (Kumar *et al,* 2018). Electron microscopy showed ileocaecal area of infected SCID mice revealed basal and lateral cytoplasmic expansions that may indicate that *C. parvum* induces cancer through a change in cytoskeleton network (El-Wakil *et al,* 2023). Traditional hallmarks of colon cancer were absent in the *C. rvum*-induced metastatic change. Presence of β-catenin at significant basolateral and cytoplasmic locations, as well as changes in the cellular communication of APC and β-catenin, were shown to be associated with a non-canonical Wnt pathway (Cohn *et al,* 2022).

Also, inflammatory monocytes brought in at the sub-epithelial gaps helped *C. parvum* lower transepithelial resistance by removing E-cadherin and β-catenin from adherent junctions of intestinal epithelial cells (IECs). In this way, the infection's inflammatory response can compromise the epithelial barrier's ability to do its job. This action maintains inflammation that may foster carcinogenesis (Lamisere et al, 2022) It has been demonstrated that *C. parvum* inhibits apoptosis of infected epithelial cells by activating pro-inflammatory transduction signal pathways including nuclear factor-kappa B or NF-κβ (de Sablet *et al,* 2016). El-Kersh *et al*. (2019) in Egypt reported that *C. parvum* infection is a hazard reason for ileocecal dysplasia. The resulting pathology depends on the intensity and duration of the infection in addition to the host immune status. A competent immune system is not an absolute protecting element against the incidence of dysplasia, but rather postpones it. β-catenin/ Wnt signaling pathway is involved in *C. parvum*-induced intestinal dysplasia.

Digestive biopsies from individuals with colon neoplasia/adenocarcinoma shown to have more DNA related to *C. parvum* and *C. hominis oocytes* than those from patients without digestive neoplasia (Osman *et al,* 2017). Also, Berahmat *et al.* (2017) found that compared to the control group, children undergoing chemotherapy for cancer had a greater risk of cryptosporidiosis (3.8% vs. 0%). Despite reports of neoplastic alterations in the small intestine caused by chronic *C. parvum* infection in an immunosuppressed mouse model, which may indicate a possible involvement as a carcinogen, the *Cryptosporidium spp*. role in cancer genesis remains mainly unknown (Cheeseman *et al,* 2016).

Since just one patient out of 145 tested positive for *C. meleagridis*, this infection was classified as opportunistic. The existence of the tumor is likely to have been caused by the *C. meleagridis* infection, given that human adenocarcinoma is typically not identified for more than ten years (Subramaniam *et al,* 2016). The origin of the *C. meleagridis* subtype IIIg infection is unknown, and this patient has denied having any direct interaction with birds of prey or wild birds. However, humans are vulnerable to nearly all C. meleagridis subtypes, as shown by the presence of this subtype in addition to subtypes IIIb, IIIc, IIIe, IIIf, IIIh, & IIIi (Wang *et al,* 2013).

There were several epidemiological and experimental investigations that point to a possible connection between cryptosporidiosis and the advancement of colorectal cancer (Sawant *et al,* 2020). One of the infectious pathogens that could cause intestinal dysplasia is *C. parvum*. Nonetheless, many unknown factors contribute to pathophysiology of *Cryptosporidium* spp. infection. Experiments evidence suggested that *C. parvum* can alter the infected epithelial phenotype \cells

by influencing the host-cell cytoskeleton and intracellular signaling (Li *et al,* 2021b).

A rising body of medical data suggested a potential causative relationship between the cryptosporidiosis and human intestinal neoplasm in various cultures. A Spanish patient with cryptosporidiosis and colonic cancer died shortly after the first symptoms appeared, raising the possibility of a link between the two diseases. There was also a description of a case of cryptosporidiosis affecting the biliary system, which presented clinically as pancreatic cancer in an AIDS patient (Sawant *et al,* 2020).

Cryptosporidiosis increases incidence of colon cancer in AIDS patients and has been related to bile duct cancer in adolescents with X-linked hyper-IgM disorder and immunodeficient animals, according to other research. The authors of the later investigations speculated that the biliary epithelium could be more susceptible to *Cryptosporidium* colonization due to mutation that causes this deficiency. The next step is a persistent parasite infection, which can lead to inflammation and, ultimately, cancer (Leven *et al,* 2016). An instance of cholangiocarcinoma emerging from sclerosing cholangitis coupled with persistent cryptosporidiosis occurred in an adult patient with CD40L loss, even though this illness is generally diagnosed in children (Rahman *et al,* 2012).

Conclusion

Cryptosporidium parvum is a risk factor for colon cancer. The resulting pathology depends on intensity and duration of infection in addition to the host immune status.

Competent immune system is not an absolute protecting agent against incidence of dysplasia but rather postpones it. β-catenin/Wnt signaling pathway is involved in *C. parvum*-induced intestinal dysplasia.

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Explanation of figure

Fig. 1: Linking genetic pathways of *Cryptosporidium*-induced adenocarcinoma to hallmarks of cancer **(Certad, 2022).**