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REVIEW: Immunological Examination of *Echinococcus granulosus* as a Candidate for Cancer Treatment and Vaccine Development: A Review Study

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ABSTRACT

Echinococcus granulosus, is a cestode parasite that causes cystic echinococcosis. The vaccination procedure with tumor-associated antigens, coming from evolutionary distant organisms such as parasites, can be beneficial to override tolerance problems encountered with human tumor-associated antigens-based cancer therapeutic approaches. In this article, different databases of PubMed, Google Scholar, IranDoc and SID were examined from 2001 to 2021 and related articles were investigated. The review of related studies concerning human beings' treatment revealed the possibility of inhibition of cancer development via HCF antigens and mucin peptides extracted from this cestode. Besides, HCF treatment in animal models mostly showed that anti-cancer immune responses were activated. Of note, an influential issue in the design process of an anti-cancer vaccine is triggering efficacious anti-tumor responses by using idyllic antigens for immunization against cancer. In this realm, many antigens have been studied for this purpose and showed different ranges of effectiveness. Based on the cross-reactivity among parasitic and tumor antigens, detection of parasitic antigens that are highly homologous with cancer antigens is an ideal objective for immunization against cancer cells. As the toxicity of HCF was reported in some studies, further research are required to shed light on finding an innovative anti-cancer vaccine derived from parasites. This review article is useful for health managers and researchers working on the anti-cancer vaccine development.

Introduction

Chronic parasite infections depend on well-organized interaction with the host which leads to an appropriate immune response (1). In this realm, cystic echinococcosis (CE) and alveolar echinococcosis (AE) are zoonotic infections caused by the larval stages (metacestodes) of parasitic cestodes *E. granulosus* and *E. multilocularis* (2-4). Besides, *E. granulosus* is a tapeworm parasite that lives in the intestinal tract of meat-eaters like dogs. The larval stage of the worm is called a hydatid cyst. It grows in many tissues, like brain, liver, and lungs of intermediate hosts (4). In fact, human as an accidental host of this parasite is infected by ingesting of worm eggs (5). Also, metacestodes are capable of persisting in intermediate hosts for a long time even more than decades, without noticeable pathogenicity in the host's tissues

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(4). The most hazardous obstacle of echinococcosis is cyst perforation, causing death from septic shock or embolic complications (6-8).

It is worth pointing out that the cyst is superficially covered with a carbohydrate compound called a laminated layer. The Hydatid Cyst Fluid (HCF) of *E. granulosus* is composed of a combination of carbohydrates, cyclophilin, ferritin, glycolipid, and glycol-protein (9). Besides, HCF contains diverse antigens such as Antigen A, Antigen B, and 78KDa fraction (10). Possibly, some of these antigens of *E. granulosus* are involved in the initiation of a cross-reactive immune response which could be effective in suppressing cancer development (10). In many studies, the ability of HCF to inhibit cancer growth has been well recognized either in cell culture experiments or in experimental animal model investigations (10-13).

In this regard, some studies have reported a lower rate of hydatid cyst disease among patients experiencing surgical removal of solid tumors in comparison with normal people (14). It has been proposed that the Hydatid Cyst Wall (HCW) antigens have an essential role in stimulating the immune responses as HCW is the outer layer of hydatid cyst that is exposed to the host's immune system (15).

Concerning this issue, cytokines have been generally studied as probable curative agents against tumors (16, 17). Tumor necrosis factor-α, Interferon-γ, Interleukin (IL) -4, IL-5, IL-6, and IL-12 in the sera of animals having the primary or secondary hydatidosis and also human patients are the matter of notice (18). Chookami et al.'s (2015) study revealed that vaccination of mice by crude antigens of hydatid cyst and the subsequent challenge of them by melanoma cells led to the prevention of melanoma tumor development (13).

In this realm, immunotherapy of cancer has appeared as a noticeable approach for its capability of breaking the immune tolerance and triggering a long-lasting immune response, targeting cancer cells without autoimmunity (10). One of the major problems in cancer vaccination is the lack of noteworthy clinical results which could partially, be attributed to the incapability of induced T-cell responses to overwhelming the immune escape mechanisms of tumors (19). One of the mechanisms which provide a suitable situation for cyst survival is the activation of apoptosis in the host's immune cells, by means of many factors including the caspase enzymes as the prominent one (20).

Recently, a group of human cancer-associated simple O-glycan structures, such as Tn, TF, sialyl-Tn and Tk antigens, have been identified in several parasites (21, 22). Here, Tn antigen, a mucin-type O-linked glycan, is a well-established cell surface marker for tumors and its elevated levels have been associated with cancer development and prognosis. Tn antigen is expressed in nearly 90% of carcinomas, including 80% of breast cancer tissues. Tn antigen is a target for the progress of anticancer vaccine development (23).

On the contrary, Daneshpour et al.'s (2019) investigated the apoptotic and necrotic features of HCF antigens on mouse breast cancer (4T1) cells, but they did not detect noticeable necrosis in the treatment of breast cancer cells with hydatid cyst antigens (24).

The idea of using the patient's immune system activated by a microorganism to attack their own cancer initiated with Coley´s observations followed by the use of Bacillus Calmette-Guerin (BCG) to treat early-stage bladder cancer, which was approved by the Food and Drug Administration (FDA) in 1990 (25). Lately, it is emphasized that immunization with a Trypanosoma cruzi homogenate meaningfully suppresses colon and mammary tumor development in rat models reproducing human carcinogenesis (26). Furthermore, Toxoplasma gondii induces anti-tumor immunity, promoting regression of established primary melanoma B16-F10 tumors (27).

The correlation between cystic echinococcosis and lower cancer rate in humans was suggested in epidemiological research (14). Researchers have observed that

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vaccination with human HCF antigens pointedly prevents colon cancer development by triggering antitumor immune responses in the mice models (10). Moreover, it was represented that immunization with mucin peptides extracted from this cestode can effectively activate anti-tumor responses by increasing the rate of activated NK cells and providing splenocytes with the capability to mediate killing of tumor cells (28).
Similarly, in a recent study conducted by Berriel, et.al (2021) findings confirmed that immunization with human HCF triggers strong immune responses against lung cancer in mice by NK1.1+ cell activation. So, the first-line treatment options are hormonal therapy, radiation, chemotherapy and surgery. Besides, nonselective cytotoxicity of chemotherapeutic compounds causes adverse effects (29, 30).

Methods

In this article, different databases of PubMed, Google Scholar, IranDoc and SID were examined from 2001 to 2021 and related articles were investigated.

Results

According to the interaction of Echinococcus meta-cestodes and their intermediate hosts, unexpected effects such as the anti-cancer properties of some compounds of HCF can be observed. Concerning MAPK signaling pathway activation by HCF in liver cells of rats, Gao, et.al (2018) evaluated its effect on melanoma cell line A375 (31). It was reported that extracted HCF triggered lymphocyte apoptosis in vitro, representing a direct effect of the meta-cestode on host leukocytes. This crosstalk has opened new treatment prospects in the last decade (32-35).
In addition, extraordinary immune responses against tumors in parasite-infected patients have been stated in human studies. (36). Lots of parasite species such as *T. gondii*, *T. cruzi*, and some *Plasmodium* subtypes presented positive results in animal cancer models (37-40). Epitope homology among these parasites and cancer cells was announced as the main reason for these explanations. The immune system eliminates the parasite antigens and responds against the malignant cells due to the homology and cross-reactivity (41).
In this realm, *E. granulosus* prohibitin (EgPHB) is a recently recognized protein associated with many roles based on its localization (42). EgPHB is crucial for apoptosis in human cells (43). EgPHB was detected in the larval form of *E. granulosus*, and adult parasite with overexpression in the germinal layer. P53 is a tumor suppressor which has been widely analyzed in mammalian cells. The role of P53 in DNA repairment and apoptosis activation was recognized and an analog of P53, named Emp53 has been detected in *E. multilocularis* (35). However, the sequence of P53 is similar to human P53 is low, Emp53 presented a tertiary structure DNA-binding domain-like human P53. Emp53 is able to bind with human P53 recognition sites. It was stated that a higher apoptosis rate was triggered in E. multilocularis when exposed to UV-C irradiation, representing the probable role of Emp53 in apoptosis induction (44). Additionally, it was revealed that EgKI-1 led to apoptosis in breast cancer cells after 24h in a dose-dependent method (45).
It was also reported that HCF toxins have fatal effects on peritoneal macrophages of mice. Thus, apoptosis pathways might be triggered following contact with HCF via its excreted toxins (24). A study conducted in this realm showed that apoptosis activation rate in HCF-treated lymphocytes was meaningfully higher than nontreated cells. In the treated lymphocytes, expression of the Bax gene as a pro-apoptotic molecule was raised and the expression level of Bcl-2 mRNA as an anti-apoptotic molecule was reduced. The activity of caspase-3 was notably higher in the HCF-treated group (33). Though, in an investigation conducted by Janssen, et.al (1992) it was confirmed that some toxic compounds of the protoscolices, may diminish the survival of the macrophages in vitro (46). Nono, et.al's study showed that excretions of E. multilocularis

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cyst activate apoptosis of dendritic cells in vitro (47). All in all, the outcomes of Daneshpour, et al.'s research confirmed that some HCF antigens activate apoptosis in 4T1 cells. Therefore, HCF might be capable of being used as a medicinal material to trigger apoptosis in cancer cells (24).

Correspondingly, Berriel et al. accomplished a proteomic investigation and characterized mortalin and creatine kinase M-type (10). Besides, Daneshpour et al. (2016) represented a mutual cross-reaction among HCF antigens and secretions of cancer cells (48). In the same vein, Sharafi et al. (2016) reported the cross-reactivity between sera of patients having breast cancer with a nonglycosylated 27 kDa band of the HCW (49). Results of these researches highlight the presence of common antigens among hydatid cysts and cancer. According to Akgül et al. (2003) the patients suffering from hydatid cyst experienced lower cancer rates than patients without hydatid cysts. So, hydatidosis may be a prophylactic anti-cancer factor (14).

Based on Daneshpour et al.'s findings, the IFN-γ, IL-2 and IL-4 levels rose significantly in the treatment of melanoma-bearing mice with hydatid cyst antigens. Additionally, they showed that survival of the mice that had received HCF, 78KDa fraction, protoscolices and BCG injection, was particularly more than control mice. Besides, the TNF-α level in treated mice was meaningfully lower than the control group (50).

Recently, Berriel et al.'s investigation presented that the average size of tumors was obviously lower in HCF-vaccinated mice in comparison with the control group. Remarkably, all of the control groups had tumors, whereas only half of the HCF-vaccinated mice developed tumors. With respect to the protection made by HCF tumors of HCF-vaccinated mice were meaningfully smaller compared with the other group. In addition, immunotherapy with HCF meaningfully raised mice viability in comparison with the control group. It is worth noting that, one HCF-vaccinated mouse was reported not to respond to the treatment since it developed a big tumor like that of control mice. They highlighted the ability of anti HCF antibodies in recognition of LL/2 tumor cells by flow cytometry to evaluate the induced immune response. They reported that IgG antibodies recognized both surface and intracellular molecules of tumor cells (21).

According to the flow cytometry analysis done by Shakibapour et al. (2021), a chiefly higher percentage of 4T1 breast cancer cells respond to the HCW treated rabbit sera compared to the non-immunized rabbit's serum. In this realm, 30% of breast cancer patients' serums reacted to the HCW antigens. Their outcomes determined some homologies among the HCW antigens and surface antigens of 4T1 cells that led to cross-reaction between anti-HCW produced antibodies and surface antigens of 4T1 cells. In addition, they reported that pure Alum injected mice didn't represent any prevention of tumor development compared to the control group. While the average size of tumors rose in all groups during a 24-day follow-up after 4T1 breast cancer cells implantation, tumor growth progress was depressed in the Lower band and HCW antigens immunized groups. Therefore, the Lower and the HCW antigens immunized mice displayed the lowest rate of metastatic colony formation in the liver among all groups (51).

Vaccine development

One of the most influential issues to cause efficacious anti-tumor responses is picking idyllic antigens for immunization against cancer. In this regard, many antigens have been studied for this purpose and showed different ranges of effectiveness (52). One of the well-known consequences of the formerly used antigens for the anti-cancer vaccine is the unsatisfactory immunogenicity to activate proper immune response (53-55). To overwhelm this issue, parasitic antigens having high epitope homology with cancer antigens and noteworthy immunogenicity can be an ideal objective for immunization against cancer cells (51).

Formulation of an efficacious vaccine needs a nontoxic adjuvant, which stimulates not

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only specific and non-specific immunity but also reverses tumor-induced tolerance. By detecting tumor-associated antigens (TAA) in parasites, the assumption of effective anti-cancer reaction generation using molecules from evolutionary distant organisms, like *E. granulosus*, is reinforced (22, 56). In this realm, Berriel et al.'s (2021) research represented that human HCF triggers anti-lung tumor responses, in prophylactic and therapeutic situations, with immunizations at the short intervals (21). Similarly, Berriel, et.al's (2013) investigation on a colon tumor model, proved the efficacious anti-tumor memory induction and the activation of CD4+ T cells (10).

Research findings highlighted that cross-reactions between cancer cells and parasites might be because of carbohydrated antigens, such as Tn and sialyl-Tn structures that are secreted by *E. granulosus* (57). However, the characteristics of the parasitic compounds which induce the immune responses against tumors, remain to be clarified, the carbohydrates are considered as an essential component for the induction of the anti-tumor responses (21, 58).

In addition, Berriel, et.al (2021) have reported that the immunization with extracted peptides of an *E. granulosus* mucin (termed Egmuc) triggers strong anti-tumor activity, increasing NK cell activity and improving the ability of splenocytes to kill tumor cells (28). In the same vein, they reported that NK1.1+ cells depletion remarkably reduced HCF-induced mice viability, suggesting that these cells mediate the anti-tumor protection triggered by HCF. NK cells have been shown to have a significant effect on immune responses against tumors (59).

Furthermore, some reports represent patients with active hydatid cysts have higher NK cells rate in blood than the other group (60). For example, activated eosinophils were important for tumor rejection as they produce chemo-attractants that lead to recruitment of the tumor-specific cytotoxic T cells into the tumor site (61). Besides, neutrophils can also have anti-tumor characteristics. Undeniably, Tumor-Associated Neutrophils (TAN) can mediate tumor-rejection process (62).

In an investigation done by Daneshpour et al. (2018) it was shown that injection of different hydatid cyst antigens including HCF, the fraction, live Protoscolices, and BCG to mice with melanoma cancer, leads to a decrease of tumor size in antigen injected mice (50). Also, there are scientific proofs representing tumor preventive and anti-cancer effects of some parasitic and microbial infections (13, 17).

According to the outcomes of a research, HCF antigens decrease TNF-α in all melanoma bearing mice. In melanoma cancer, it has been demonstrated that TNF-α can induce cell invasion. Also, it was revealed that the cytokine upraises malignant melanoma migration and invasion in vitro (63). Besides, as the hydatid cyst antigens diminish TNF-α, it is estimated that they have a role in tumor control. Thus, immunotherapy with this cytokine has been permitted for metastatic melanoma and metastatic renal cell carcinoma (16).

Conclusion

Tumors arise from numerous genetic and epigenetic changes in healthy host cells that result in gaining forbidden characteristics such as immortality and uncontrolled proliferation and growth (64). Consequently, these features lead to changes in the antigen profiles of neoplastic cells compared with healthy cells (65). Hence, host reaction against these antigens can lead to the initiation of the immune responses (66). Due to immune system memory, the anti-tumor response will be long-lasting and inhibits tumor reappearance (67). The point is that the mechanism of anti-cancer effects of hydatid cyst antigens is not clear. It is probable that upraised immune response against these antigens, non-specifically interact with the cancer antigens and interfere with cancer development. In this realm, the existence of common antigens among cancers and parasites has been confirmed in many researches (22). Though, the capability of parasitic antigens in interfering with cancer

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cells progress in culture medium does not confirm this idea. For instance, it has been reported that hydatid cyst Protoscolices activate cell death in fibrosarcoma cells and prevent the proliferation of baby hamster kidney fibroblasts in vitro. Other thinkable mechanisms of anti-cancer effects of hydatid cyst may be caused by toxicity of its antigens on cancer cells. This hypothesis is compatible with the anti-cancer effect of hydatid cyst antigens in culture medium (11).

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Conflicts of interest

Authors declare no conflict of interests.

Authors' contributions

All authors have intellectually committed to the study design and process. The final manuscript was revised and accepted by all authors.

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