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Use of vaccines against public health significant gastrointestinal nematodes

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ABSTRACT

The GIT nematodes have reduced the quality of life in both human and veterinary care sectors. Anthelmintic resistance has been reported in both sectors, and vaccines can indeed serve as an efficient way of therapy. However, there are multiple attempts being undertaken for vaccine development but the challenges in the development of vaccines against GIT nematodes still exist. Several global health initiatives have been proposed for focusing on improving the quality of life against GIT nematodes.

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Introduction

The proportion of the global population infected with soil infected helminths reported in 2010 was 1.45 billion (1). Gastrointestinal nematodes (GIN) such as *Strongyloides stercoralis, Ascaris lumbricoides, Trichuris trichiura, Necator americanus, Ancylostoma duodenale*, and *Enterobius vermicularis* have great public health significance considering their prevalence and potential to cause diseases in humans (2, 3, 4, 5). The above-mentioned GIT nematodes have a direct life cycle which means there is only one host involved (6). There are also other potential infections transmitted in a zoonotic manner such as Toxocariasis, Hookworm infections through *Ancylostoma ceylanicum* and *Ancylostoma caninum*, and Strongyloidiasis (7, 8, 9). For the sake of treatment, the recommended anthelmintics in humans mass drug administration (MDA) campaigns are benzimidazoles, albendazole (400 mg), and mebendazole (500 mg) while the recommended drugs against nematodes in veterinary use are probenzimidazole, benzimidazole, avermectins and milbemycinsn (10, 11, 12). With an increase in usage of anthelmintic drugs, the anthelmintic resistance has also been reported in both humans and livestock (13). For combatting anthelmintic resistance and a more efficient way of therapy, vaccines and other alternate control strategies can play a crucial role against GIT nematodes (14).

Current Challenges in Vaccine Development Against GIT Nematodes

Immune systems against helminths usually follow type 2 response through signaling CD4+ T helper 2 (TH2) cells which produces a broad range of cytokines including interleukin-4 (IL-4) and IL-13 (15). But the challenges occurring in the vaccine development are maturation and migration of the nematodes in different tissues at different stages. They are a large size which means they require a sustained and prolonged immune response. They also have complex life cycles along with their genomes and proteomes (16). Other challenges are antigenic variations due to polymorphism, inducing partial immunity, and the target helminths don't express themselves fully over time. Moreover, previous infections could cause a hyperreactivity to vaccine antigens or show an antigen specific immune tolerance (17).

Advancements in Vaccine Research for GIT Nematodes

The damage caused by parasitic nematodes to public health and food security is a significant concern in both developing and developed regions (18).

Following is the advancements in vaccine research for the gastrointestinal nematodes:

Antigen Selection

The development of vaccines based on antigens is a widely used technique. Alternative approaches are undertaken which are focused on antigens which provide protection against individual nematodes rather than a generalized multi-faceted response and utilization of natural antigens like secretory/excretory products of parasites. These approaches include usage of antigens H11, H-gal-GP located on the brush borders of the intestinal lumen of *H. contortus* and OPA the *Ostertagi* Polyprotein allergen is under evaluation (19).

Recombinant Proteins

Therapeutic use of recombinant proteins like complex glycoproteins and antibodies has increased enormously due to high production demands based on their potency (20). Recombinant proteins, A133 and Ss-IR are found to be effective against strongyloidiasis which is caused by *Strongyloides stercoralis* nematodes (21). Recombinant protein As37 is an *Ascaris suum* expressed immunodominant antigen which has shown valuable protective immunity in mice against Ascaris however, no fruitful data is available regarding its immunogenic action in humans (22). Another important recombinant protein "*Bacillus thuringiensis* crystal protein 5B (Cry5B)" obtained from *Bacillus thuringiensis* bacteria is found to have anthelmintic action because it has shown potency against nematodes *in-vitro* and against human hookworm infections in mice *in-vivo* (23). The protective action of humans against nematodes also depends on the interaction of host-parasite Galectins which are proteins having ability to-bind as well as be-bound by the antibody (24). Helminth vaccines for human usage largely depend on the recombinant proteins for their efficacy and immunogenicity except few like Na-ASP-2 (for hookworms in humans) which causes generalized urticaria (25).

Epitope-Based Vaccines

Epitope-based vaccines are not like traditional preventive measures. They provide prophylactic as well as therapeutic effects with a number of advantages like prolonged immunity, absence of undesirable immune responses, less time consuming and budget friendly (26). Multi-stage fruitful research was carried out by Zawawi and his colleagues in order to identify *Trichuris* epitope vaccine antigens from surface proteins similar in nature to human and mice proteins in order to rule out potential auto-immune reactions (27).

Nucleic Acid Vaccines

Nucleotide vaccines are getting prominent nowadays. DNA vaccines are basically, bacterial plasmids with genes incorporated to express specific encoded proteins upon *in-vivo* administration (28). RNA vaccines are very flexible in action since they produce both humoral as well as cellular immunity response and WHO (World Health Organization) has formulated a new therapeutic class named mRNA (Messenger RNA) to counter multiple health problems (29). No RNA vaccines have been made against helminthic infections while DNA vaccines lack the immunogenicity for which the scientists are using molecular adjuvants and DNA vector probes (30).

Global Health Initiatives against GIT Nematodes

With the emerging global issues like climate change and global migration of native bio life along with the abrupt rise of lethal diseases like HIV, malaria etc., which have devastated the human health, the potential damage which the zoonoses of gastrointestinal nematodes cause is often under-estimated and they fall under the umbrella of "Neglected Tropical Diseases" (NTDs) (31). Among the neglected tropical diseases, gastrointestinal nematodes affect mass populations with an estimated number of > 1.5 billion individuals (32). Gastrointestinal nematodes i.e., *Trichinella* and *Ascaris* severely affect food security because of poor hygiene practices and consumption of raw meat, so WHO has declared them as one of the main causes of morbidity and mortality, affecting more than one-fifth of world's human population (33). However, prevention and control of nematodes is particularly more difficult in developing countries having low income, poor sanitary conditions and lack of food safety (34).

In 2001, World Health Assembly made a resolution to contain and eliminate the Soil transmitted helminths (STHs) which were responsible for causing a number of communicable diseases and for this purpose WHO provided a once-a-year treatment with anthelmintic drugs namely, Mebendazole (500 mg) and Albendazole (400 mg) (35). It is a legal requirement in United States and European Union to report Tricinellosis cases in meat used for human consumption i.e. European Commission regulation no. 2075/2005 demands meat inspection before consumption of slaughtered animals susceptible to *Trichinella* infection and the United States has evaluated legislation to certify Trichinella-free-pork production (36). Moreover, WHO has targeted *Ancyclostoma duodenale* and *Necator americanus* (hookworms) for elimination as a public health problem goal by 2030 using Mass Drug Administration (MDA) which is a technique of preventive chemotherapy (37). In October 2018, an international group of experts from (Soil Transmitted Helminths) STH-endemic countries along with partners from institutions supporting STH prevention and control activities met in Basel, Switzerland and identified STH control targets for 2030. These six targets are, (1) Establishing and maintaining the elimination of STH morbidity in preschool-age and school-age children; (2) Decreasing the number of anthelmintic tablets needed in preventive chemotherapy for STH; (3) Increasing domestic financial support for preventive chemotherapy for STH; (4) Establishing control programs in adolescent, pregnant and lactating women of reproductive age; (5) Establishing an efficient strongyloidiasis control program in school-age children; and (6) Providing universal access to at least basic sanitation and hygiene in STH-endemic areas (38).

Conclusion

The prevalence of gastrointestinal nematodes has greatly impacted on the lives of people and animals. Use of vaccines and avoiding the misuse of anthelmintic drugs to avoid resistance along with control programs can create a difference in fighting against these potential disease-causing agents. More comprehensive research needs to be done in controlling and preventing these gastrointestinal nematodes in developing countries

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