Soil Transmitted helminths

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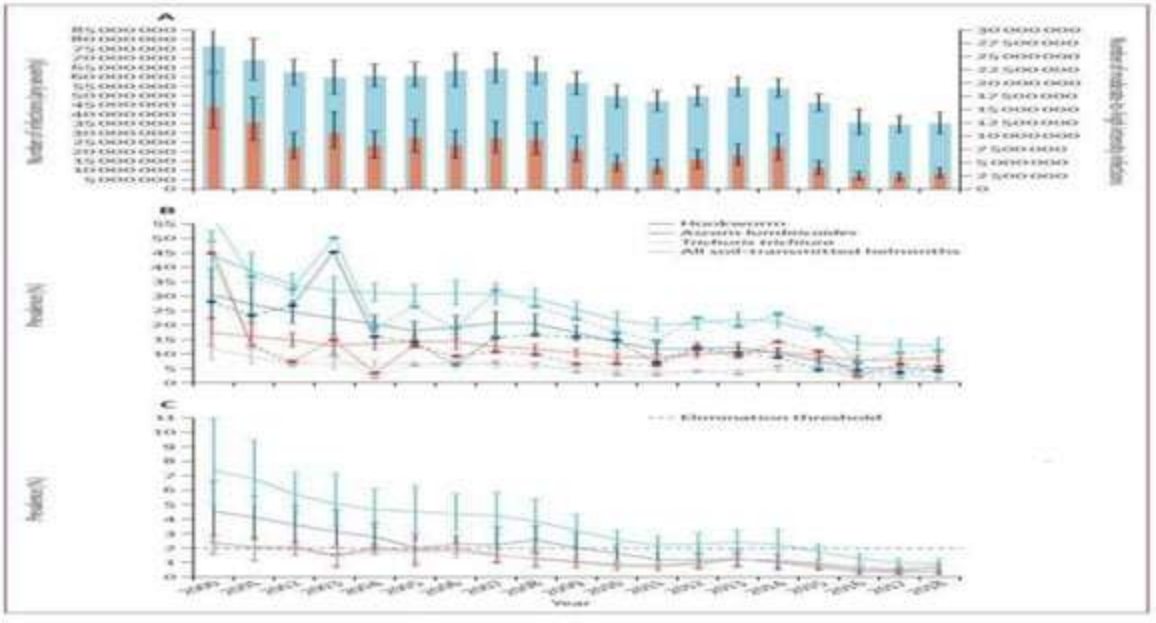
CHANGING GLOBAL EPIDEMIOLOGY OF HELMITHES

- There is a reduction in the prevalence of soil-transmitted helminths in children aged 5–14 years in sub-Saharan Africa, from 44% in 2000 to 13% in 2018, driven by sustained delivery of preventive chemotherapy, improved sanitation, and economic development.
- Nevertheless, 25% of implementation units still had an estimated prevalence of moderate-to-heavy intensity infection exceeding the 2% target threshold.

- In 2018, largely concentrated in nine countries ie Nigeria, Democratic Republic of the Congo, Ethiopia, Cameroon, Angola, Mozambique, Madagascar, Equatorial Guinea, and Gabon.
- Although helminth parasites infect over 25% of the world's population these infections are one of the most "neglected" tropical diseases with no effective vaccines available for humans.


A
B
C
Hookworm
Ascaris lumbricoides
Trichuris trichiura
All soil-transmitted helminths
Elimination threshold
Year

HELMINTHS MODULATING IMMUNE SYSTEM

- Helminth parasites are masters at manipulating host immune response by targeting of pattern recognition receptors (PRRs) including
  - toll-like receptors, C-type lectin receptors, and the inflammasome.
  - These play a critical role in intracellular pathways and regulating innate inflammatory responses as well as directing adaptive immunity toward Th1 and Th2 responses
- Helminths derived products ultimately converge host immunity toward hyporesponsiveness and immunological tolerance.

TOLL LIKE RECEPTOR

- Stimulation of TRL receptors is done with helminth derived products(HDPs), which trigger the mitogen activated protein kinase pathway (MAP K) which is responsible for the production of cytokines and dendritic maturation.
- Stimulation of MAP K it enhance stimulation of extracellular signal related kinases 1 and 2 (ERK 1/2) which will enhance dendritic cell maturation,cytokines, and it favour the Th2 respone which will reduce the inflammatory process and favour parasite

- There is also other pathway which start from from stimulation of TRL receptor which will stimulate MAP K pathway which lead to stimulation of suppressor of cytokine signalling 3(SOCS3) which will lead to the inhibition of signalling ofor cytokine production,

C-TYPE LECTIN

- HDPs once they bind to the C-type receptor they
  - ✓ Induce Th2 suppression
  - ✓ Induce Treg proliferation which will create a balance between Th1 and Th2
  - ✓ stimulation of both Th1 and Th2 will lead to the production of IL12 and TNF which lead will to the production of T reg hence will reduce inflamatory process hence favors parasite survival.

INFLAMMASOME

- It has a receptor called Node like receptor were by HDPs products which will cause suppression of Th2 response by production of IL 18,IL1

NON PRR PATHWAYS

- Imparement of antigen presentation cell by blocking B cell receptor which act by weaking signal to the naive T cell hence it cannot recognise parasite
- IgE signalling interference the degranulation of mast cell
- Mimmicky key mediators like TGF alpha and PGE2, whichg lead to conversion of Th1 and TH2
- Blocking pottasion gatted chanell causing dysfunction of t cells

EXTRACELLULAR VESICLE (EVs)

- These are vesicle released by the helminth which they contain different materilas like protein,lipid, miRNA,RNA
- In host cells miRNA normally regulating post transcription gene expression , but parasite miRNA block gene expression of host cells products inculding cytokines.
- RNA inducing silencing complex og the host gene expession for the products like cytokines.

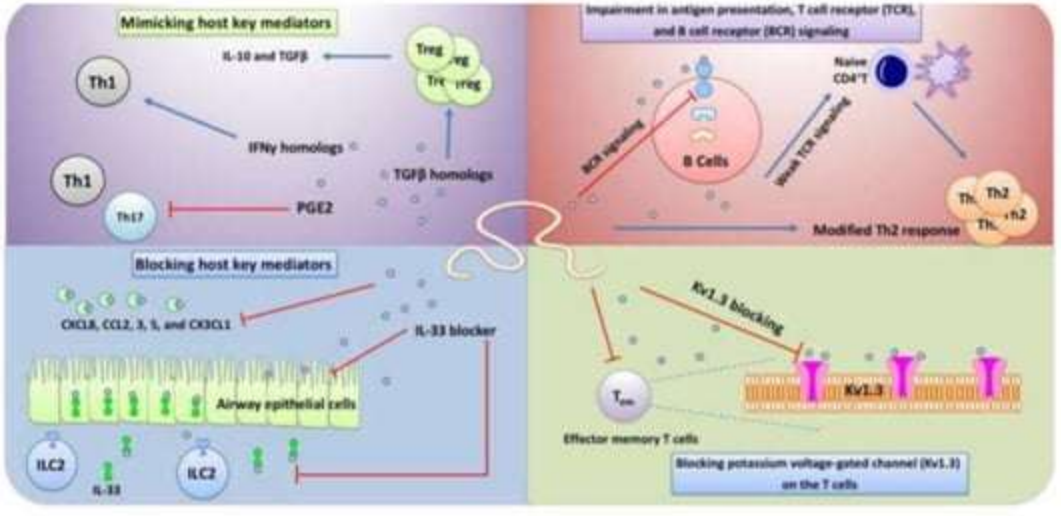


FIGURE 2 | Some HDPs has been shown to target non-PRRs sensors including Kv1.3 and TCRs on T cells. Blocking Kv1.3 can significantly decrease Th1 cell activity and proliferation. Also, presenting HDPs on the MHCII leads to induction a weak TCR signaling in naive CD4 T cells which corroborates Th2 differentiation. Of note, the main phenotype of Th2 response elicited by helminths and their products is "modified Th2" immunity in which IL-5, IL-13, eosinophilia, and IgE are all downregulated, while IL-4, TGFβ, and IL-10 are increased. BCR signaling has also been shown to be impaired by some HDPs which prevent B cell activation. HDPs have recently been more considered as magic components which are able to mimic or block several host key mediators which play an important role in immunosuppression and Th2 amplification, respectively.

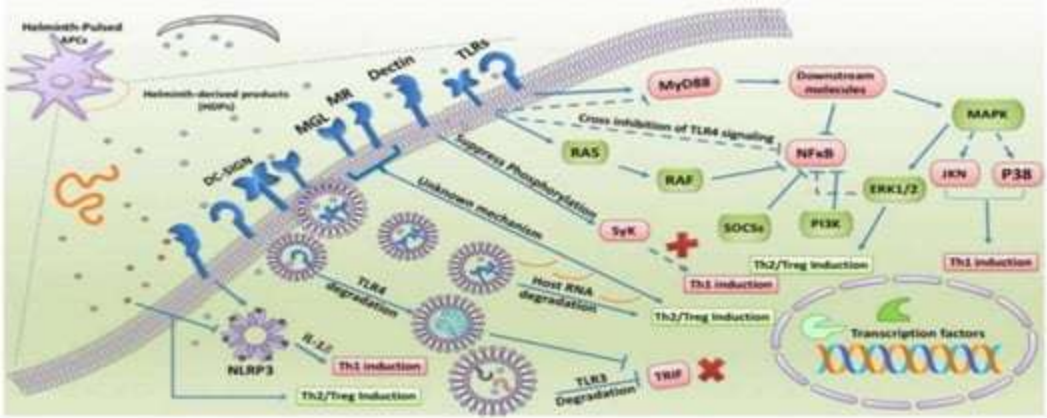


FIGURE 1 | Involvement of TLRs and CLRs during interaction with HDPs. TLRs and CLRs are widely targeted by HDPs during induction of immunomodulation and hyporesponsiveness in APCs. HDPs not only alter the expression of TLRs and CLRs in APCs but also masterfully manipulate their intracellular signaling. Some HDPs are able to redirect TLR4 signaling toward MAPK pathway and ERK1/2 activation supporting Treg/Th2 induction. In addition, co-engagement of DC-SIGN along with TLR4 enables HDPs to trigger unknown intracellular pathways which cross-inhibit MyD88 and NF-κB activation. HDPs can further restrain NF-κB activity via DC-SIGN-mediated RAF signaling along with upregulation of negative regulators of TLRs signaling, such as SOCSs and PI3K. Obviously, strict inhibition of NF-κB as the main transcription factor supporting inflammation results in prevention of priming Th1 cells. Other CLRs have been reported to participate in priming Treg/Th2 cells upon stimulation by HDPs. For example, some HDPs suppress phosphorylation of Dectin1/2-induced Syk molecule and through which inhibit deviation of immune response toward Th1. On the other hand, MR and MGL upon activation by HDPs through an unknown mechanism support Treg/Th2 differentiation. Degrading host key intracellular molecules is another strategy that HDPs exploit to reprogram host immunity. Omega-1, ES-62, and FheCL1 by degrading host mRNA, endosomal TLR4, and TLR3, respectively, not only strengthen Treg/Th2 responses but also forestall anti-parasite immunity. NLRP3 also has been revealed to be targeted by some HDPs to modulate inflammatory responses. However, there has been reported that some HDPs are able to fight anti-worm immunity by stimulation of NLRP3 leading to release of IL-1B and Th1 amplification.

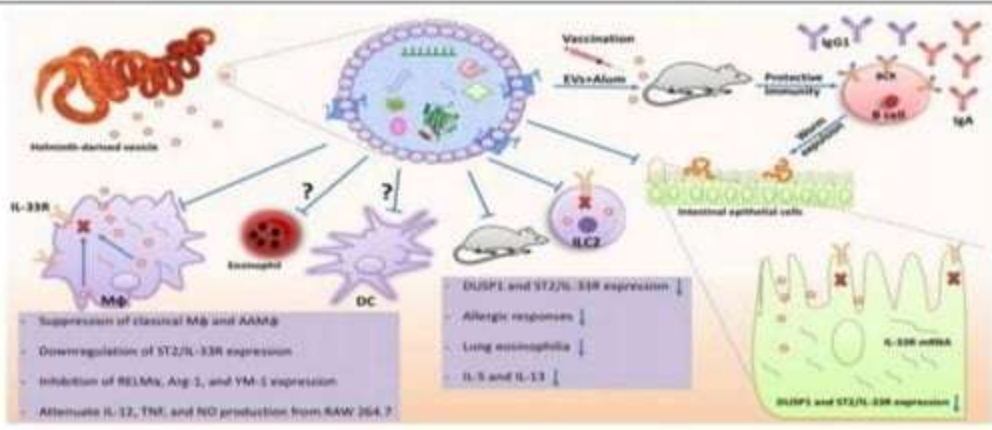


FIGURE 3 | Schematic illustration of known effects imposed by helminth-derived EVs during interaction with host immunity. As illustrated here, EVs can affect different host cells including immune cells and intestinal epithelial cells (IECs). Also, they can potentially be used to develop new vaccines against helminths. EVs deliver cargo containing various biomolecules to host cells which can interfere with host cell gene transcription. EVs are internalized by macrophages and IECs via unknown mechanism and target IL-33R and DUSP1 expression reducing signal transmission and leads to inhibition of helminth expulsion. EVs have also shown great potential in priming host immunity along with Alum as a vaccine complex against helminth infections. Effective suppression of both classical Mϕ and AAMϕ have also been reported, implying EVs are well-equipped with a wide range of active components. In addition to *in vitro* studies, immunomodulatory functions of EVs have also been monitored in *in vivo* model in which allergic responses, associated cytokines, ILC2, and eosinophilia are down-regulated in Alternaria-exposed mice.

INTERACTION BETWEEN HELMINTHIASIS AND OTHER DISEASES

1.INTERACTION BETWEEN HELMINTH WITH TUBERCULOSIS AND BCG

Tuberculosis and helminth infections are coendemic in many parts of the world, which raises the possibility of modulating tuberculosis through host responses to helminths.

- A lower IFN-γ response and greater IL-10 response has been observed in helminth-coinfected patients with tuberculosis than patients with tuberculosis alone.

- Concurrent helminth infection in people exposed to M. tuberculosis can increase their risk of becoming latently infected with M. tuberculosis.
- Deworming of people before vaccination against BCG enhanced the IFN-γ response, whereas the TGF-β response was lower than for people who did not receive deworming treatment
- Sugesting that the poor immunogenicity of BCG in the helminth-infected population could have been due to increased TGF-β production.

2. INTERACTION BETWEEN HELMINTHS AND MALARIA

- Epidemiological studies suggest that helminth infection in humans may alter the development of malaria not only by increasing the replication of Plasmodium parasites but also by modulating the severity of the pathological sequelae associated with malaria.
- Thus, by altering the TH2-TH1 balance, helminth infection may be a substantial contributing factor to the delayed acquisition of clinical immunity to malaria.

3. INTERACTION BETWEEN HELMINTHS AND HIV

- The helminth-induced immune response may have several components that compromise the immune responses needed to keep the HIV infection in check, including the production of TH2 cytokines and impaired function of antigen-presenting cells.

- However, those same mechanisms through dampening the activation of cells of the innate and adaptive immune systems may potentially affect the early stages of HIV infection.

- Macrophages treated with IL-4 and IL-13 inhibited the entry of virus by downregulating expression of the CCR5, CXCR4 and CD4 receptors for viral entry.

- Thus, although the viral load of HIV may in some cases ultimately be increased after helminth infection, those potential mechanisms that decrease infectivity may offset the advantages of antihelminth treatments.

4. METABOLIC DISEASES

- Epidemiological studies suggest that chronic helminth infections may influence the development of metabolic diseases.
- Individuals with a previous or current helminth infection were 50% less likely to have an outcome of metabolic dysfunction such as hyper glycaemia or insulin resistance compared to those uninfected.

REFFERENCE

- Zakeri A, Hansen EP, Andersen SD, Williams AR and Nejsum P (2018) Immunomodulation by Helminths: Intracellular Pathways and Extracellular Vesicles available on www.fontersin.org