



Mini-review

Helminths and our immune system: Friend or foe?

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ABSTRACT

Helminths are able to modulate and suppress the hosts' immune response in order to promote their own survival. This ability to alter immune responses could be of potential detriment to the host if it interferes with the development of protective immune responses against other infections. However, helminth infections have also been suggested to be beneficial in the control of excessive inflammatory reactions. In this review I will highlight some of the data suggesting both positive and negative effects of helminth infections in humans and in experimental models.

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1. Introduction

Helminth infections are amongst the most common infections of humans and are notoriously chronic in nature, with some species of worms surviving within their host for many years, in some cases even decades. In order to facilitate such longterm survival within an immunocompetent host these organisms have developed sophisticated survival strategies, including the ability to modulate and

manipulate our immune system. This ability to alter immune responses could be of detriment to the host if it interferes with the development of protective immune responses against other infections. However, since helminths and the human immune system have co-evolved over millennia it has also been suggested that helminth infections may have a beneficial role in controlling autoimmune and other excessive inflammatory responses and that these organisms may even provide a source of novel anti-inflammatory therapeutics. Parasitic helminth infections may therefore constitute a double-edged sword for human health and it is of vital importance to clarify any beneficial or detrimental roles these infections may have on public health, in addition to their role as single infections.

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2. Helminths and the immune system

The mammalian immune system is a carefully tuned orchestra consisting of a large number of different members, producing humoral (antibody) and cellular immunity. Central to most of the immune functions are T helper (Th) cells. Th cells play a critical part in instructing and controlling the various players of the immune response against invading pathogens. Several different types of T helper cells exist, primarily based on the type of cytokines they produce. Th1 cells secrete IFN- γ , are involved in the classical activation of macrophages and play a central part in the cellular immune response against intracellular pathogens. Th2 cells on the other hand secrete IL-4, IL-5 and IL-13, and are involved in the activation of mast cells, eosinophils, alternatively activated macrophages and increased production of IgE antibodies. In addition to Th2 cells, a new distinct IL-9-producing T helper subset (Th9), was recently identified [1]. Depending on the cytokine environment these cells can originate from Th2 cells, or they can also be induced de novo. Importantly, these Th9 cells were shown to mediate, at least in part, resistance to *Trichuris* infection in mice [1]. Another recent addition to the T helper cell family receiving much attention are the IL-17 producing Th17 cells, which have been shown to be involved in inflammatory and autoimmune reactions. As part of the inflammatory response they have also been shown to be involved in the pathology of certain helminth infections [2]. Importantly, many of the different Th subsets negatively regulate each other so that the activation of one subset inhibits the activation of the others. Thus, the immune response to different types of infections tends to be dominated by one Th subset over any other. Infections with helminth parasites generally induce a strong polarization towards a Th2 type response, leading to the hallmark features of high Th2 cytokine production, eosinophilia, mastocytosis, goblet cell hyperplasia and high levels of IgE antibodies [3]. Despite the successful generation of the Th2 response, worms are often able to survive in the host for long periods of time, causing chronic infections. This longterm survival within an immunocompetent host is facilitated by the induction of immunoregulatory mechanisms, including regulatory T cells (T reg), capable of secreting immunosuppressive cytokines such as IL-10 and/or TGF- β , resulting in an anti-inflammatory environment [4]. This regulatory environment prevents the elimination of worms but also protects the host against excessive inflammation. However, given the fact that the immune system needs to strike a careful balance between pro- and anti-inflammatory responses in order to function efficiently against several pathogens simultaneously, it is possible that this helminth-induced regulatory environment could impact on immune responses to concurrent infections and perhaps even alter disease progression. Therefore, there has been much interest in recent years regarding how much the presence or absence of helminth infections may impact on the function of our immune system. Suggestions have been made that the absence of natural helminth infections in westernized countries may be associated with an increase in allergic and autoimmune disorders, while the continued presence of such helminth infections in developing countries may have a detrimental effect on vaccination and on the immune response to concurrent infectious diseases, such as malaria.

3. The friendly helminth?

3.1. Helminths and allergic disorders

Allergic diseases include asthma, atopic dermatitis and rhinitis. These are inflammatory diseases caused by immune reactivity to environmental allergens. The prevalence of allergic disease is generally low in rural areas of Europe [5] and in developing countries [6], while they are considered an increasingly important cause of morbidity in westernized countries. It is clear that children with

several older siblings or attending day care have a reduced risk of developing allergies [7] and a number of studies have demonstrated the inverse relationship between childhood infections and an increased risk of asthma and atopy [7,8]. Helminth parasites stimulate a similar type of immune response to that induced by allergens (Th2 type response), but they also induce strong regulatory responses and in recent years there has been considerable interest in the potential role of helminth infections in modulating/regulating allergy risk in helminth-endemic areas. Indeed, the inverse association between helminth infections and allergy has been reported by several studies [9–11]. The underlying mechanisms are suggested to involve the regulatory presence of parasite-induced IL-10, a cytokine able to modulate and/or suppress the response to allergen [12,13].

However, despite the inverse association between helminth infections and allergy, intervention studies using anthelmintic treatment to clear worm burdens, have failed to demonstrate consistent results in terms of allergen skin-test reactivity. Some studies have reported increased skin test reactivity after treatment [14,15] while others demonstrate no such effect [16]. Furthermore, a few studies have also reported a reduction in asthmatic symptoms after treatment [17,18], suggesting that helminth infections can actually exacerbate allergic responses, perhaps via non-specific potentiation of IgE synthesis. Thus, this range of clearly contradictory results point to the possibility that several factors are involved, e.g. infection intensity, the frequency of infections, timing of infections, helminth species involved etc, that may affect the degree of suppression, or stimulation, for each individual. It could be that occasional, transient or low-level infections have a stimulatory effect, while frequent or high-level infections act as suppressors of the allergen response. Additionally, it may be that the timing of infections and/or treatments in life are of importance, such that exposure to helminths in infancy, or even in utero, rather than later in life, are of consequence [19].

In terms of intervention studies using anthelmintic drug treatments it is also important to consider that most such treatments, including repeated treatments, are of limited effectiveness for certain species of helminths, in particular *Trichuris trichiura*. Cure rates of *T. trichiura* infection after standard albendazole or mebendazole treatment are remarkably low, frequently as low as 20% [20]. Even after repeated treatments the prevalence of *T. trichiura* remain relatively high, although the intensity of infection is reduced [15,16]. Considering that we currently have little knowledge regarding the levels of helminth infections needed to affect immune responses, or regarding the timescale for how long such helminth-induced immune alterations can persist after infection and treatment, it is currently difficult to draw any firm conclusions from these studies other than more field studies are certainly needed.

3.2. Mouse models of helminths and allergic inflammation

The model of asthma-like allergen-mediated pulmonary inflammation, induced by intraperitoneal immunization with ovalbumin (OVA) followed by intratracheal OVA challenge [21] is a murine model that has been helpful for allergy research. This model of pulmonary inflammation is characterised by eosinophilia, increased Th2 cytokine and IgE levels, peribronchial inflammation and increased airway hyper reactivity (AHR). A number of experimental studies have utilized this airway model to analyse the influence of concurrent helminth infection, as well as purified helminth products, on pulmonary hyperreactivity. The results show that a concurrent gastro-intestinal helminth infection, such as *Strongyloides stercoralis*, *Heligmosomoides polygyrus* and *Nippostrongylus brasiliensis*, can inhibit the development of pulmonary inflammation and AHR [22–25]. Depletion of a population of CD25 positive cells reversed the inhibitory effect of *H. polygyrus* infection [23] suggesting the involvement of some form of regulatory T cell. The role of IL-10 is more ambiguous, however, with some studies showing that the asthma-inhibitory effects of

helminth infection is dependent on IL-10 [24,25] while others demonstrate no such dependency [23,26]. Interestingly, one study reported that administration of purified helminth products significantly inhibited OVA-specific Th2 cytokine production, while simultaneously stimulating a helminth-specific Th2 response [26] indicating that there was no general reduction in Th2 activity but rather a change, or diversion, in the specificity of the response.

Species of helminths other than gastro-intestinal nematodes have also been used to model helminth-induced inhibition of allergic reactivity in mice. Infection with the filarial nematode *Litosomoides sigmodontis* resulted in significant inhibition of AHR, while in this case the depletion of CD25 positive cells, or neutralisation of the immunosuppressive cytokine TGF-beta abolished the protective effects on the bronchial hyperreactivity, but did not alter airway inflammation [27]. Similarly, studies using purified filarial products have also demonstrated suppressive effects on AHR [28,29]. Intriguingly, a study utilizing filarial cystatin found that the suppressive effect was dependent on macrophages and IL-10, but not on regulatory T cells [28], again suggesting a complex network of several factors involved in helminth-induced immunomodulation. Similarly to gastro-intestinal and filarial nematodes, infection with the trematode helminth *S. mansoni* also reduced AHR, however, this was only achieved by single sex infections, suggesting that schistosome eggs are not involved in the suppression of AHR [30]. This was also demonstrated in single sex *S. japonicum* infection [31]. However, another study using purified *S. japonicum* egg antigen reported the induction of IL-10-producing CD4+CD25+ T cells that were efficient inhibitors of AHR [32], suggesting that both adult schistosomes as well as eggs can act as potent immunomodulators, but probably acting via different immunomodulatory pathways.

Although dramatic inhibition of AHR in mice have been reported for both nematode and trematode infections, not all types of helminth infections appear to be able to reduce such pulmonary inflammation and hyperreactivity. Infection with *Toxocara canis* exacerbated AHR and increased Th2 cytokine production in OVA treated mice [33] and infection with egg-laying *S. mansoni* was reported to exacerbate AHR [30]. However, Smits et al. recently demonstrated that *S. mansoni* infection could indeed protect against AHR, but this was dependent on timing and dose of infection [34]. The differential modulation of allergic disease by the different stages of a helminth infection was also demonstrated in a different type of allergic disease model. By utilizing an allergic eyedisease model (rag weed sensitization followed by ocular challenge) it was demonstrated that mice with acute *Ascaris suum* infection (14 days) responded with significantly enhanced allergic eye disease, while mice with a chronic *Ascaris* infection (60 days) were protected and showed no allergic symptoms [35]. Transfer of CD25+ T cells from chronic to acutely infected animals significantly reduced the influx of eosinophils to the conjunctiva, again demonstrating a possible role for helminth-induced T regs in the inhibition of allergic disease. Furthermore, purified *A. suum* pseudocoelomic fluid was shown to inhibit allergic inflammation in vivo in an IL-10-independent fashion while treatment of dendritic cells with the parasite products reduced activation-induced surface marker expression and cytokine production in vitro [36].

Taken all together, the experimental studies clearly demonstrate that a number of factors, including parasite species, parasite load and timing of infection, influence whether helminth infections can protect against, or enhance, allergic manifestations in mice. Similarly, the immunological mechanism(s) involved appear to involve a diverse array of participants, most probably including regulatory T cells in some form, while the role for IL-10, at least in the mouse models, remains uncertain.

In summary, it is probably safe to conclude that based on the current human and experimental literature it is not possible to firmly establish whether helminth infections really do protect against allergic disease. There is little doubt, however, that helminth infections can under specific experimental conditions affect allergic reactivity, in both positive and negative ways. Whether this is a feature

in helminth-infected humans remains to be established. In this context it is also important to consider that many different types of infections have been shown to reduce OVA-induced AHR in mice, including mycobacteria [37], respiratory syncytial virus [38], influenza virus [39] and mycoplasma infection [40], suggesting that a general immune activation or diversion of the immune response away from the allergen is perhaps the most important factor. Similarly to mice, several types of infections other than helminth infections have also been shown to correlate with protection against atopic disease in humans [7]. Therefore, a reduction in exposure to helminth infections in the westernized world is only one of many possible suggested reasons for the increase in atopic diseases, and it may perhaps be the case that a general stimulation of the immune response in a particular direction, and at the right time, is the critical factor in diverting the immune system away from making abnormal responses to environmental allergens. No doubt, further human studies will provide more definitive clues over the coming years.

3.3. Helminths and inflammatory disorders

The healthy immune system has a remarkable ability to balance between destroying invading pathogens without damaging self. However, when this balance is not functioning properly, autoimmunity and other inflammatory disorders can occur. This may be due to failure of regulation, either at central T cell selection level or via inadequate regulation in the periphery. Similarly to atopic diseases, autoimmune and inflammatory disorders are on the increase in the western world. A striking rise in the incidence of inflammatory bowel diseases (IBD) is evident over the course of the 20th century, suggesting a strong possibility for environmental factors [41] and in recent years there has been a surge of interest in the possible therapeutic effect of helminth infections on IBDs such as Crohns disease and Ulcerative colitis. Several highly publicized studies have reported the use of oral treatment with the porcine whipworm *Trichuris suis* in IBD patients [42–44], and recently a proof of concept study using the human hookworm *Necator americanus* was published [45]. The studies all report significant beneficial effects of helminth infestation on the clinical score of IBD in patients with both Crohns and Ulcerative colitis. Positive as this is for the patients, there is, however, little information available regarding the longterm effects from repeated or prolonged treatments with intestinal nematodes. Furthermore, reports of iatrogenic infestations as a consequence of such helminth therapy [46] as well as various ethical and hygiene issues, suggest that the identification, and artificial production, of purified anti-inflammatory helminth products are perhaps a more palatable option. If it is possible to overcome immunological obstacles such as oral tolerance, or the risk of developing hypersensitivity reactions, remains to be established.

In terms of mouse model work there is significantly more data available and a number of studies have confirmed the beneficial effects of concurrent helminth infection on bacterial and chemically induced colitis (Th1 type colitis) [47–51] and the injection of *S. mansoni* and *S. japonicum* eggs alone was shown to be sufficient for the inhibition of colitis [52,53]. Similarly to the results from the mouse asthma model, some uncertainties regarding the underlying anti-inflammatory mechanisms are evident. The majority of studies suggest that the beneficial effect of helminth infections on intestinal inflammation is likely to be mediated via the inhibition of the inflammatory Th1 response by the helminth-induced Th2 response, however one study demonstrated that IL-10-producing dendritic cells are involved in reducing the antibacterial response during bacterial colitis [48] and a second study suggested the involvement of anti-inflammatory alternatively activated macrophages, again resulting in impaired anti-bacterial capacity [47]. Importantly, one study also reported the exacerbation of disease using a Th2-type colitis (oxazolone induced) [54], highlighting the caveat of assuming that

all inflammatory disorders may benefit from helminth therapy as this is clearly not the case.

With respect to autoimmune disorders and concurrent helminth infections in humans the literature is most definitively limited, if not almost non-existent. One single study reported that helminth infected multiple sclerosis patients had significantly better disease progression than uninfected patients [55], and this was correlated to higher levels of IL-10 producing B cells [56]. Animal experiments, however, have demonstrated beneficial effects of concurrent helminth infections, or helminth-derived products, on Graves disease [57], diabetes [58–60], arthritis [61,62] and experimental autoimmune encephalomyelitis (EAE, an animal model of multiple sclerosis) [63–66]. Similarly to the colitis models, the majority of the experimental studies suggest that the beneficial effect of helminth infection is via the counter-regulation of the inflammatory Th1 response and, significantly, most of the studies demonstrate a need for the helminth infection to be established prior to the onset of the autoimmune disorder for it to have the desired inhibitory effect, thus casting some doubt over the therapeutic potential.

4. The enemy within?

4.1. Helminths and vaccination

Many modern vaccines are designed to induce a Th1 response for optimal efficiency. Since helminth infections in general induce either a Th2 or a regulatory response, or both, there has been much discussion and speculation on whether concurrent helminth infections are responsible for reducing vaccine efficacy. Clear evidence exist from murine models that helminth infections can alter the nature of immune responses to non-parasite or 'third-party' antigens [67–69] via the skewing of the cytokine response towards a Th2 biased response. In terms of reduction in vaccine efficacy there is less information available from the murine models, but some studies certainly suggest that this may be the case [70–72], again primarily via a reduction of the protective Th1 response.

Several humans studies on cholera [73], BCG [74] and tetanus [75–77] vaccination report immune skewing during helminth infection. In general these studies suggest reduced Th1 responses to the vaccine [75–78], and impaired antibody titers [75,76,78–80], and with de-worming treatment significantly improving vaccine-specific responses [73,74,78]. Whether the enhancement of the in vitro response to the vaccine after drug treatment is manifested in improved clinical immunity remains to be established. Interestingly, in utero sensitization to filariasis and schistosomiasis was shown to reduce Th1 type immunity after BCG vaccination in infants [81], suggesting that maternal helminth infection may be of detriment for BCG vaccination of newborns.

4.2. Helminths and co-infection with malaria

Much interest has focused on a potential link between helminth infections and other infectious diseases, in particular malaria. Since both helminth and malaria infections are prevalent throughout many areas of the tropics, co-infections with helminth and malaria parasites are frequently observed. The immune response to malaria, similarly to many other infectious diseases, needs to be carefully balanced so as not to result in an excessive inflammatory response that may harm the host, while retaining the ability to control parasite growth. This balance may be disrupted by helminth co-infections. This field has become the most debated and controversial area of co-infection research and by now a fairly large number of studies have been published. As is the case with many other studies regarding the negative or positive effects of helminth co-infections, the published results are often contradictory and variable, making it difficult to compare studies and draw any definite conclusions.

Several human studies have suggested that helminth infection increases the susceptibility to malaria infection. The risk of clinical malaria was shown to be reduced in children free of intestinal nematode infections compared to nematode-positive children [82], and the incidence of malaria attacks was higher in children infected with *S. mansoni*, especially in subjects with the highest helminth loads [83]. A positive association of intestinal helminths and infection with *P. falciparum* was also reported in Thai adults [84]. On the other hand, several studies have also reported that helminth infections may protect against malaria. *S. haematobium* is so far the only helminth suggested to be associated with protection, and light infections appear to protect better than heavier infections. Furthermore, indications are that the age of the study population may be important as younger children may be better protected than older [85,86].

Further conflicting results have been reported regarding the impact of helminth infections on severity of malarial disease. A Senegalese study concluded that *Ascaris* infection was associated with an increase in the prevalence of severe malaria [87], while *Ascaris* infection was shown to be associated with protection against cerebral malaria [88], or from renal failure [89] in Thailand.

A number of factors might explain the wide variation of results reported from the different studies. This includes the fact that definition of clinical malaria is not always uniform, and the period of follow-up is also variable between studies. Furthermore, the intensity, and even the species, of the helminth infections are not always taken into account although it is increasingly clear that the outcome of co-infections are strongly influenced by the species and the intensity of helminth infection, and the age of the study population. Given that so many by now known parameters are involved, and many more as yet unknown are likely to play a part, it is perhaps not really surprising that such striking differences in results have been reported up until now.

The murine models of helminth/malaria co-infections have largely confirmed the wide range of results observed in human studies. Various strains of rodent malarias can be used to model different aspects of human malaria infections and although no single species possess all the different aspects of human infections, they have proven to be very useful in studies of specific components of the antimalarial response, or certain aspects of malarial pathogenesis. With respect to schistosome/malaria co-infections, experimental studies have shown that the outcome of infection varies depending on the genetic background of the mice, as well as the strain of malaria used [90–93]. A study using the filarial worm *Litomosoides sigmodontis* demonstrated a more severe course of malaria infection, as measured by weight loss, but without increasing malaria parasitemia [94], while concurrent infection with the gastro-intestinal nematode *H. polygyrus* increased parasitemia and mortality from *P. chabaudi* infection in association with a lower Th1 response [95].

In the *P. berghei* ANKA mouse model of cerebral malaria, pathology is associated with increased inflammatory cytokine production, and it has been suggested that the regulatory cytokines induced by concurrent helminth infections may be able to decrease the inflammatory response and suppress the development of cerebral malaria. Indeed, in one study where CBA/J mice were pretreated with irradiated larvae of *Brugia pahangi*, the development of cerebral malaria was ameliorated [96], while our own work using co-infection with *H. polygyrus* was unable to demonstrate any helminth-mediated effects on the development of murine cerebral malaria [97].

In summary it is clear that results from the murine models of helminth and malaria co-infections is critically dependent on the genetic background of the mice, the species of helminth used, the strain of malaria used, and the stage and intensity of infections. As such, it is easy to dismiss them as unreliable and perhaps even too unreal. However, these animal models do continue to provide us with the critically important tools to fully understand the intricacies of co-infections, and the underlying biological mechanisms in a way that

human studies will never be able to. The mouse studies also highlight the very clear message that infections with different helminth species may result in completely different outcomes in a co-infection situation, pointing to the fact that we still do not know enough regarding the biological and immunological differences between individual species of parasitic helminths. As long as we do not possess an in-depth biological knowledge about these organisms as single infections it will continue to be very difficult to interpret data from co-infections.

5. Concluding remarks

There is now little doubt that helminth infections really do have the ability to influence the development of immune responses. Both animal and human studies have demonstrated this repeatedly and convincingly. However, what remains to be established is if this ability is of any real public health significance. It is clear that many studies are still conducted based on assumptions regarding what is probably a somewhat simplistic immunological view of helminths, who tend to be generally lumped together in a “Th2/T regulatory” family, often resulting in omission of the critical analyses of differences between species, biological niches within the host, and stages of infection. Indeed, careful dissection of immune responses in the murine models have revealed that Th1 responses are induced at various stages of infection with intestinal nematodes [98–102], and the sequential induction of Th1 followed by Th2 responses is also a well-established fact in schistosome infections [103]. Thus, it is obvious that the stage of infection is likely to play a role with respect to concurrent immune responses during a primary infection. As already mentioned, this has indeed been confirmed to be the case in many animal studies. Importantly, we also know very little regarding the immune response during repeated, trickle or drug-abrogated helminth infections and even less of how such responses may affect concurrent immune responses. The wide, and sometimes completely contradictory, range of results reported from human as well as animal studies clearly suggest that the impact of helminth co-infections on the immune response is far more complicated than we would hope and it is obvious that we are in fact rather limited in our knowledge regarding the interactions between these parasites and the immune system. But our immune system has evolved to combat infections, and helminth parasites, in particular, have co-evolved with it over millions of years, making it unlikely that the presence or absence of helminth infections are the single most important answer to our questions regarding allergies, autoimmunity or other aspects of co-infection. The wide range of results reported from human co-infection studies probably reflect on basic differences in study design, choice of statistics and differences in statistical power, the choice of drugs and intervention strategies as well as the type of assays and other immunological investigations. But it is also clear from animal studies that helminth species, timing and intensity of infections play major roles in the outcome of co-infections, and these factors have only recently begun to be considered in human studies. The potential importance of other factors that may influence immune reactivity during single and co-infections, such as nutritional status, have not yet been considered at all. A degree of publication bias is probably also evident, in particular for the animal models where negative data is, unfortunately, in general not considered very attractive from a publication point of view, and based on the current literature it is easy to get the impression that helminth infections will always, in one way or another, affect the outcome of any concurrent immune response.

So the question remains: are helminths friend or foe? The answer is quite simply that based on the current literature it is not possible to say yet. Some of the key, and to some perhaps controversial, questions that remain to be addressed have been summarized in **Box 1**. It is obvious that at the moment we appear to have generated more questions than we have answered in this field, however, future

Box 1

Some key, and perhaps controversial, variables which will need addressing regarding helminth infections and their effects on concurrent immune responses

Parasitological/biological/medical variables:

- Importance of dose
- Species differences (intestinal vs. tissue, migration vs. no migration)
- Stage of infection (eggs, larvae, adult, acute and chronic)
- Timing of helminth infection in comparison to concurrent infection
- Timing of helminth infection, or the exposure to helminth products, in life (in utero, early childhood, late childhood, adult)
- Frequency of exposure (incl. trickle infections, drug cure and re-infection)
- Cure rate and timing after anthelmintic treatment during intervention studies. Length of follow-up period.
- The complexity of live infection vs. modulation by parasite products
- The longterm effects of “Helminth therapy”
- Possible interactions with nutritional and environmental components
- Unknown genetic factors.

Immunological variables:

- The range of suggested underlying immunological mechanisms (current suggestions: IL-10 or other anti-inflammatory cytokines, Th2-dominated responses, T regulatory cells, alternatively activated macrophages, “modulated” dendritic cells)
- Do we know enough regarding the immunology of single individual helminth infections, in mice and in humans, or do we sometimes extrapolate from “established” dogmas?

Academic variables:

- Unwillingness by authors and/or publishers to publish negative data?
- Study design, choice of statistics.

intervention-based human studies will no doubt provide us with more solid answers regarding public health significance, while animals studies will most certainly provide us with a better molecular and immunological understanding.

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