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Immunological and Molecular Roles of Interleukin 17 Receptor A in Protective Immunity Against Giardia

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Abstract: Interleukin-17 receptor A (IL-17RA) plays an important role in coordinating mucosal immunity against Giardia, an intestinal protozoan parasite that colonizes the small intestine. This review examines the immunological and molecular functions of IL-17RA, emphasizing intestinal gene regulation, immunoglobulin A (IgA) transport, and downstream defense mechanisms. Particular attention is given to receptor-associated signaling, the polymeric immunoglobulin receptor, mannose-binding lectin, and antimicrobial proteins. The distinction between increased expression of defense-related genes and demonstrated antiparasitic activity is essential for interpreting these mechanisms. Host age, intestinal microbiota, epithelial function, and parallel physiological responses further influence the effectiveness of protection. Although human studies support the involvement of IL-17A-producing memory $CD4^+$ T cells, most causal evidence derives from experimental animal models. IL-17RA therefore provides an important framework for understanding how cytokine signaling coordinates intestinal defense against a lumen-dwelling parasite. Further cell-specific investigations and longitudinal human studies are needed to clarify its clinical relevance and potential value in biomarker research and preventive strategies.

Keywords: Giardia; IL-17RA; mucosal immunity; gene expression; immunoglobulin A.

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Introduction

Giardia is a intestinal protozoan parasite with asymptomatic carriage to diarrheal disease, malabsorption and weight loss. Variability of infection is a result of the interaction between parasite characteristics, host resistance and gut environment. These interactions are important to understanding the mechanisms by which some hosts clear infections while others carry them for long periods or suffer with ongoing intestinal dysfunction [1].

Parasite is mainly in the lumen and on the surface of the intestine. Thus, protective immunity requires juxtapositioning responses within the mucosa to those at the luminal interface. This is accomplished by combinations of T cells, antibodies, epithelial products, mast cells, and physiological changes. Transcriptomic studies also show that defense programs for parasites are not distinct but overlap [2]. It has been newly identified that the cytokines Interleukin-17A (IL-17A) and its receptor subunit Interleukin-17RA (IL-17RA) play an important role in this coordinated response. Experimental lack of either the cytokine or the receptor leads to poor parasite clearance, and the

central finding of Paerewijck et al. is that receptor signaling is linked to transcriptional programs in the intestine. This review assesses that evidence, separates data that is direct from that which is extrapolative, and prioritizes translation to giardiasis in humans.The concept of protective immunity needs to be defined according to the outcome in question [3]. The parasite burden decreases, the parasites stop shedding, symptoms improve, and the function of the intestine is restored. This does not necessarily happen at the same time. There might then be a different association between a cytokine involved in clearance and symptoms. This is especially important in the case of giardiasis where host response may play a role in both controlling the parasite and causing intestinal dysfunction. A receptor may even control multiple effector programs without actually coming into contact with the parasite [4]. Therefore, the function of IL-17RA is to convey an immune signal into alterations of the intestinal defense environment. The issue is whether these changes collectively make the habitat less suitable for persistence of the parasites and what are the components that are actually necessary functionally [5].

Immunological and Molecular Basis of Protection

Cellular and humoral foundations of protection

Both singer and Nash have shown using T-cell deficient mouse models that T cells control experimental giardia infection. This does not involve direct killing of trophozoites by T cells. T cells can modulate B cell activity, and regulate epithelial and innate immune function via cytokines [6]. IL-17A-producing responses do not compete with other mechanisms of protection, but rather are part of a broader network of T-cell-dependent protection.Also, using gene-targeted mice, it was demonstrated that IgA plays an important role in anti-Giardia defense. However, there must be a difference in antibody production and delivery. Antibodies generated in tissue need to travel across the epithelium to reach their target as trophozoites are in the luminal compartment. The spatial requirement may be a limiting part of intact humoral immunity.Further studies of infection revealed the involvement of IL-6 and mast cells [7]. There are additional immune–physiologic and immune–biochemical mechanisms, such as adaptive immunity-dependent intestinal hypermotility and epithelial nitric oxide production, which may impact the control of parasites. All these responses are multiply, which is why expression of a single cytokine is not likely to reflect overall protective competence.Giardia specific T cells associate antigen recognition with activation of other compartments. They produce cytokines which can affect cells at the epithelial interface, antibody response cells. Thus, the protective network should be considered as a series of interconnected populations of cells and not as a direct confrontation between a trophozoite and a lymphocyte. This interpretation is in agreement with the luminal localization of Giardia and the known need for T-cell dependent control [8].

Materials and Methods

It also has an extra dimension in the form of human memory responses. Previously detected CD4+ cells which are Giardia responsive also suggest that immune recognition may remain beyond the period of immediate infection. However, in the laboratory response capacity to cytokine stimulation describes laboratory production of cytokines in memory cells, not cytokine levels at the intestinal surface. These two types of measurement are different, and cannot be used interchangeably to answer different questions.

Antimicrobial proteins in the broader intestinal context

In mice, transcriptomic analyses of infected animals indicated several possible effector programs, as well as suggested a concept of functional redundancy. These programs may include the use of antimicrobial proteins, but each such protein should be evaluated for its antimicrobial activity. Hooper et al. have identified microbicidal activities in the angiogenin family. In another parasitic model, the goblet cells were found to be the origin of angiogenin 4 in the large intestine following infection with Trichuris muris. These studies give biological background information, but do not indicate anti-Giardia activity or same intestinal regions regulation.

Single effector experiments can be difficult to interpret if they are functional redundant. Because multiple intestinal products may limit the ability of parasites to survive, removing one of these products may not have a significant impact, as the other products can buffer the impact. Deleting an upstream receptor, on the other hand, may have multiple programs affected and may result in a greater phenotype. Therefore, the lack of a strong phenotypes following IL-17RA knockout would not necessarily argue against the role of IL-17RA in the upstream pathway. How much compensation will be awarded will need to be tested and not assumed.

The microbiota and developmental context

Singer and Nash showed that the susceptibility to Giardia is affected by the intestinal flora in mice. Maertens et al. then compared antibiotic treated and non-treated animals to study the effect of the microbiota on the response. The authors report that induction of certain immune markers can continue even in the absence of protection in a dysregulated microbial niche. The expression of cytokines should therefore be considered in the context of the ecological niche in which the response is expressed.

There are others modifiers like host age. In neonatal mice, Paerewijck et al., reported that intestinal responses to parasite challenge required IL-17A, Mbl2 and protective immunity to respond to parasites, involving IL-17A. These observations justify investigation of age-dependent immunity but cannot be directly correlated with childhood disease. In separate experiments, the role of immunity in the intestinal disaccharidase defect was found to be a possible factor. The clearance and recovery of parasites are, therefore, linked but not synonymous results.

The microbiota may be an environmental condition and a contributing factor to the immune response. Modifies the surroundings for the parasite and the cells reacting to infection. The added complexity of antibiotic-induced changes is due to the fact that multiple intestinal functions may be affected by microbial depletion. Consequently, a difference in parasite burden due to antibiotic treatment can not be simply explained by a single immune mediator, unless further experiments are conducted.

Comparisons must be developed in a similar fashion. All of these are dynamic and evolve together in early life. The late onset of protective responses that is seen in neonatal mice therefore represents a biological pattern of aging, but the relative importance of these interacting factors remains unelucidated. For humans, this developmental context can only be represented by age alone in studies. Useful accompanying variables to investigate are nutritional status and recent antimicrobial exposure.

Receptor composition and intracellular signaling

IL-17A is communicating through a receptor complex, which consists of IL-17RA and IL-17RC. Through basic cellular research, ACT1 was found to be a key receptor-associated adaptor. ACT1 is recruited and interacts with signalling proteins like TRAF6 and is connected to the pathways involving NF-kappa B and mitogen-activated proteins. It has E3 ubiquitin ligase activity involved in IL-17 dependent signaling organization.

The experiments reported here illustrate how extracellular (outside the cell) recognition of cytokines can turn on or off intracellular (within the cell) control of genes. However, the ACT1-TRAF6 sequence was not specifically mapped in all cell subsets in the central Giardia study. Furthermore, IL-17RA is involved in other receptor complexes and a lack of IL-17RA is not the same as absence of IL-17A. Extra consequences of receptor deletion should be interpreted.

A differentiation between the availability and competences of cytokine receptors is crucial. A tissue might have an abnormal receptor complex or machinery for the IL-17A receptor, even though it has IL-17A. On the other hand, the expression of receptors does not show active signaling. Thus, a combination of ligand measurements, localization of the receptor, downstream molecular readouts and functional outcomes are all helpful in interpreting activity on a pathway.

The SEFIR present in the receptor–adaptor interface provides a molecular explanation for ACT1 recruitment. Signaling interactions are then activated and this affects transcriptional responses, mediated by ACT1. This demonstrates that the lack of a signaling adaptor has effects beyond merely a change in the level of the cytokines. These interactions, however, have not been shown in general cellular systems in order to establish the relative importance of these interactions in intestinal cells infected with Giardia. This connection has to be filled in with tissue-specific experiments.

The same is true if the animals are receptor deficient. The IL-17RA deletion has a biological effect of the inability of the organism to signal through a common receptor component across the entire organism. The global effect needs to be compared to cytokine-specific interventions and, if applicable, restoration experiments to differentiate its contribution from the specific effect of IL-17A.

Results

IgA transport and the polymeric immunoglobulin receptor

Polymeric immunoglobulin receptor (pIgR) is involved in transport of polymeric immunoglobulins in epithelia. The expression level makes it possible to link immune activation of the mucosa with antibody availability in the intestinal lumen. A central study correlated the expression of pIgR with IL-17RA signaling. The fecal IgA was also significantly lower in IL-17A deficient animals in experimental infections as shown by Dann et al **[9]**.

In intestinal immune-homeostasis models, Cao et al. demonstrated that IL-17 responses via Th17 increase the expression of pIgR and promote intestinal IgA responses. These two findings corroborate the conclusion that IL-17 signaling contributes to the localization of antibody defenses to the site of luminal infections. Establishing the efficacy of this transport process in the absence of serum IgA does not prove efficacy of this transport process, and measurements of antibodies in serum cannot be considered to be equivalent to measurements of antibody delivery in the mucosa **[10]**.

The pIgR pathway is an example of how localization is important in immunity. A good response needs to be coordinated on the tissue side with the availability of antibody on the other side—across the epithelial barrier. If there is some antibody production, failure at the transport stage may result in diminished luminal protection. As a result, studies that evaluate just serum levels of immunoglobulins can miss an important functional limitation **[11]**.

IgA against parasites and the total level of IgA should also be differentiated. The total concentration is a broad mucosal product, and antigen-specific concentrations better quantify antigen-specific recognition of Giardia. Both measurements are not indicative of neutralization/parasite elimination. However, if they were used in conjunction with pIgR expression, parasite burden and timing of infection, a more informative picture of the proposed IL-17RA–IgA relationship would be achieved **[12]**.

Angiogenin 4 and the limits of transcriptional inference

Increased expression of Ang4 was found during infection, and the protein was detected in small-intestinal Paneth cells, in the central study. When tested under the conditions used, the viability of G. duodenalis trophozoites was not directly inhibited up to 100 micromolar (μM) of the recombinant Ang4. This is especially important because this classification of the drug as an antimicrobial may result in the unqualified assumption that the ability to kill the trophozoite **[13]**.

The results do not provide direct anti-Giardia activity data, but rather provide information about induction and localization. Only hypotheses are made about the indirect effects on the microbial environment or on tissue responses. However, an expression signal should be considered as a possible functional link until perturbation experiments are performed and related to parasite load or intestinal health **[14]**.

There is a definite scope for negative direct-killing assays. It indicates that neither the concentration nor the assay system tested and the duration of exposure resulted in a decrease in the

viability of trophozoites in the sample tested. It does not prove that there is no biological function for the protein in the infected intestine. Similarly, possible indirect functions are not to be provided as examples of explanations **[15]**. To improve the functional interpretation in the future, it would be beneficial to see if changing Ang4 activity affects in vivo infection and if this effect is independent of changes in the microbiota. Ang4 is a candidate for an effector, although it has not been proven to directly act on Giardia, it has been found linked to the receptor. This will keep the biological interest of the finding without overemphasizing the mechanism **[16]**.

Mannose-binding lectin and complement-associated responses

It was noted that the gene for mannose binding lectin (Mbl2) is regulated by IL-17RA, and that it codes for the mannose-binding lectin that is involved in innate recognition and the lectin complement pathway. This was the subject of additional experiments in the middle study where protein assay, binding-related assays and genetically engineered mice were used. Results include an extension of the receptor-associated response to innate recognition systems, and adaptive immune communication **[17]**.

But the higher level of Mbl2 transcript does not create an effective complement mediated activity on the surface of the parasite. There are 3 tiers of evidence: recognition, pathway activation and measurable infection impact. The difference is needed in the construction of a molecular model of protection **[18]**.

The same applies for complement associated molecules, as well. Linking a recognition factor to a target is not sufficient to complete a downstream effector cascade. The nature of the recognition (whether it is functionally consequential) depends on the availability of interacting components and conditions at the mucosal interface. Therefore, the level of expression of Mbl2 provides clues to the regulation of the pathway, but should be considered alongside functional evidence **[19]**.

Barrier regulation and circadian responses

Independent intestinal experiments demonstrate that IL-17 has a role in promoting epithelial barrier function, which is not IL-23 dependent . The observations do not exclude the possibility of studying barrier related effects in giardiasis, but they do not mean that all mechanisms are identical with giardiasis. Similarly, in inflammatory models, IL-17-producing subsets are regulated by IL-23, but this does not necessarily imply the necessity of IL-23 in the case of Giardia infection **[20]**.

Discussion

A central transcriptomic study also revealed the modifications of circadian related genes such as Per1, Per2, and Per3 **[21]**. Further sampling at a single time of day eliminated the confounding effect of the normal daily variation. Circadian regulation of host responses to Salmonella was also independently shown by Bellet et al. However, the importance of these changes in the clock genes in Giardia has not been determined and requires experiments that link these changes with immunity, motility, or persistence of the parasite **[22]**.

Barrier maintenance and parasite elimination can support each other, and neither of these can be surmised based on a cytokine profile alone. A more complete evaluation would include a tissue function and epithelial permeability evaluation as well as a parasite count. With other intestinal models, evidence of a role of IL-17 in maintaining barrier integrity provides a plausible basis for this question, and it remains to be tested directly in giardiasis **[23]**.

The additional requirement for study standardization is added by circadian observations. If the expression fluctuates naturally throughout the day, the sampling schedules may affect apparent differences in infected and control groups. This is partly overcome by the fixed-time validation in the central study **[24]**. Changes in the amplitude, time or significance of the daily rhythms due to infection will need repeated sampling, not just one measurement. The discovery of Salmonella confirms the greater biological plausibility of this question, but does not confirm a solved Giardia mechanism **[25]**.

Parallel physiological mechanisms

Intestinal hypermotility contributes to anti-Giardia defense, while mast cells influence smooth muscle contractility during infection. Yet these mechanisms cannot automatically be positioned downstream of IL-17RA. Dann et al. reported that IL-17A loss did not disrupt infection-associated intestinal hypermotility in their model. The evidence therefore supports parallel protective pathways, with their relative contributions varying across experimental settings [26].

Limitations of the Available Evidence

The deletion of receptors is defined as global, and as such affects several interacting compartments and is not a reflection of what the critical responding cell is **[27]**. The signals from heterogeneous populations are also combined when using whole-tissue RNAseq. Cell-specific deletion, immune-cell separation, spatial analysis or single-cell approaches would help to elucidate if expression changes are due to the changes in the cell number or due to changes in cellular activity.

The whole process of infection can't be reflected in the snapshots of experiments, and the early recognition, maximal response and recovery may follow different paths. All of these are required for other processes such as valid differential-expression estimation, appropriate quantification of sequence-features, accurate mapping of the transcriptome, and interpretation of molecular evidence **[28]**. One of the major challenges of quantitative PCR is the use of reference genes and the need to be mindful of the assumptions for normalization and amplification. Analytical robustness contributes to the strength of the measurements of molecules, but does not establish biological causation.

There are limitations to this review. It is a selective synthesis focussed on key publications and not an extensive systematic review. It does not have a pooled effect size and it does not have mechanistic work from other infections unless qualified by the relevance of the mechanistic work. There is a large amount of animal evidence and a relatively small amount of recent direct clinical inference, so there is a limit on the amount of direct clinical inference used.

Priorities for further investigation

Conclusions

IL-17RA is involved in protective immunity against Giardia, regulates gut response mechanisms such as antibody transport, antimicrobial programs and innate recognition. The results of the central transcriptomic study add to those of the pathway dependence study, investigating candidate molecular mechanisms, and the results of the Ang4 study underscore the caution needed when interpreting the relationship between transcriptional induction and direct antiparasitic activity. Studies in humans support the involvement of IL-17A, but few studies have evidence of causality. Human longitudinal studies and validation of the functional aspects in cell specific are therefore required for clinical interpretation.

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