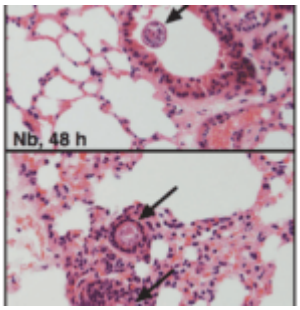
Intestinal helminth co-infection promotes control against lung migrating parasites



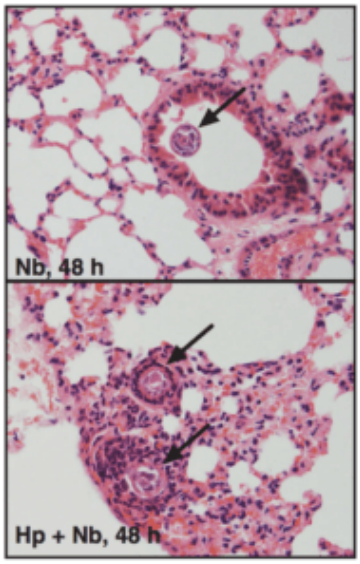


Figure 1d: Representative H&E stained sections of lung from 48 h post Nb infection. Cross-sections of larvae are indicated with an arrow. Filbey *et al.*, 2018

Helminth co-infection has ben shown to have a negative effect on immune-mediated control of bacterial and viral infection. However, some studies have shown that helminth co-infection may have beneficial outcome against other helminth infections. Filbey et al., aimed to determine how chronic *Heligmosomoides polygyrus* (*Hp*) gastrointestinal infection can influence systemic and localised immunity against other helminth infections. Researchers utilised *Nippostrongylus brasiliensis* (*Nb*) as the other helminth infection, as Nb infection is acute, beginning with entry through skin followed by a larvael stage in the lung then a mature (adult) gastrointestinal stage to allow expulsion of the parasite. Thus researchers, were able to interrogate both local and systemic *Hp* cross-protection.

Using B and T cell deficient mice, and monoclonal depletion of either antibodies (IgG) or T cells, researchers showed that *Hp*-mediated cross-protection against *Nb* requires T cells. This protection was attributed to secretion of IL-5 by CD4 T cells. IL-5 is the major differentiation, maturation and accumulation factor of eosinophils. Filbey et al., demonstrated increased eosinophil recruitment to the lungs of *Hp-Nb* coinfected mice, which was also associated with successful cross-protection against *Nb*. Interestingly IL-5 secretion by CD4 T cells was only induced in the presence of active *Nb* infection, thus researchers aimed to determine the mechanistic induction of IL-5 in *Hp-Nb* co-infected mice.

Studies have shown that the alarmin IL-33 is rapidly produced after *Nb* infection. IL-33 is important for induction of type 2 immune responses, and has also been shown to induce IL-5 expression in the lung. Using both *in vivo* and *in vitro* experiments, researchers showed that *Hp-Nb* co-infection results in significantly higher IL-33 induction than both *Hp* and *Nb* only infections. IL-33 directly via its receptor ST2 results in significant induction of IL-5, which provides protection against *Nb* during co-infection. This finding was

further confirmed to occur in an antigen-independent manner, where *in vitro* recombinant IL-33 treatment CD4 T cells, also resulted in lower *Nb* burden when transferred to naïve mice. Finally researchers showed that the cross-protection is not limited to *Hp*, but can also be conferred by other gastrointestinal helminths such as *T. muris*.

In conclusion, this elegant study demonstrated the chronic gastrointestinal infection with *Hp* (or *T.muris*) confers a cross-mucosal systemic protection against *Nb* infection. By limiting the dissemination of *Nb* from the lung to the the gastrointestinal tract. This protection was mediated by IL-33 activation of CD4 T cells to produce IL-5 which in turn mediated eosinophil-dependent larvae killing.

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