Untangling the role of eosinophils in trichinellosis: a never ending story

Fabrizio Bruschi
Dipartimento di Patologia Sperimentale, B.M.I.E.
Scuola Medica
Università di Pisa
Via Roma, 55
56126 Pisa Italy
E-mail address: bruschi@med.unipi.it

{848 words}
The role of eosinophils in inflammatory responses has long remained unknown. In the 1970s, *in vitro* models demonstrated their potential effector functions against different migrant stages of helminth parasites (including *Schistosoma mansoni* schistosomula, *Trichinella spiralis* newborn larvae (NBL) and *Onchocerca volvulus* microfilariae) [1].

Peripheral blood and tissue eosinophilia, as well as increased total IgE levels, are typical of human trichinellosis and of other helminth infections. Both processes are the consequence of T helper cell type 2 (Th2) activation [2].

After ingestion by a susceptible host, the larvae (L1) of the parasitic nematode *Trichinella spiralis* reach the intestine, where they mature into adult worms. After 4–6 days, these adult worms release (NBL) that pass through the intestinal mucosa and enter the lymph, and then the blood, from which they extravasate to invade the skeletal muscle fibres. After invasion, these fibres acquire a new phenotype known as the ‘nurse cell’ [3].

There is no doubt that, in both animal and human models, eosinophils can adhere to and kill *Trichinella spiralis* NBL *in vitro*, via antibody-dependent cellular cytotoxicity ADCC [4,5]. Several eosinophil-derived molecules (such as major basic protein, eosinophil cationic protein, eosinophil peroxidase, eosinophil-derived neurotoxin) are responsible for the cytotoxic effect. However, the role of these cells in host defense against *T. spiralis, in vivo*, has been a matter of debate [2].

A recent review on eosinophils and *Trichinella* [2], stated that the ‘discrepancy of the role of eosinophils in protection might be due to the mouse strains, the stages of the parasites and/or the experimental models used’.

For example, in interleukin (IL)-5-deficient mice, IL-5 transgenic mice, or in mice depleted of eosinophils after treatment with specific monoclonal antibodies (mAbs) the worm burden during a primary infection was found to be moderately higher, or unchanged, compared to control animals [6–8]. More recently, mice deficient in CCR3 (one of the receptors for several eosinophil chemokines, constitutively present on the surface of eosinophils, together with CCR1), failing to recruit eosinophils to the nurse cell–parasite complex, after infection with *T. spiralis*, showed an
increase in the number of cysts and a reduction in necrotic nurse cells in histological sections of
tongue, compared to wild-type animals [9], supporting a conclusion that eosinophils function in
host defense against muscle-stage *T. spiralis*. The recruitment of eosinophils in response to
chemokines such as eotaxin-1 (CCL11), for example, seems to play a relevant role also at mucosal
level [10].

In a recent paper, Fabre et al. [11] studied *T. spiralis* infection in two models of eosinophil ablation:
(i) mice bearing a deletion of the high-affinity double GATA site in the GATA-1 promoter (Δdbl-
GATA−/−), where the eosinophil differentiation is blocked; and (ii) eosinophil peroxidase diphtheria
toxin transgenic mice (PHIL). PHIL mice were engineered to incorporate a coding sequence for the
diphtheria toxin A chain in the eosinophil peroxidase locus.

Infiltrates surrounding infected muscle cells of wild-type mice were particularly rich in eosinophils,
and eosinophils were (as expected) completely absent in the blood and skeletal muscles of
genetically modified mice; surprisingly, however, *T. spiralis* muscle larvae died in large numbers,
with significant reduction of larvae recovered from both animal models (67–77% reduction in PHIL
mice, and 48% in Δdbl-GATA−/− mice). Reduction in the parasite burden correlated with enhanced
Th1 response (as shown by increased levels of IFN-γ in lymph node cell cultures) and
downregulated Th2 response (decreased IL-4 levels). By blocking inducible nitric oxide (NO)
synthase (iNOS) with specific inhibitors, Fabre et al. observed improved larval survival, implicating
NO production in parasite destruction. In double deficient IL-10−−/−/PHIL mice, there was a dramatic
reduction in the larval burden (93%), compared with mice deficient only in IL-10. Furthermore,
when these animals were treated with the iNOS inhibitor, in both IL-10+/− or IL-10−−/−/PHIL mice, the
production of NO resulted lower in lymph node cell cultures, and larval improved survival. These
results show that the destruction of muscle larvae is driven by Th1 response, which is down
regulated by eosinophils. According to the results of the Fabre’s paper eosinophils have a role of
regulatory cells in immune response to parasites, as already described in allergic disease [1]. The
results suggest that the parasite induces eosinophilia to protect itself.
This is just a new episode of the never-ending story regarding the understanding of the \textit{in vivo} role of eosinophils versus helminth parasites, in particular \textit{Trichinella}.

Two lessons can be learnt, however, from this recent paper: (i) experimental infection with \textit{Trichinella} is more complex than those with other helminths, due to the important interaction of host cells with the parasite, at muscular level and (ii) infection in genetically modified animals has drawn completely opposite conclusions (eosinophils resulted host protective using CCR3 deficient mice where eosinophils, although present, are unable to extravasate to inflammation site and parasite protective when infection was carried out in \textit{Δdbl-GATA} \textsuperscript{-} mice which completely lack eosinophils).

Which is the truth, it is difficult to say, it is to note that in trichinellosis patients, however, a sudden fall in eosinophil levels is considered a sign of a bad prognosis, this would suggest an \textit{in vivo} host-protective role of these effector cells [2].
References