

# Worms tame mast cells

Edward J Pearce

**A protein produced by parasitic roundworms that inhibits the inflammatory response is shown to prevent mast cell activation. The protein could potentially be used for the management of allergies and asthma (pages 1375–1381).**

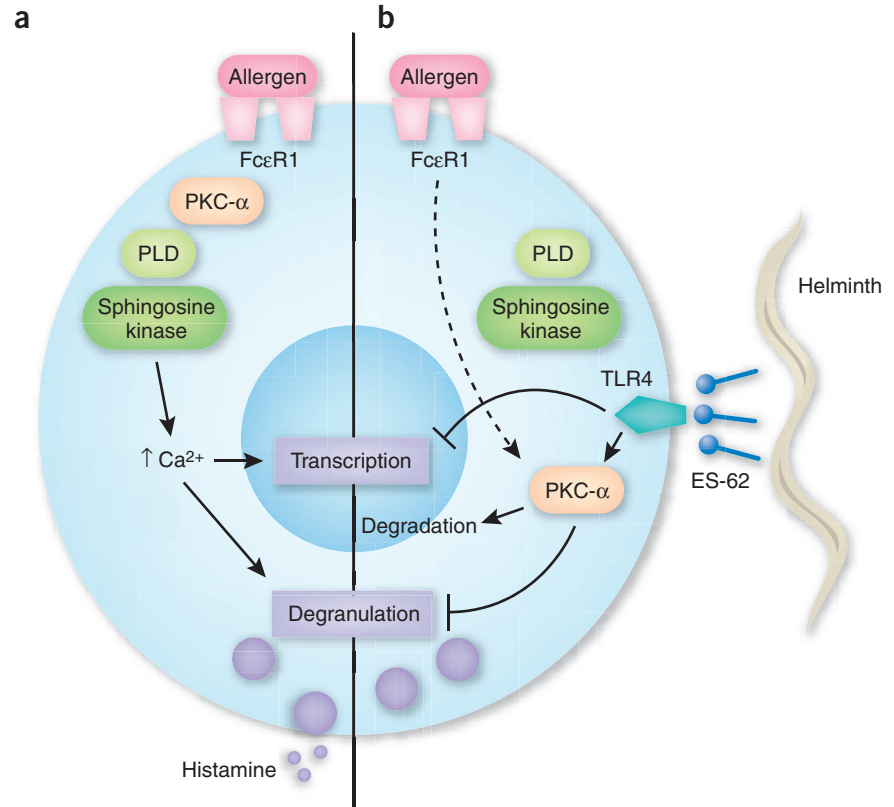
Helminth nematodes are incredibly successful pathogens, afflicting billions of people and causing such 'neglected' tropical diseases as elephantiasis and river blindness. Chronic infections require a fine-tuned host-parasite relationship if both parties are to survive and reproduce. In this dynamic, the parasites produce anti-inflammatory mediators to maintain a permissive environment. The best-studied helminth-derived immune response modulator is ES-62 (ref. 1), a protein made by filarial nematodes.

In the hosts, helminths appear to have provided the evolutionary pressure to generate a major branch of the mammalian immune response—so-called 'type 2 immunity'. Type 2 immunity involves the actions of several cell types, including eosinophils, basophils and T cells, to generate the cytokines that are important for immunity to parasitic helminths, such as interleukin (IL)-4 and IL-13 (ref. 2).

In developed countries, where worm infections are rare, type 2 immunity now frequently manifests itself as the underlying cause of allergies, asthma and certain inflammatory conditions, such as ulcerative colitis. People with helminth infections are less likely to suffer from these disease states, giving rise to the 'hygiene hypothesis' of allergies<sup>3,4</sup>.

Understanding how helminth infections protect people from these inflammatory disorders is of great interest to researchers wanting to develop new therapeutic approaches. In this issue of *Nature Medicine*, Melendez *et al.*<sup>5</sup> describe a mechanism that may underlie this effect: nematode-made ES-62 inhibits the activation of mast cells, preventing allergic inflammation.

Mast cells are bone marrow-derived immune cells that monitor the environment and mobilize immune responses after exposure to antigens<sup>6</sup>. They are found throughout the body and are often associated with epithelial surfaces, which constitute the body's inside-outside interface. Mast cells express



**Figure 1** ES-62, a secreted phosphorylcholine-containing glycoprotein from a parasitic helminth, inhibits FcεR1-initiated mast cell activation. (a) Normally, PKC-α couples FcεR1 to a pathway that results in increased calcium concentration and cell activation. (b) In the presence of ES-62, which binds TLR4, PKC-α is sequestered away from FcεR1 (dashed arrow) and targeted for degradation, and thus key mast cell activities are blocked.

Toll-like receptors (TLRs), which allow them to detect and respond to potentially dangerous situations, such as bacterial infection. They also express high-affinity receptors for antibodies, specifically FcεR1, which allows mast cells to bind the IgE antibodies that are made preferentially during type 2 immune responses.

When so armed, mast cells can respond with the antigenic specificity of the surface-bound IgE. Upon encountering antigen, FcεR1 is cross-linked, which causes the mast cell to degranulate, releasing an array of mediators that includes histamine, the well-known cause of many allergic symptoms. In fact, the acute symptoms associated with allergic pathologies largely result from the degranulation of mast cells.

ES-62, a phosphorylcholine-containing glycoprotein secreted by filarial nematodes, can inhibit the activation of a variety of immune cells, including B and T lymphocytes, dendritic cells and macrophages<sup>7</sup>. Melendez *et al.*<sup>5</sup> reasoned that ES-62 might be equally effective against mast cells and could be used to prevent allergic reactions.

They first tested whether ES-62 prevented mast cell activation. FcεR1 cross-linking initiates mast cell degranulation through the activation of phospholipase-Cγ, which leads to sustained increases in cytoplasmic calcium concentrations and to the activation of protein kinase C (PKC)<sup>8</sup> (Fig. 1). When the authors exposed mast cells to ES-62 at concentrations equivalent to those measured in the bloodstreams of filaria-infected humans,

Edward J. Pearce is in the Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, 380 South University Ave., Philadelphia, Pennsylvania 19104, USA. e-mail: ejpearce@mail.med.upenn.edu

Kim Caesar

FcεRI cross-linking did not trigger degranulation<sup>5</sup>. The authors noted that the phospholipase-Cγ signaling pathway was activated as expected, prompting them to examine a secondary calcium release pathway that is phospholipase-Cγ independent.

This second pathway, which involves phospholipase D and sphingosine kinase, induces a transient early calcium flux after FcεRI ligation. Melendez *et al.*<sup>5</sup> found that neither of these enzymes were activated after FcεRI cross-linking in the presence of ES-62. In monocytes, PKC-α couples phospholipase D to FcR signaling<sup>9</sup>. By using antisense RNA to lower the expression of PKC-α in mast cells, the authors showed that the sphingosine kinase pathway has a crucial role in FcεRI-triggered activation<sup>5</sup>. The authors found that PKC-α regulates the release of the pre-formed mediators such as histamine, and also the production of late-response components such as leukotrienes, prostaglandins and several proinflammatory cytokines<sup>5</sup>. These findings emphasize a previously underappreciated role for PKC-α in mast cell activation.

Melendez *et al.*<sup>5</sup> then looked into how ES-62 represses this alternative calcium release cascade and, consequently, inflammation. Previous experiments from the Harnett's laboratories showed that the receptor for ES-62 is TLR4, the innate receptor for the bacterial cell-wall component lipopolysaccharide. In this new study, the authors show that ES-62 signals through TLR4 to prevent FcεRI-initiated mast cell signaling. Melendez *et al.*<sup>5</sup> observed internalized ES-62–TLR4 complexes that recruit large amounts of PKC-α,

thereby reducing the availability of this enzyme for FcεRI signaling<sup>5</sup>. Importantly, the interaction between lipopolysaccharide and TLR4 did not recruit PKC-α and did not inhibit FcεRI-triggered signaling.

Thus, ES-62 manipulates TLR4 to sequester a key signaling intermediate, PKC-α, away from the FcεRI pathway, preventing degranulation (Fig. 1). PKC-α activity is further repressed because the interaction with the ES-62-bound TLR4 marks PKC-α for degradation in a little-studied perinuclear degradation site<sup>10</sup>. It remains unclear whether ES-62's modulatory roles in other immune cells involve processes fundamentally similar to those at work in mast cells.

Melendez *et al.*<sup>5</sup> concluded their study with a hint that this helminth-derived protein might lead to the development of real-world therapeutics for allergies and asthma. They showed that ES-62 can prevent mast cell-dependent cutaneous and pulmonary allergic reactions *in vivo*. As the authors point out, with regard to its potential as a candidate for a drug base, ES-62 has in its favor the fact that the millions of people who are infected with filarial worms tolerate them for years on end—which is exactly what is needed in a drug intended for the ongoing treatment of a chronic condition such as asthma. From previous work, it appears that many of ES-62's immunomodulatory properties are dependent on phosphorylcholine<sup>1</sup>. New therapeutics may be derived from this small compound, which already forms a base for several medically relevant products, from contact lens solutions to the new antileishmanial drug miltefosine.

In contrast to what we now know about the effects of ES-62 on mast cells, we know little about what ES-62 does for the parasites that make it. That its sole role is to allow the parasite to regulate host immunity is an assumption. The implication would be that filarial worms unable to produce ES-62-like molecules would induce unusually serious inflammation, perhaps resulting in either eradication of the infection or acutely lethal disease. Either of these situations would be less than optimal for the parasite, and both such outcomes have been observed in other types of helminth infections in which host, rather than parasite, immunoregulatory mechanisms are compromised<sup>11,12</sup>. Recent developments in the application of RNAi in filarial nematodes<sup>13</sup> indicate that these exciting issues may soon be investigated *in vivo*.

1. Harnett, W. & Harnett, M.M. *Clin. Exp. Pharmacol. Physiol.* **33**, 511–518 (2006).
2. Voehringer, D., Shinkai, K. & Locksley, R.M. *Immunity* **20**, 267–277 (2004).
3. Smits, H.H. & Yazdanbakhsh, M. *Ann. Med.* **39**, 428–439 (2007).
4. Zaccane, P., Fehervari, Z., Phillips, J.M., Dunne, D.W. & Cooke, A. *Parasite Immunol.* **28**, 515–523 (2006).
5. Melendez, A.J. *et al. Nat. Med.* **13**, 1375–1381 (2007).
6. Galli, S.J. *et al. Annu. Rev. Immunol.* **23**, 749–786 (2005).
7. Harnett, W., Goodridge, H.S. & Harnett, M.M. *Parasitology* **130** Suppl., S63–S68 (2005).
8. Gilfillan, A.M. & Tkaczyk, C. *Nat. Rev. Immunol.* **6**, 218–230 (2006).
9. Melendez, A.J. & Khaw, A.K. *J. Biol. Chem.* **277**, 17255–17262 (2002).
10. Leontieva, O.V. & Black, J.D. *J. Biol. Chem.* **279**, 5788–5801 (2004).
11. Hoffmann, K.F., Cheever, A.W. & Wynn, T.A. *J. Immunol.* **164**, 6406–6416 (2000).
12. Taylor, M.D. *et al. J. Immunol.* **174**, 4924–4933 (2005).
13. Pfarr, K., Heider, U. & Hoerauf, A. *Int. J. Parasitol.* **36**, 661–669 (2006).

## A MSC-ing link in metastasis?

Douglas R Hurst & Danny R Welch

**Mesenchymal stem cells promote the dissemination of neoplastic cells in a mouse model of breast cancer. The findings sound a cautionary note for anticancer therapies that rely on these cells and provoke a re-evaluation of how metastases form.**

Metastases are derived from distinct subpopulations of cells that exist within a tumor. In a classic example, the melanoma cell subtype B16 can be selected from a primary

tumor and enriched for an increased tendency to colonize lung<sup>1</sup>. Tumor cell behavior, however, is often remarkably plastic. The cells have some properties reminiscent of those of cells undergoing epithelial-mesenchymal transition (EMT), a normal developmental process in which embryonic cells temporarily disrupt tissue architecture by disassembling junctional structures, and then expressing mesenchymal proteins and migrating<sup>2</sup>. It has been hypothesized that in

cancers, EMT confers motility by changing cell-cell interactions and adhesive characteristics.

Some researchers have put forward the idea that the EMT pathway is usurped by tumor cell populations so that they become transiently metastatic<sup>3</sup>. A recent study in *Nature* by Weinberg and colleagues supports another possible mechanism: mesenchymal stem cells within a primary tumor might elicit a transient enhancement of metastasis<sup>4</sup>.

Danny R. Welch is Leonard H. Robinson Professor and Douglas R. Hurst is an investigator in the Department of Pathology at the University of Alabama at Birmingham, 1670 University Blvd. VH-G019A, Birmingham, Alabama 35294-0019, USA. e-mail: danwelch@uab.edu