Leishmania RNA Virus Controls the Severity of Mucocutaneous Leishmaniasis

Annette Ives, *et al.*

Science **331**, 775 (2011);
DOI: 10.1126/science.1199326

6. F. I. M. Craik, E. Tulving, *J. Exp. Psychol. Gen.* **104**, 268 (1975).
7. J. D. Karpicke, H. L. Roediger, *Science* **319**, 966 (2008).
8. H. L. Roediger, J. D. Karpicke, *Psychol. Sci.* **17**, 249 (2006).
9. S. K. Carpenter, H. Pashler, *Psychon. Bull. Rev.* **14**, 474 (2007).
10. H. Pashler, D. Rohrer, N. J. Cepeda, S. K. Carpenter, *Psychon. Bull. Rev.* **14**, 187 (2007).
11. M. A. Pyc, K. A. Rawson, *J. Mem. Lang.* **60**, 437 (2009).
12. For a review, see (*28*).
13. See (*29*) and (*30*), however.
14. L. W. Anderson *et al*., *A Taxonomy for Learning, Teaching, and Assessing: A Revision of Bloom's Taxonomy of Educational Objectives* (Longman, New York, 2000).
15. R. E. Mayer, *Learning and Instruction* (Prentice Hall, Upper Saddle River, NJ, 2008).
16. J. D. Novak, D. B. Gowin, *Learning How to Learn* (Cambridge Univ. Press, New York, 1984).
17. J. D. Novak, *Res. Sci. Educ.* **35**, 23 (2005).
18. J. C. Nesbit, O. O. Adesope, *Rev. Educ. Res.* **76**, 413 (2006).
19. Materials, methods, and additional results are available as supporting material on *Science* Online.
20. J. Dunlosky, J. Metcalfe, *Metacognition* (Sage, Thousand Oaks, CA, 2009).
21. M. A. McDaniel, G. O. Einstein, *Educ. Psychol. Rev.* **1**, 113 (1989).
22. L. K. Cook, R. E. Mayer, *J. Ed. Psy.* **80**, 448 (1988).
23. J. G. W. Raaijmakers, R. M. Shiffrin, *Psy. Rev* **88**, 93 (1981).
24. R. R. Hunt, M. A. McDaniel, *J. Mem. Lang.* **32**, 421 (1993).
25. J. S. Nairne, *Memory* **10**, 389 (2002).
26. J. S. Nairne, in *Distinctiveness and Memory*, R. R. Hunt, J. Worthen, Eds. (Oxford Univ. Press, New York, 2006), pp. 27–46.
27. J. D. Karpicke, F. M. Zaromb, *J. Mem. Lang.* **62**, 227 (2010).
28. H. L. Roediger, J. D. Karpicke, *Perspect. Psychol. Sci.* **1**, 181 (2006).
29. J. D. Karpicke, H. L. Roediger, *Mem. Cognit.* **38**, 116 (2010).
30. M. A. McDaniel, D. C. Howard, G. O. Einstein, *Psychol. Sci.* **20**, 516 (2009).

31. This research was supported by a grant from the National Science Foundation (0941170). We thank C. Ballas, B. Byrer, H. Cannon, and B. Etchison for help with this research.

Supporting Online Material

www.sciencemag.org/cgi/content/full/science.1199327/DC1
Materials and Methods
Fig. S1
Table S1
References

20 October 2010; accepted 10 January 2011
Published online 20 January 2011;
10.1126/science.1199327

Leishmania RNA Virus Controls the Severity of Mucocutaneous Leishmaniasis

Annette Ives,[1] Catherine Ronet,[1] Florence Prevel,[1] Giulia Ruzzante,[1] Silvia Fuertes-Marraco,[1] Frederic Schutz,[2] Haroun Zangger,[1] Melanie Revaz-Breton,[1]* Lon-Fye Lye,[3] Suzanne M. Hickerson,[3] Stephen M. Beverley,[3] Hans Acha-Orbea,[1] Pascal Launois,[4] Nicolas Fasel,[1]† Slavica Masina[1]

Mucocutaneous leishmaniasis is caused by infections with intracellular parasites of the *Leishmania Viannia* subgenus, including *Leishmania guyanensis*. The pathology develops after parasite dissemination to nasopharyngeal tissues, where destructive metastatic lesions form with chronic inflammation. Currently, the mechanisms involved in lesion development are poorly understood. Here we show that metastasizing parasites have a high *Leishmania RNA virus*–1 (LRV1) burden that is recognized by the host Toll-like receptor 3 (TLR3) to induce proinflammatory cytokines and chemokines. Paradoxically, these TLR3-mediated immune responses rendered mice more susceptible to infection, and the animals developed an increased footpad swelling and parasitemia. Thus, LRV1 in the metastasizing parasites subverted the host immune response to *Leishmania* and promoted parasite persistence.

Leishmania parasites are obligate intracellular protozoan parasites transmitted to the mammalian host by the bite of an infected sand fly, where they predominantly infect macrophages. In Latin America, leishmaniasis caused by the *Leishmania Viannia* (*L.Viannia*) subgenus is endemic, causing cutaneous (CL) and mucocutaneous (MCL) leishmaniasis (*1*). Clinical MCL involves parasitic dissemination to the nasopharyngeal areas of the face, leading to destructive metastatic secondary lesions and hyperinflammatory immune responses (*2*–*4*). About 5 to 10% of individuals asymptomatic or with resolved CL lesions may develop MCL (*1*, *5*, *6*).

MCL development is associated with persistent immune responses showing proinflammatory mediator expression with high tumor necrosis factor α (TNF-α), CXCL10, and CCL4; a mixed intralesional T helper 1 (T_H1)/T_H2 phenotype; and elevated cytotoxic T cell activity (*7*–*10*). In addition to parasite-derived virulence factors, host genetics [such as polymorphisms for TNF-α and interleukin-6 (IL-6)] and immune status appear to influence MCL development (*11*, *12*).

Hamsters infected with *L.Viannia* parasites isolated from human MCL lesions reproduce the metastatic phenotype with primary and secondary lesion development (*13*). Using this model, we characterized clones derived from the metastasizing *L.guyanensis* WHI/BR/78/M5313-*L.g.*M5313(M+) strain as metastatic (*L.g.*M+) or nonmetastatic (*L.g.*M−) after infection, depending on their ability to reproducibly develop secondary metastatic lesions (*14*). Previously, we showed that *L.g.*M+ clones derived from *L.g.*M5313 were more resistant to oxidative stress than *L.g.*M− clones and persisted in activated murine bone-marrow–derived macrophages despite their elevated nitric oxide levels (*15*).

On the basis of these observations, we hypothesized that *Lg.*M+ and *L.g.*M− parasites differentially modulate the host macrophage responses. Using DNA microarrays, we identified differential gene expression between uninfected macrophages and *L.g.*M+ (1672) or *L.g.*M− (1513) infected macrophages, and *L.g.*M− directly compared to *L.g.*M+ (294) infected macrophages. Statistical significance was determined at ≥1.5-fold, $P \leq 0.05$. We focused on genes involved in the immune response because of their relevance in MCL pathology.

In vitro, infected macrophages expressed significantly greater amounts of chemokines and cytokines CCL5, CXCL10, TNF-α, and IL-6 after infection with *L.g.*M+ parasites compared with *L.g.*M− parasites or *L. major* LV39 (Fig. 1, A and B) (*16*). We observed similar increased cytokine and chemokine expression after infection with *L.g.* from human MCL lesions (h-MCL-Lg1398) as compared to cytokine and chemokine expression during *L.g.* infection from human CL lesions (h-CL-Lg1881) (Fig. 1C). Thus, the elevated cytokine and chemokine levels after macrophage infection are associated with metastasizing parasites.

Leishmania parasites enter the macrophage endosomal compartment and form a phagolysosome (*17*). Pretreatment of macrophages with chloroquine, which induces vacuolar alkanization and impairs recognition of pathogen-derived motifs by cells (*18*), or cytochalasin D, which inhibits parasite phagocytosis by inhibiting actin polymerization (*19*), showed that *L.g.*M+ parasite-dependent induction of proinflammatory mediator required parasite entry into the cell and sequestration into a mature phagolysosome (fig. S1A). Therefore, we investigated the role of the macrophage endosomal Toll-like receptors (TLRs) of the myeloid differentiation factor 88 (MyD88) (TLR7 and TLR9) and/or of the TIR domain–containing adapter-inducing interferon-β (TRIF)-dependent pathways (TLR3). Using macrophage functionally deficient for TLR3, 7, or 9, or for the adaptors MyD88 and TRIF, we found that the TLR3-TRIF–dependent pathway was essential for increased proinflammatory mediator expression after macrophage infection with *L.g.*M+ (Fig. 2 and fig. S1B). In addition, MyD88-dependent TLR7 activation within the macrophage was required for maximal secretion of the proinflammatory mediators after infection with M+ parasites (Fig. 2 and fig. S1B). In our system, TLR9 was not involved in *L.g.*M+-dependent macrophage responses, suggesting that recognition of *Leishmania*-derived DNA motifs by the host's TLR9 does not differ between the *Leishmania* strains (Fig. 2A).

In other murine models of infection, TLR3 ligation up-regulates proinflammatory mediators (TNF-α, IL-6, and chemokines) and type I interferons,

[1]Department of Biochemistry, University of Lausanne, 1066 Epalinges, Switzerland. [2]Swiss Institute of Bioinformatics, University of Lausanne, 1015 Dorigny, Switzerland. [3]Department of Molecular Microbiology, Washington University, School of Medicine, St Louis, MO 63110, USA. [4]World Health Organization–Immunology Research and Training Centre, 1066 Epalinges, Switzerland.

*Present address: Route de Berne 7A, 1700 Fribourg, Switzerland. †To whom correspondence should be addressed. E-mail: nicolas.fasel@unil.ch

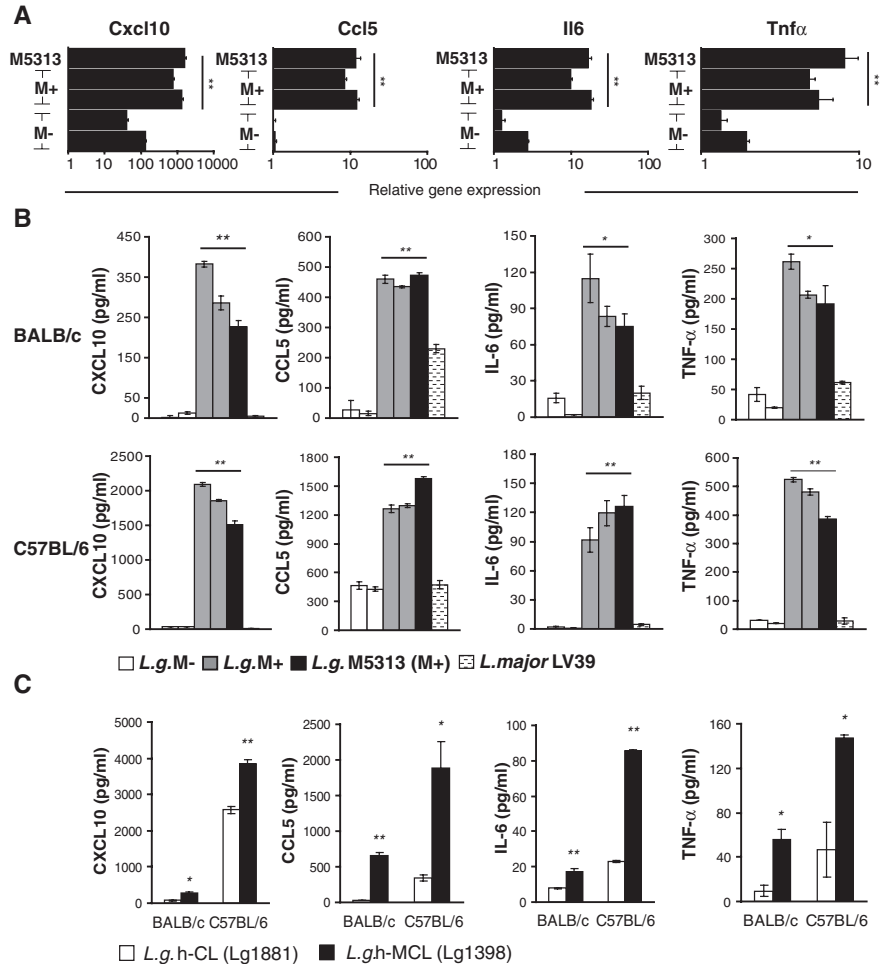

Fig. 1. Metastasizing *L.g.* parasites activate bone-marrow macrophages to elevate proinflammatory cytokine and chemokine levels. (**A**) Transcript and (**B** and **C**) secreted protein levels induced after C57BL/6 or BALB/c macrophage infection (ratio 1:10) with *Leishmania* parasites [two *L.g.*M– clones (Lg03 and Lg17); two *L.g.*M+ clones (Lg13 and Lg21); *L.g.*M5313(M+); *L.g.* derived from h-MCL (–*L.g.*1398) or hCL (*L.g.*1881) lesions; and *L.major* LV39] for 6 hours. Results were confirmed in several independent experiments ($n > 3$), and data reflect mean ± SD transcript or protein increase relative to unstimulated controls. Significance was determined at $*P \leq 0.05$, and $**P \leq 0.01$ for *L.g.*M+ or h-MCL versus *L.g.*M–, h-CL, and/or *L. major* LV39-stimulated macrophages.

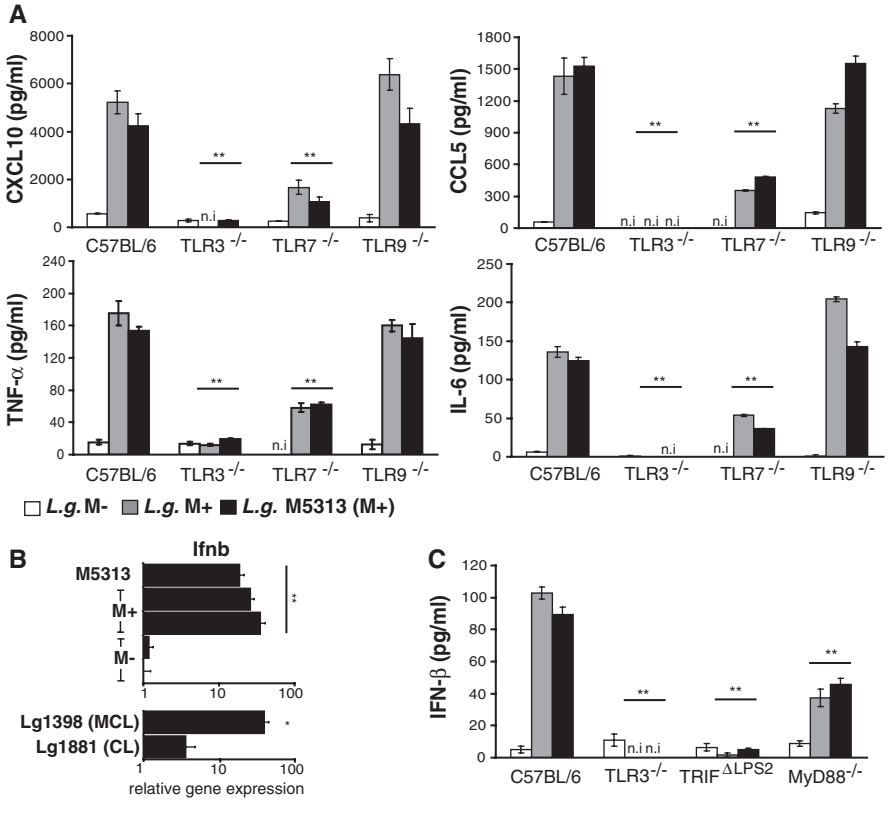

Fig. 2. *L.g.*M+ or h-MCL parasite-dependent induction of IFN-β and proinflammatory mediators by macrophages uses TLR3 and TRIF. (**A** and **C**) Secreted protein and (**B**) transcript levels of cytokines and chemokines induced after infection of macrophages (ratio 1:10) with *Leishmania* parasites [two *L.g.*M+ clones (Lg13 and Lg21), two *L.g.*M– clones (Lg03 and Lg17), and *L.g.*M5313(M+)] for 6 and 2 hours, respectively. Results were confirmed in several independent experiments ($n = 3$), and data reflect mean ± SD transcript or protein increase relative to unstimulated controls of *L.g.*M+ or *L.g.*M–. Significance was determined between C57BL/6 and deficient macrophages (A and C) or between *L.g.*M+ or h-MCL and *L.g* M– and h-CL parasites (B) at $*P \leq 0.05$ and $**P \leq 0.01$. n.i, not induced.

resulting in organ damage (*20*–*22*). To confirm the role of TLR3 in the recognition of *L.g.*M+ parasites, we analyzed IFN-β expression. Infection with *L.g.*M+ induced significantly more IFN-β transcripts (31.14 ± 23.46) than *L.g.*M− clones (5.83 ± 4.27) after 6 hours by comparison with unstimulated macrophage controls. This increase was observed as early as 2 hours after infection (Fig. 2B). At the protein level, after macrophage infection, *L.g.*M+

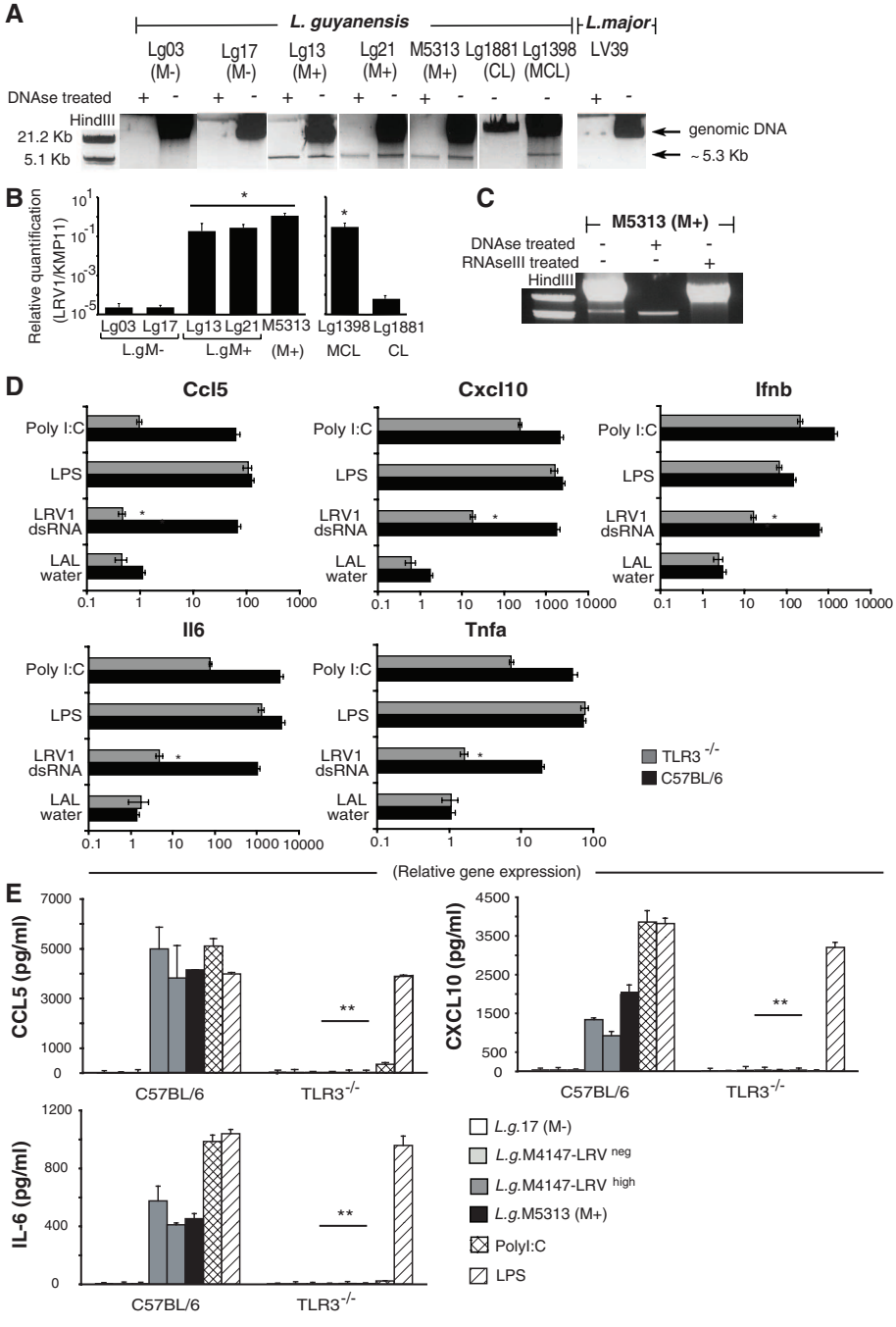

Fig. 3. High LRV1 burden within metastasizing *L.g.* promastigotes stimulates cytokine and chemokine production in macrophages via TLR3. (**A**) ssRNAse-treated nucleic acids were DNAse treated, and the 5.3-kb LRV1 dsRNA band visualized by gel electrophoresis. (**B**) LRV1 virus burden within *Leishmania* parasites was assessed by qRT-PCR with LRV1 and *Leishmania* Kmp11 gene primers; significance was determined between metastasizing (*L.g.*M+ and h-MCL) versus nonmetastasizing (*L.g.*M− and h-CL) parasites. (**C**) Nucleic acids from *L.g.*M5313(M+) promastigotes, pretreated with a ssRNA-specific RNAse, were treated with DNAse or with the dsRNA-specific RNAse III and separated by gel electrophoresis with the marker Lambda-DNA–Eco RI + Hind III (HindIII). (**D**) Macrophages were stimulated with purified LRV1 dsRNA (1 μg/ml) in endotoxin-free (LAL) water, poly(I:C) (1 μg/ml), or lipopolysaccharide (LPS, 100 ng/ml) for 4 hours. Transcript levels were assessed relative to unstimulated C57BL/6 macrophages by qRT-PCR. Results are expressed as mean ± SD ($n = 2$). (**E**) Protein abundance was quantified after infection of macrophages (ratio 1:10) with *L.g.*M4147–LRV^{high} (clones 2 and 3) or *L.g.*M4147–LRV^{neg} (clones 3 and 4) parasites after 6 hours. Controls: *L.g.*M− (Lg17), *L.g.*M5313(M+), poly(I:C) (2 μg/ml), and LPS (100 ng/ml). Data reflect mean ± SD of protein secretion relative to unstimulated controls ($n = 2$). Significance was determined at $^{*}P \leq 0.05$ or $^{**}P \leq 0.01$.

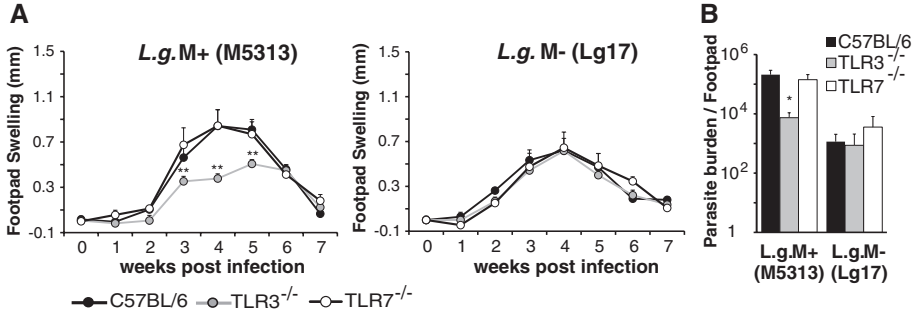

Fig. 4. TLR3$^{-/-}$ mice infected with *L.g.*M+ parasites have decreased disease pathology when compared to wild-type C57BL/6. Footpads ($n \geq 4$) were infected with 3×10^6 parasites. (**A**) Footpad swelling was measured weekly and (**B**) parasite burden ($n = 3$) was determined at 4 weeks after infection by qRT-PCR with *Leishmania* Kmp11 gene-specific primers. Representative data of two experiments, expressed as mean ± SEM of all mice infected per group, with statistical significance at $^{*}P \leq 0.05$ and $^{**}P \leq 0.01$.

M5313-derived and h-MCL induced higher IFN-β secretion than *L.g.*M− parasites or h-CL parasites (Fig. 2C). Furthermore, this expression was TLR3-TRIF dependent, with the MyD88 signaling pathway augmenting secretion (Fig. 2C).

Endosomal TLRs recognize nucleic acid motifs, with TLR7 and TLR3 recognizing single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA), respectively (*23*). Our experimental evidence suggested that nucleic acid–derived motifs were involved in the host macrophage response to infection with metastasizing *L.g.* parasites. We observed increased production of CCL5, TNF-α, and IL-6 in macrophages exposed to single-stranded ribonuclease (ssRNAse)– and deoxyribonuclease (DNAse)–treated nucleic acids derived from *L.g.*M+ parasites, compared with *L.g.*M− and *L.major* LV39 (fig. S2). Although not statistically significant, these results suggested that the nucleic acid motif is resistant to ssRNAse and DNAse treatments and is likely to be dsRNA.

L.Viannia parasites, including *L.g.*M5313(M+) and *L. guyanensis* and *L. braziliensis* MCL human isolates, harbor the dsRNA *Leishmania RNA virus 1* (LRV1) (*24*–*26*). These viruses have a capsid coat protecting a 5.3-kb dsRNA genome (*27*). Metastasizing promastigotes had greater levels of LRV1 (*L.g.*M+ or h-MCL-LRV^{high}) than nonmetastasizing promastigotes (*L.g.*M− or h-CL-LRV^{low}) as shown by the presence of a ~5.3-kb, DNAse-insensitive, RNAse III–sensitive band in agarose gels, and LRV1 quantification by quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR) (Fig. 3, A to C, and fig. S3A). We thus verified that macrophages treated with purified LRV1 dsRNA (fig. S3) induced a phenotype similar to that of macrophage infected with metastasizing parasites, and as shown by an increased expression of CXCL10, CCL5, TNF-α, IL-6, and IFN-β transcripts, this increase was TLR3 dependent (Fig. 3D). Because the *L.g.*M5313 M+ and M− parasites were not isogenic, we performed new experiments with parasites derived from the WHO reference strain *L.g.*M4147 that metastatizes in the hamster (*28*) and carries the LRV1-4 virus (*29*). Macrophage infection with *L.g.*M4147-LRV^{high} parasites produced significantly greater amounts of cytokines and chemokines than infection with its respective isogenic virus-free derivative *L.g.*M4147LRV^{neg}, in a TLR3-dependent manner (Fig. 3E and fig. S4) (*30*, *31*). Similar parasite burdens were observed for all parasites infected into the wild-type and the TLR-, TRIF-, and MyD88-deficient macrophages (table S1).

A role for TLR3 and LRV1 in leishmaniasis development was analyzed in vivo, with TLR3$^{-/-}$, TLR7$^{-/-}$, and WT mice that were infected in the footpad. A significant decrease in footpad swelling, and diminished parasite burden, were observed in TLR3$^{-/-}$ mice infected with *L.g.*M+LRV^{high} (M5313) or *L.g.*M4147–LRV^{high} parasites compared with wild-type mice (Fig. 4 and fig. S5). No consistent, significant decrease in disease pathology was observed between TLR3$^{-/-}$ and wild-type mice infected with *L.g.*M−LRV^{low} (Lg17) or *L.g.*M4147–LRV^{neg} or between TLR7$^{-/-}$ and wild-type infected mice with the different parasite isolates (Fig. 4 and Fig. S5). Further experimentation is required to elucidate the role of TLR7-dependent immune responses with respect to infection with LRV1-containing *Leishmania* parasites.

Our work showed that recognition of LRV1 within metastasizing *L.g.* parasites by the host promoted inflammation and subverted the immune response to infection to promote parasite persistence (*2*, *3*, *32*). Because recognition of LRV1 within the metastasizing *L.g.* parasites arises early after infection, we hypothesize that LRV1 dsRNA is released from dead parasites, unable to survive within the host macrophage. These results could open the door to better diagnosis of risk for MCL disease and facilitate the development of new and more efficient treatment regimes.

References and Notes

1. K. Weigle, N. G. Saravia, *Clin. Dermatol.* **14**, 433 (1996).
2. C. Vergel *et al.*, *J. Infect. Dis.* **194**, 503 (2006).
3. J. E. Martinez, L. Alba, *Trans. R. Soc. Trop. Med. Hyg.* **86**, 392 (1992).
4. A. Barral *et al.*, *Am. J. Pathol.* **147**, 947 (1995).
5. V. S. Amato, F. F. Tuon, H. A. Bacha, V. A. Neto, A. C. Nicodemo, *Acta Trop.* **105**, 1 (2008).
6. J. Arevalo *et al.*, *J. Infect. Dis.* **195**, 1846 (2007).
7. D. R. Faria *et al.*, *Infect. Immun.* **73**, 7853 (2005).
8. S. T. Gaze *et al.*, *Scand. J. Immunol.* **63**, 70 (2006).
9. C. Pirmez *et al.*, *J. Clin. Invest.* **91**, 1390 (1993).
10. D. A. Vargas-Inchaustegui *et al.*, *Infect. Immun.* **78**, 301 (2010).
11. J. M. Blackwell, *Parasitol. Today* **15**, 73 (1999).
12. L. Castellucci *et al.*, *J. Infect. Dis.* **194**, 519 (2006).
13. B. Travi, J. Rey-Ladino, N. G. Saravia, *J. Parasitol.* **74**, 1059 (1988).
14. J. E. Martínez, L. Valderrama, V. Gama, D. A. Leiby, N. G. Saravia, *J. Parasitol.* **86**, 792 (2000).
15. N. Acestor *et al.*, *J. Infect. Dis.* **194**, 1160 (2006).
16. Materials and methods are available as supporting material on *Science* Online.
17. C. Bogdan, M. Röllinghoff, A. Diefenbach, *Immunol. Rev.* **173**, 17 (2000).
18. F. H. Abou Fakher, N. Rachinel, M. Klimczak, J. Louis, N. Doyen, *J. Immunol.* **182**, 1386 (2009).
19. R. Ben-Othman, L. Guizani-Tabbane, K. Dellagi, *Mol. Immunol.* **45**, 3222 (2008).
20. K. A. Cavassani *et al.*, *J. Exp. Med.* **205**, 2609 (2008).
21. R. Le Goffic *et al.*, *PLoS Pathog.* **2**, e53 (2006).
22. K. S. Lang *et al.*, *J. Clin. Invest.* **116**, 2456 (2006).
23. S. L. Doyle, L. A. O'Neill, *Biochem. Pharmacol.* **72**, 1102 (2006).
24. L. Guilbride, P. J. Myler, K. Stuart, *Mol. Biochem. Parasitol.* **54**, 101 (1992).
25. G. Salinas, M. Zamora, K. Stuart, N. Saravia, *Am. J. Trop. Med. Hyg.* **54**, 425 (1996).
26. M. M. Ogg *et al.*, *Am. J. Trop. Med. Hyg.* **69**, 309 (2003).
27. T. L. Cadd, M. C. Keenan, J. L. Patterson, *J. Virol.* **67**, 5647 (1993).
28. J. A. Rey, B. L. Travi, A. Z. Valencia, N. G. Saravia, *Am. J. Trop. Med. Hyg.* **43**, 623 (1990).
29. G. Widmer, A. M. Comeau, D. B. Furlong, D. F. Wirth, J. L. Patterson, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 5979 (1989).
30. L. F. Lye *et al.*, *PLoS Pathog.* **6**, e1001161 (2010).
31. Y. T. Ro, S. M. Scheffter, J. L. Patterson, *J. Virol.* **71**, 8991 (1997).
32. A. Barral *et al.*, *Am. J. Trop. Med. Hyg.* **53**, 256 (1995).

33. We are grateful to N. Saravia (CIDEIM, Colombia) and Instituto Oswaldo Cruz, for *L. guyanensis* strains; S. Akira (Frontier Research center, Osaka University), P. Romero (LICR, Lausanne), and B. Ryffel (CNRS, Orléans) for knockout and mutant mice; M. Delorenzi (SIB, Lausanne) for bioinformatics expertise; F. Morgenthaler (Cellular Imaging Facility, Lausanne), S. Cawsey, and M.-A. Hartley for technical assistance; and J. Patterson and Y. T. Ro for the *L.g.*M4147 strains. This work was funded by FNRS grants 3100A0-116665/1 (N.F.) and 310030-120325 (P.L.), Foundation Pierre Mercier (S.M.), and NIH A129646 (S.M.B.). Microarray data are available within the Gene Expression Omnibus database (GSE21418) and at http://people.unil.ch/nicolasfasel/data-from-fasels-lab/.

Supporting Online Material

www.sciencemag.org/cgi/content/full/331/6018/775/DC1
Materials and Methods
Figs. S1 to S4
Table S1
References

20 October 2010; accepted 23 December 2010
10.1126/science.1199326

Posttranslational Modification of Pili upon Cell Contact Triggers *N. meningitidis* Dissemination

Julia Chamot-Rooke,[1,2] Guillain Mikaty,[3,4] Christian Malosse,[1,2] Magali Soyer,[4,5] Audrey Dumont,[4,5] Joseph Gault,[1,2] Anne-Flore Imhaus,[4,5] Patricia Martin,[3,4] Mikael Trellet,[6] Guilhem Clary,[4,7,8] Philippe Chafey,[4,7,8] Luc Camoin,[4,7,8] Michael Nilges,[6] Xavier Nassif,[3,4,9] Guillaume Duménil[4,5]*

The Gram-negative bacterium *Neisseria meningitidis* asymptomatically colonizes the throat of 10 to 30% of the human population, but throat colonization can also act as the port of entry to the blood (septicemia) and then the brain (meningitis). Colonization is mediated by filamentous organelles referred to as type IV pili, which allow the formation of bacterial aggregates associated with host cells. We found that proliferation of *N. meningitidis* in contact with host cells increased the transcription of a bacterial gene encoding a transferase that adds phosphoglycerol onto type IV pili. This unusual posttranslational modification specifically released type IV pili-dependent contacts between bacteria. In turn, this regulated detachment process allowed propagation of the bacterium to new colonization sites and also migration across the epithelium, a prerequisite for dissemination and invasive disease.

The Gram-negative bacterium *Neisseria meningitidis* is a leading cause of septicemia and meningitis in humans (*1*). Initially, individual bacteria adhere to the nasopharynx epithelium via their type IV pili, a filamentous organelle common to numerous pathogenic bac-