TISSUE REPAIR

Local amplifiers of IL-4Rα–mediated macrophage activation promote repair in lung and liver

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The type 2 immune response controls helminth infection and maintains tissue homeostasis but can lead to allergy and fibrosis if not adequately regulated. We have discovered local tissue-specific amplifiers of type 2–mediated macrophage activation. In the lung, surfactant protein A (SP-A) enhanced interleukin-4 (IL-4)–dependent macrophage proliferation and activation, accelerating parasite clearance and reducing pulmonary injury after infection with a lung-migrating helminth. In the peritoneal cavity and liver, C1q enhancement of type 2 macrophage activation was required for liver repair after bacterial infection, but resulted in fibrosis after peritoneal dialysis. IL-4 drives production of these structurally related defense collagens, SP-A and C1q, and the expression of their receptor, myosin 18A. These findings reveal the existence within different tissues of an amplification system needed for local type 2 responses.

The type 2 cytokines interleukin-4 (IL-4) and IL-13, which signal through IL-4 receptor alpha (IL-4Rα), trigger a specialized macrophage phenotype [M(IL-4)] (*1*) that promotes control of helminth infection (*2*) and tissue repair (*3*, *4*). M(IL-4)s also contribute to pathology associated with type 2 immunity, including allergy, asthma, and fibrosis (*4*). However, little is known about tissue-specific factors that might promote both beneficial and detrimental actions of M(IL-4)s.

In the lung, alveolar macrophages (aMϕs), together with the respiratory epithelium, are covered by pulmonary surfactant, a lipid-protein network in which surfactant protein A (SP-A) constitutes the major protein component (*5*). SP-A is a versatile recognition protein (*5*) that is a member of a group of secreted soluble defense collagens that include the first component of the complement system (C1q), collectins (e.g., SP-A, SP-D, mannan-binding lectin), ficolins, and adiponectin (*6*). Because of its abundance and known role in immune defense (*5*), we asked whether SP-A was involved in the local regulation of M(IL-4) effector function in the lung.

M(IL-4)s have a critical role in lung repair after infection with the lung-migrating nematode *Nippostrongylus brasiliensis* (*3*). We therefore infected wild-type (WT), IL-4Rα–deficient, and SP-A–deficient mice with *N. brasiliensis* infective larvae. Larvae migrate to the lung, where they mature for ~2 days, and reach the small intestine by 3 days postinfection (p.i.). The type 2 response peaks 6 to 7 days after inoculation. We observed an increase in the expression of SP-A protein (Fig. 1A) and mRNA (fig. S1A) in lungs of *N. brasiliensis*–infected C57BL/6 mice at 6 days p.i., which was dependent on IL-4Rα. Consistent with a role for SP-A during type 2 immunity to nematode infection, SP-A–deficient mice had greater adult worm burdens (Fig. 1B) and egg output (fig. S1B), and significantly impaired lung repair processes (Fig. 1, C and D) than WT mice. The failure to heal was associated with a failure to up-regulate tissue-repair–related gene *Col1a1* (collagen, type I, alpha 1) (Fig. 1E) and increased expression of *Mmp12*, an extracellular matrix–degrading enzyme (Fig. 1F). Greater lung damage in SP-A–deficient mice was indicated by increased numbers of red blood cells and neutrophils in bronchoalveolar lavage (BAL) at 6 days p.i. (Fig. 1, G and H). The absence of SP-A resulted in reduced expression of the M(IL-4) proteins RELMα (Fig. 1I), Ym1, and arginase (fig. S1, C and D) in aMϕs. Secretion of RELMα and Ym1 protein into the alveolar fluid (fig. S1E) was also reduced in SP-A–deficient mice as compared with WT mice.

Consistent with the known ability of IL-4 to cause macrophage proliferation during helminth infection (*7*), aMϕs from WT mice exhibited significant proliferation (Fig. 1, J and K) and increased aMϕ numbers (fig. S1F) 6 days after *N. brasiliensis* infection. However, SP-A–deficient mice failed to exhibit significantly enhanced aMϕ proliferation (Fig. 1, J and K), resulting in fewer total macrophage numbers relative to WT mice (fig. S1F). There was no evidence that differences were caused by a failure of SP-A–deficient mice to mount appropriate type 2 innate lymphoid cell (ILC2), T helper 2 cell (T_H2) (fig. S1, G and H), or local type 2 cytokine responses (fig. S1I). Notably, aMϕs from uninfected SP-A–deficient mice were normal in number, phenotype, and ability to respond to IL-4 ex vivo (fig. S2, A to D).

To ascertain if defects in SP-A–deficient mice were caused by defective IL-4Rα responsiveness in vivo, we injected WT and SP-A–deficient mice intraperitoneally (ip) with IL-4 complex (IL-4c). IL-4c delivery increased the amount of SP-A protein in BAL (Fig. 1L) in WT mice and induced M(IL-4) markers and proliferation in aMϕs isolated from BAL (Fig. 1, M and N, and fig. S3, A to C) of WT but not SP-A–deficient mice, reflected by diminished secretion of RELMα and Ym1 to the alveolar fluid in SP-A–deficient mice (fig. S3D). IL-4c delivery decreased IL-4Rα expression in both WT and SP-A–deficient aMϕs (fig. S3E).

Enhancement of M(IL-4)s may underlie the previously reported contribution of SP-A to tissue integrity in other models of acute lung injury (*8*, *9*). The pro–type 2 effects we report here contrast with studies that associate SP-A with protection in asthma (*10*). However, in addition to promoting M(IL-4) and proliferation of macrophages, the anti-inflammatory properties of SP-A (*5*, *6*, *8*, *9*, *11*) may suppress the strong inflammatory responses that are responsible for more severe asthma. Our data are supported by the finding that SP-D–deficient mice, which lack SP-A (*12*), also have reduced M(IL-4) responsiveness (*13*).

To determine whether SP-A acts directly on aMϕs, we first tested the ability of adherence-purified macrophages from the alveolar and peritoneal spaces to proliferate in vitro in response to IL-4 (1 μg/ml); aMϕs exhibited significant proliferation, but peritoneal macrophages (pMϕs) failed to proliferate despite expressing M(IL-4) activation markers (fig. S4A). We then tested the ability of SP-A to enhance IL-4 treatment and included C1q as a control because it is a defense collagen structurally homologous to SP-A (*5*, *6*). We found that SP-A, but not C1q, significantly boosted IL-4–mediated aMϕ proliferation and M(IL-4) markers (Fig. 2A). IL-4Rα–deficient aMϕs showed no proliferation or activation when stimulated with IL-4 (1 μg/ml) in the absence or presence of SP-A (fig. S4B). Notably, SP-A significantly enhanced proliferation and activation induced by IL-4 in both human (fig. S4C) and rat aMϕs (fig. S4D).

Unexpectedly, C1q, but not SP-A, significantly increased IL-4–mediated proliferation and M(IL-4)

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marker expression in pMϕs (Fig. 2A). To verify these findings in vivo, IL-4c was delivered to C1qa-deficient mice. Consistent with the in vitro studies, mice lacking C1q exhibited reduced IL-4–dependent activation and proliferation in pMϕ but not aMϕ (Fig. 2B). Similar to SP-A in the lung (Fig. 1L), C1q levels increased in the peritoneal fluid after IL-4c delivery (fig. S5A), indicating that IL-4 drives production of a local signal to amplify its effect on tissue macrophages. Notably, the pMϕ phenotype, number, and ability to respond to IL-4 ex vivo are normal in C1qa-deficient mice (fig. S5, B to F). Thus, SP-A and C1q were induced by IL-4 in the lung and peritoneal cavity, respectively, where they acted to enhance proliferation and M(IL-4) activation in a tissue-specific manner.

To determine which receptor mediates SP-A effects on IL-4–stimulated aMϕs, we inhibited known receptors for SP-A (*5*). We observed that the blockade of myosin 18A (Myo18A; also called SP-R210), but not signal inhibitory regulatory protein α (SIRPα) or calreticulin (cC1qR), abrogated SP-A–mediated enhancement of IL-4–induced arginase activity in rat aMϕs (fig. S6A). Blockade or RNA silencing of Myo18A consistently abolished SP-A–mediated enhancement of IL-4–induced proliferation and activation of mouse (Fig. 2C), human (fig. S6B), and rat (fig. S6C) aMϕs. Myo18A is an unconventional myosin that does not operate as a traditional molecular motor, having both intracellular and cell-surface locations (*14*), and was recently defined as CD245 (*15*). Immune activation results in Myo18A localization on the cell surface, where it binds to the collagen-like domain of SP-A (*6*, *16*), and we confirmed that an intact collagen-like domain is required to enhance IL-4–mediated type 2 responses (fig. S6D).

Because C1q is structurally homologous to SP-A in its supratrimeric assembly and collagen tail (*5*, *6*), we addressed whether Myo18A was also responsible for the actions of C1q. Indeed, blockade of Myo18A prevented C1q enhancement of IL-4–driven activation and proliferation of pMϕs (Fig. 2C). In vitro, IL-4 promoted Myo18A localization on the cell surface of both aMϕs and pMϕs (fig. S7, A and B), which was maximal 24 hours after stimulation. Cell surface expression of Myo18A was similarly observed in vivo after IL-4c delivery (fig. S7, C and D), independent of the presence or absence of SP-A or C1q. We confirmed the role of Myo18A in vivo by intranasal or intraperitoneal delivery of antibodies against Myo18A (anti-Myo18A). Receptor blockade significantly reduced IL-4–induced proliferation and M(IL-4) activation of aMϕs and pMϕs (Fig. 2D), as well as secretion of RELMα and Ym1 to the alveolar and peritoneal fluid (fig. S7, E and F). Thus, Myo18A receptor blockade in the lung or peritoneal cavity phenocopied SP-A or C1qa deficiency, respectively. Together these data indicate that Myo18A is a common receptor or co-receptor for defense collagens present on aMϕs and pMϕs, which determines macrophage capacity to respond to IL-4 and whose cell surface expression is itself induced by IL-4. Myo18A lacks a transmembrane domain (*14*) and thus must act in concert with transmembrane co-receptors for signal transduction that likely impart tissue specificity.

Unlike most other complement components, the majority of C1q is produced by myeloid cells in peripheral tissues (*17*), supporting the relevance of C1q as a local factor that enhances type 2 responses. To determine the physiological relevance of C1q in this context, we evaluated its role in a murine model of peritoneal fibrosis (*18*). Peritoneal fibrosis is a frequent and serious consequence of peritoneal dialysis (*19*) associated with alternatively activated macrophages in both humans and mice (*18*–*20*). We administered

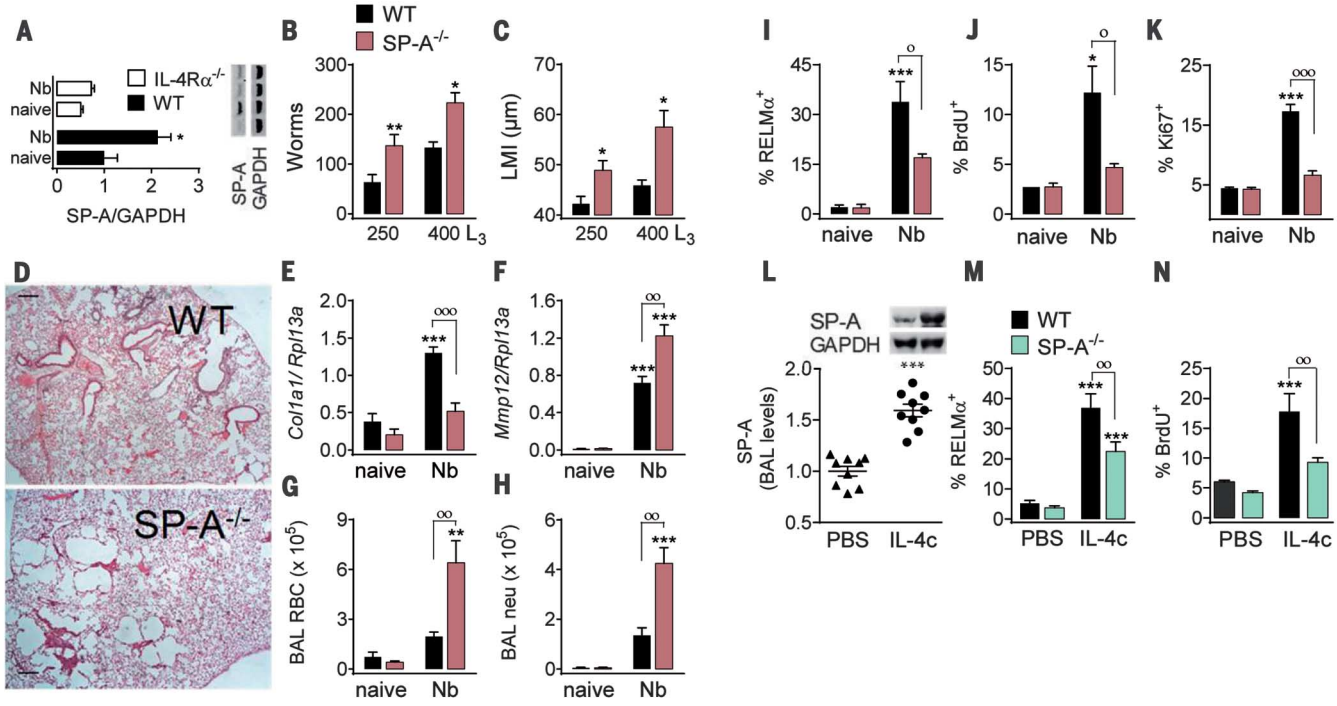

Fig. 1. Higher worm burden, greater nematode-induced lung damage, and reduced IL-4–induced proliferation and activation in mice lacking SP-A. Samples were assessed 6 days after *N. brasiliensis* (Nb) infection. (**A**) SP-A protein expression in lung tissue of WT and IL-4Rα$^{-/-}$ mice. (**B**) Adult larvae in the small intestine. (**C**) Lung damage, quantified by "mean linear intercept" from micrographs of hematoxylin and eosin (H&E)–stained lung sections, and (**D**) microscopy of H&E-stained lung sections (scale bars, 500 μm) in WT and SP-A$^{-/-}$ mice. (**E**) Amplification of *Col1a1*- and (**F**) *Mmp12*-encoding mRNA in lung tissue. Number of (**G**) red blood cells and (**H**) neutrophils isolated in BAL. Expression of (**I**) RELMα by aMϕs from BAL. (**J**) BrdU (5-bromo-2′-deoxyuridine) incorporation and (**K**) Ki67 expression by aMϕs from BAL. Data are representative of two independent experiments (mean ± SEM; naïve: 3 mice, *Nb*: 6 mice). (**L** to **N**) WT and SP-A$^{-/-}$ mice treated with 5 μg of IL-4c (i.p.) at days 0 and 2 and analyzed at day 4. (L) Relative SP-A levels in BAL (representative western blot shown) of WT mice treated with IL-4c or phosphate-buffered saline (PBS). (M) RELMα expression and (N) BrdU incorporation in aMϕs. Data pooled from three independent experiments (means ± SEM) (PBS: 9 mice; IL-4c: 11 mice). Analysis of variance (ANOVA) followed by the Bonferroni multiple-comparison test was used. *P < 0.05, **P < 0.01, and ***P < 0.001 when compared with the untreated/uninfected group. °P < 0.05, °°P < 0.01, and °°°P < 0.001 when WT versus SP-A$^{-/-}$ groups are compared.

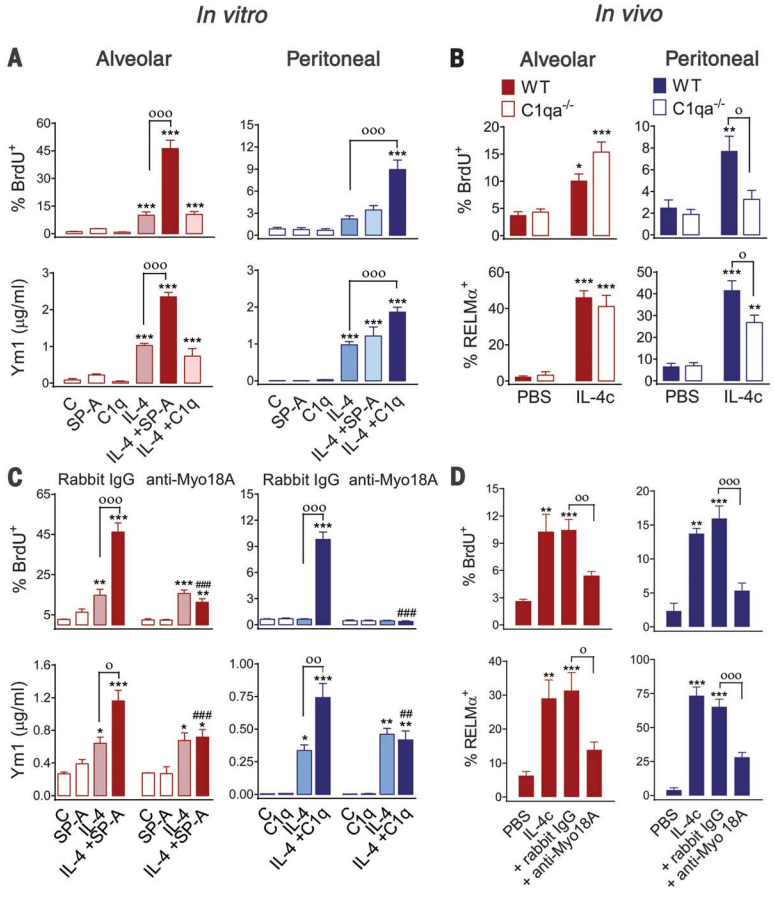

Fig. 2. SP-A and C1q act through Myo18A to enhance IL-4–induced proliferation and activation of alveolar and peritoneal macrophages, respectively. (**A**) Murine macrophages were treated with IL-4 in the presence or absence of SP-A or C1q. BrdU incorporation and Ym1 secretion are shown. (**B**) For aMϕs (red), 5 μg of IL-4c was delivered ip at days 0 and 2, and BAL cells were analyzed at day 4. For pMϕs (blue), 1 μg of IL-4c was delivered ip at day 0, and resident peritoneal cells were analyzed at day 1: BrdU incorporation and RELMα expression are shown. (**C**) Murine macrophages were treated with anti-Myo18A or rabbit immunoglobulin G (IgG) plus either IL-4+SP-A (aMϕ) or IL-4+C1q (pMϕ). BrdU incorporation and Ym1 secretion are shown. (**D**) Concurrently with IL-4c delivery, some WT mice were treated intranasally or ip with either anti-Myo18A or rabbit IgG. BrdU incorporation and RELMα expression are shown in aMϕs and pMϕs. All statistical analysis was performed by ANOVA followed by the Bonferroni multiple-comparison test. (A and C) Results are presented as means (±SEM) from three different cell cultures with at least three biological replicates. $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ when compared with untreated cells; $°P < 0.05$, $°°P < 0.01$, and $°°°P < 0.001$ when SP-A+IL-4– or C1q+IL4–treated are compared with IL-4–treated; $\#\#P < 0.01$ and $\#\#\#P < 0.001$, the effect of anti-Myo18A antibody on cells treated with SP-A+IL-4 or C1q+IL4. (B and D) Data were pooled from three independent experiments (means ± SEM) (PBS: 6 mice, other groups: 9 mice). $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ when compared with PBS-treated mice; $°P < 0.05$ when WT versus C1qa$^{-/-}$ mice treated with IL-4c are compared (B); $°P < 0.05$, $°°P < 0.01$, and $°°°P < 0.001$ when anti-Myo18A versus rabbit IgG treatment is compared in IL-4c–treated mice (D).

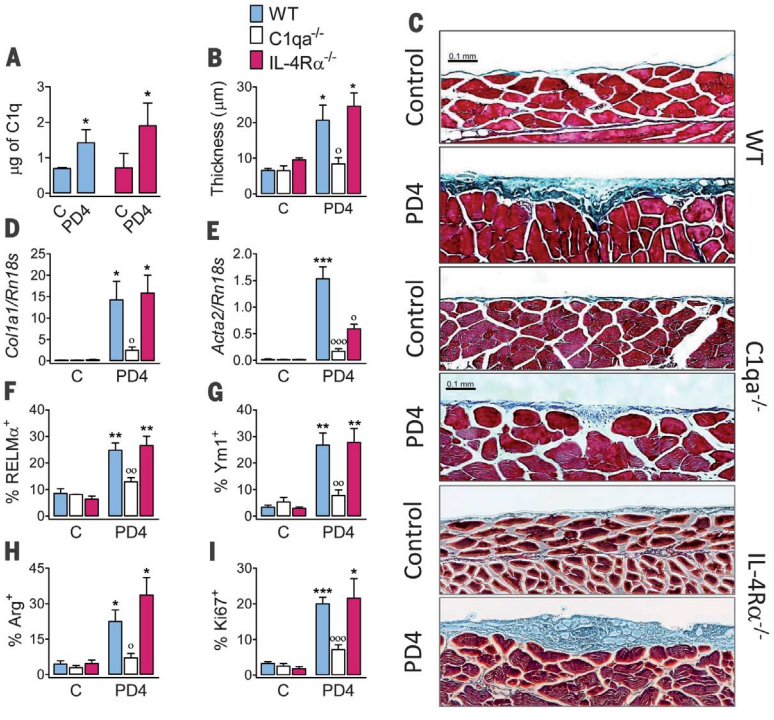

Fig. 3. C1q enhances peritoneal fibrosis induced by a lactate dialysate. WT, C1qa$^{-/-}$, or IL-4Rα$^{-/-}$ mice were either untreated (C) or injected ip with Dianeal-PD4 every other day for 28 days. Samples were analyzed a day after the last delivery. (**A**) Total amount of C1q in the peritoneal washes was determined by enzyme-linked immunosorbent assay . (**B**) Quantification of the thickness of the submesothelial compact zone from (**C**) microscopy of Masson's trichrome stained parietal peritoneum slices (scale bars, 0.1 mm). Amplification of (**D**) *Col1a1*- and (**E**) *Acta2*-encoding mRNA in peritoneal tissue. Expression of (**F**) RELMα, (**G**) Ym1, (**H**) Arg, and (**I**) Ki67 by pMϕs. Results are representative of two independent experiments (means ± SEM) (untreated: 3 mice, PD4: 6 mice). ANOVA followed by the Bonferroni multiple-comparison test or Student's *t*-test (A) was used. $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ when compared with control group; $°P < 0.05$, $°°P < 0.01$, and $°°°P < 0.001$ when WT versus C1qa$^{-/-}$ mice treated with Dianeal-PD4 are compared.

Dianeal-PD4, a clinically used lactate-based dialysate, every other day for 28 days to WT, C1qa-deficient, and IL-4Rα–deficient mice. In WT, but not in C1qa-deficient mice, Dianeal-PD4 treatment provoked the induction of C1q (Fig. 3A) and morphologic changes in tissue sections of the parietal peritoneum, showing significant enlargement of the submesothelial zone caused by collagen deposition (Fig. 3, B and C). Dianeal-PD4 treatment induced markers of fibrosis, including collagen mRNAs (*Col1a1* and *Col3a1*) (Fig. 3D and fig. S8A), alpha–smooth muscle actin (*Acta2*) (Fig. 3E), and vascular endothelial growth factor (*Vegf*) (fig. S8B). Substantial up-regulation of these markers was not observed in C1qa-deficient mice. Conversely, *Mmp12* mRNA was up-regulated in C1qa-deficient mice relative to WT mice (fig. S8C), consistent with monocyte infiltration (fig. S8D) (*21*) and an anti-inflammatory role for C1q (*22*). Dianeal-PD4 treatment also induced intracellular expression and protein secretion of the M(IL-4) markers RELMα, Ym1, and Arg (Fig. 3, F to H) and moderate proliferation of pMϕs (Fig. 3I) in WT but not C1qa-deficient mice. Despite the clear induction of M(IL-4) markers by PD4 delivery and their dependence on C1q, responses of IL-4Rα–deficient mice were equivalent to those of WT mice (Fig. 3, A to I, and fig. S8, A to D). Although initially surprising, Dianeal-PD4 is a lactate-based solution, and lactate can induce M(IL-4) markers by acting downstream of IL-4Rα through stabilization of hypoxia-inducible factor alpha (HIF1α) protein (*23*). Indeed, we observed that the induction of proliferation and M(IL-4) markers following Dianeal-PD4 delivery was essentially absent in mice lacking HIF1α in macrophages (fig. S9). Together, our data indicate that C1q significantly amplifies peritoneal fibrosis by promoting a type 2 macrophage phenotype driven by lactate and dependent on HIF1α. These results are consistent with human studies in which C1q is strongly associated with increased fibrosis of skeletal muscle (*24*).

Critically, we sought to ascertain whether C1q functioned as a type 2 amplifier in tissues beyond the peritoneal cavity and settings that are dependent on IL-4Rα. We thus assessed Myo18A expression on the cell surface of resident macrophages from mice treated with or without IL-4c (Fig. 4A). Consistent with our functional data, Myo18A was expressed in macrophages from the lung and peritoneal cavity, as well as in liver, spleen, and adipose tissue, and was significantly increased by IL-4 exposure. By contrast, there was minimal Myo18A on pleural cavity macrophages, which explained our failure to identify a role for C1q in the pleural cavity after IL-4c delivery (fig. S10). As predicted by the Myo18 expression data, we found that macrophages from the liver of C1qa-deficient mice had significantly lower levels of proliferation and M(IL-4) activation compared with WT mice following IL-4c delivery (Fig. 4B). Notably, we observed C1q up-regulation in the liver of IL-4c–treated mice (Fig. 4C). Of relevance, the number and phenotype of liver macrophages are normal in C1qa-deficient mice (fig. S11). Antibody blockade of Myo18A after IL-4 treatment of isolated liver macrophages verified that C1q generated its effects through Myo18A (fig. S12). We thus sought a model in which M(IL-4)s in the liver played a substantive role.

Infection of the liver by the Gram-positive bacterium *Listeria monocytogenes* causes necroptotic death of resident liver macrophages (Kupffer cells) followed by recruitment of monocytes, which control *L. monocytogenes* infection (*25*) and repopulate the liver macrophage population (*26*). After an initial type 1 response, the type 2 response begins at 3 days p.i., with IL-4–mediated activation and proliferation of liver macrophages acting to repair infection damage (*26*). To ascertain the relevance of C1q and confirm the role of IL-4Rα in this process, we infected

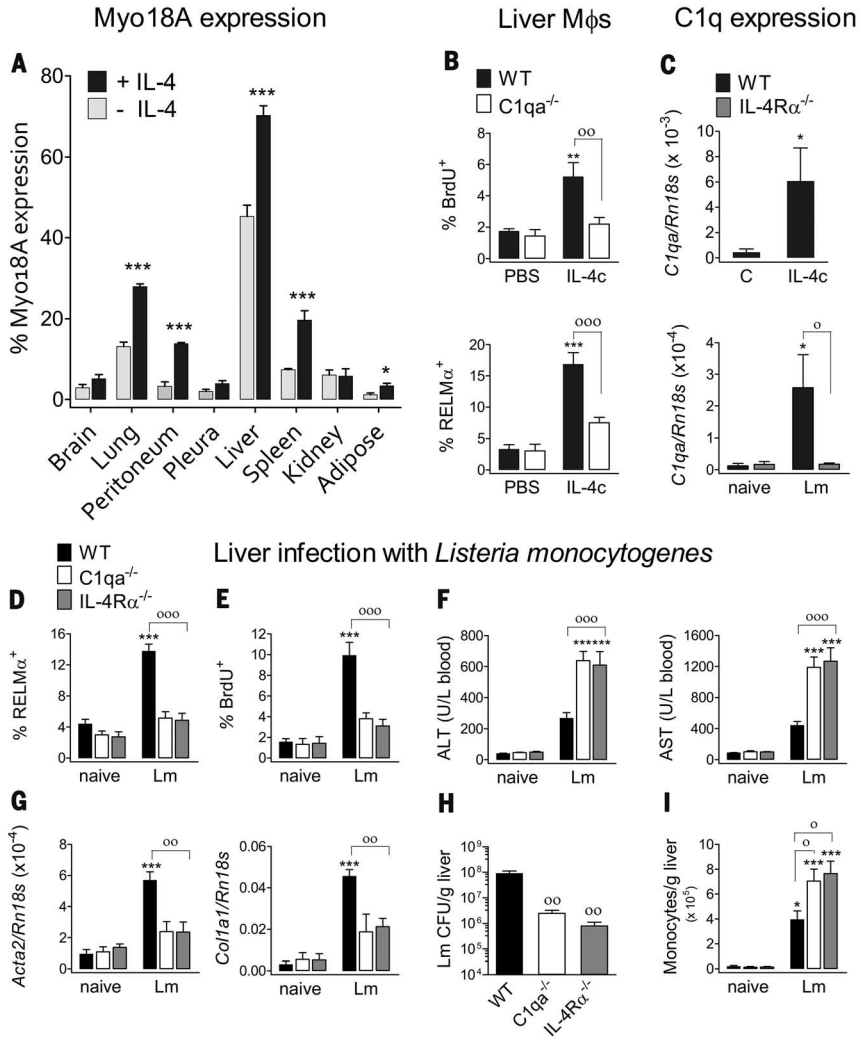

Fig. 4. C1q is required for appropriate macrophage activation in the liver during *Listeria monocytogenes* infection. (**A** to **C**) WT or C1qa$^{-/-}$ mice received 1 μg of IL-4c (ip) at day 0, and samples were analyzed at day 1. (A) Myo18A expression on the surface of resident macrophages (identified as described in the methods) from the indicated tissues. (B) BrdU incorporation and RELMα expression of liver macrophages. (C) (Upper panel) IL-4–induced amplification of *C1q*-encoding mRNA in the liver. (**C** to **I**) WT, C1qa$^{-/-}$, or IL-4Rα$^{-/-}$ mice were left uninfected or received intravenous infection with 10^4 *L. monocytogenes* (Lm) colony-forming units, and samples were assessed at 3.5 days p.i. (C) (Lower panel) *L. monocytogenes*–induced amplification of *C1q*-encoding mRNA. (D) Expression of RELMα by liver macrophages. (E) BrdU incorporation by liver macrophages. (F) Quantification of alanine transaminase (ALT) and aspartate transaminase (AST) in serum. (G) Amplification of *Acta2*- and *Col1a1*-encoding mRNA in the liver. (H) Liver bacterial load. (I) Number of monocytes in liver single-cell suspensions. Data are representative of two independent experiments (mean ± SEM; naïve: 4 mice, *Lm*: 5 mice). ANOVA followed by the Bonferroni multiple-comparison test was used. **P* < 0.05 and ****P* < 0.001 when compared with the uninfected group; °*P* < 0.05, °°*P* < 0.01 and °°°*P* < 0.001 when WT versus C1qa$^{-/-}$ or IL-4Rα$^{-/-}$ infected groups are compared.

WT, C1qa-deficient, and IL-4Rα–deficient mice with *L. monocytogenes* and performed sample analysis 3.5 days later. Infection resulted in IL-4Rα–dependent up-regulation of C1q mRNA in liver (Fig. 4C), whereas enhanced expression of RELMα and Ym1 by liver macrophages (Fig. 4D and fig. S13A) and macrophage proliferation (Fig. 4E and fig. S13B) were dependent on both IL-4Rα and C1q. Consistent with the requirement for basophil-derived IL-4 in *L. monocytogenes*–induced liver macrophage proliferation (*26*), we observed increases in IL-4 and IL-13 cytokines in liver homogenates (fig. S13C). C1q and IL-4Rα deficiency were associated with increased liver injury as assessed by liver transaminases in blood (Fig. 4F) and a failure to up-regulate tissue-repair–related genes (*Acta2* and *Col1a1*) (Fig. 4G). Notably, at 3.5 days p.i., liver bacterial burden was higher in WT than in C1qa- or IL-4Rα–deficient mice (Fig. 4H). Gene-deficient mice had increased numbers of recruited monocytes (Fig. 4I) and higher inducible nitric oxide synthase (iNOS) expression in monocytes ($CD11b^+$ $Ly6C^+$) and liver macrophages ($CD11b^+$ $F4/80^+$) (fig. S13, D and E), but proinflammatory cytokines in liver homogenates were comparable (fig. S13F). These data suggest that C1q, through its ability to orchestrate IL-4Rα–dependent type 2–mediated responses, decreases the bactericidal capacity of monocyte-derived macrophages but also limits liver injury and promotes the return to homeostasis (Fig. 4, D to I, and fig. S13).

M(IL-4)s have recently emerged as important players in homeostatic processes (*27*), but IL-4Rα–dependent pathways are amplified during helminth infection, with uncontrolled amplification leading to fibrosis (*4*, *28*, *29*). Our data show that IL-4 drives production of local specific factors (SP-A and C1q) and expression of their receptor (Myo18A) on the macrophage surface for full M(IL-4) activation and proliferation (fig. S14). These findings reveal the existence within distinct tissues of an amplification system needed for type 2 function. SP-A and C1q are typically produced by alveolar epithelial type II and myeloid cells, respectively, indicating that several different cell types must respond to IL-4 for signal amplification.

The study raises a number of critical questions. What are the Myo18A co-receptors that mediate tissue specificity? What factors negatively regulate or stop the positive M(IL-4) loop? What are the intracellular signaling pathways regulated by Myo18A and its co-receptors? Critically, SP-A, C1q, and Myo18A are highly conserved across mammalian species, and we have shown the ability of SP-A and Myo18A to enhance human alveolar M(IL-4) proliferation.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/356/6342/1076/suppl/DC1
Materials and Methods
Figs. S1 to S14
Tables S1 and S2
References (*30*–*46*)

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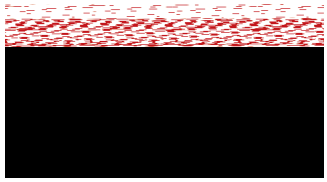

Local amplifiers of IL-4Rα–mediated macrophage activation promote repair in lung and liver

Carlos M. Minutti, Lucy H. Jackson-Jones, Belén García-Fojeda, Johanna A. Knipper, Tara E. Sutherland, Nicola Logan, Emma Rinqvist, Raquel Guillamat-Prats, David A. Ferenbach, Antonio Artigas, Cordula Stamme, Zissis C. Chroneos, Dietmar M. Zaiss, Cristina Casals and Judith E. Allen (May 11, 2017)

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Editor's Summary

Local macrophage clean-up

Infection, especially by helminths or bacteria, can cause tissue damage (see the Perspective by Bouchery and Harris). Minutti *et al.* studied mouse models of helminth infection and fibrosis. They expressed surfactant protein A (a member of the complement component C1q family) in the lung, which enhanced interleukin-4 (IL-4)-mediated proliferation and activation of alveolar macrophages. This activation accelerated helminth clearance and reduced lung injury. In the peritoneum, C1q boosted macrophage activation for liver repair after bacterial infection. By a different approach, Bosurgi *et al.* discovered that after wounding caused by migrating helminths in the lung or during inflammation in the gut of mice, IL-4 and IL-13 act only in the presence of apoptotic cells to promote tissue repair by local macrophages.

Science, this issue p. 1076, p. 1072; see also p. 1014