Retinoic acid (RA), a vitamin A metabolite, modulates mucosal T helper cell responses. Here we examined the role of RA in regulating IL-22 production by γδ T cells and innate lymphoid cells in intestinal inflammation. RA significantly enhanced IL-22 production by γδ T cells stimulated in vitro with IL-1β or IL-18 and IL-23. In vivo RA attenuated colon inflammation induced by dextran sodium sulfate treatment or Citrobacter rodentium infection. This was associated with a significant increase in IL-22 secretion by γδ T cells and innate lymphoid cells. In addition, RA treatment enhanced production of the IL-22–responsive antimicrobial peptides Reg3β and Reg3γ in the colon. The attenuating effects of RA on colitis were reversed by treatment with an anti–IL-22 neutralizing antibody, demonstrating that RA mediates protection by enhancing IL-22 production. To define the molecular events involved, we used chromatin immunoprecipitation assays and found that RA promoted binding of RA receptor to the IL-22 promoter in γδ T cells. Our findings provide novel insights into the molecular events controlling IL-22 transcription and suggest that one key outcome of RA signaling may be to shape early intestinal immune responses by promoting IL-22 synthesis by γδ T cells and innate lymphoid cells.

© 2013 Mielke et al. This article is distributed under the terms of an Attribution-Noncommercial-Share Alike-No Mirror Sites license for the first six months after the publication date (see http://www.rupress.org/terms). After six months it is available under a Creative Commons License (Attribution-Noncommercial-Share Alike 3.0 Unported license, as described at http://creativecommons.org/licenses/by-nc-sa/3.0/).
IL-22 in the intestine induces epithelial cell repair and secretion of antimicrobial peptides that limit bacterial dissemination and intestinal inflammation (Zheng et al., 2008; Sonnenberg et al., 2012). IL-22–deficient mice are more susceptible to colitis (Zenewicz et al., 2008), and IL-22 production is increased in the intestine of patients with Crohn's disease or ulcerative colitis (Geremia et al., 2011); however, little is known about the regulatory pathways controlling IL-22 production. The IL-23R signaling pathway and the nuclear factors aryl hydrocarbon receptor (AhR) and RAR-related orphan receptor gamma (ROR-γt) have been implicated in promoting IL-22 (Simonian et al., 2010; Qiu et al., 2012), although how these pathways interact with the IL-22 locus and the requirement for additional factors have not been investigated. γδ T cells and ROR-γt-expressing lamina propria innate lymphoid cells (ILC3; Spits et al., 2013) are two key sources of innate IL-22 (Chen et al., 2002; Sutton et al., 2009; Simonian et al., 2010; Li et al., 2011; Sawa et al., 2011; Spits and Di Santo, 2011), although IL-22 expression is not limited to these cell types (Zenewicz et al., 2007).

In the present study, we show that RA protects against colitis by promoting innate IL-22 production. RA enhanced IL-22 production by γδ T cells and ILC3, and this correlated with attenuated dextran sodium sulfate (DSS)– and Citrobacter rodentium infection–induced colon inflammation.

RESULTS AND DISCUSSION
RA enhances IL-22 production by LN γδ T cells and intestinal ILC3

We have previously shown that γδ T cells in LNs of mice can produce IL-22 in response to IL-1β or IL-18 with IL-23 independent of TCR stimulation (Sutton et al., 2009; Lalor et al., 2011), but the effects of RA on IL-22 production have not been investigated. Purified LN γδ T cells expressed both Rarα and Rarγt, and their expression increased upon stimulation with IL-1β and IL-23, as did Rorc expression (Fig. 1 A).

We examined the effect of RA on IL-22 production by LN γδ T cells. Addition of RA to purified γδ T cells significantly enhanced IL22 mRNA production induced by IL-1β and IL-23 or IL-18 and IL-23 (Fig. 1 B). RA also enhanced IFN-γ but suppressed IL-17 production by γδ T cells (Fig. 1 B).

We observed similar results when cytokine production was analyzed by flow cytometry (Fig. 1 C). CD27− γδ T cells produced IL-17 and IL-22 after stimulation with IL-1β and IL-23 (Fig. 1 D and not depicted), and RA appears to act as a molecular switch to inhibit IL-17 and promote IL-22 production. Treatment with an RAR inhibitor (RARi) hindered IL-22 production induced by purified γδ T cells stimulated with IL-1β and IL-23 (Fig. 1 E).

NKp46+ ILC3 (NCR+ ILC3) purified from the intestinal lamina propria also expressed Rara and Rarγt (Fig. 1 F). Furthermore, RA enhanced IL-22 production by NCR+ ILC3 (Fig. 1 G) and γδ T cells from the lamina propria (Fig. 1 H). In contrast, RA did not enhance IL-22 production by CD4+ T cells, although it did suppress IL-17 (not depicted). These results suggest that RA plays an important role in enhancing innate lymphocyte production of IL-22.

DSS treatment induces RA production in the colon, and RA is protective against colon inflammation

We tested the hypothesis that RA acts to enhance IL-22 production in vivo leading to protection against colitis. First we examined whether endogenous RA is produced during development of DSS-induced colitis. We examined expression of active aldehyde dehydrogenases, enzymes involved in RA production, by cleavage of a fluorescent synthetic substrate, ALDEFLUOR, which accumulates within the cell after cleavage. The total number of ALDEFLUOR+ CD11c+ DCs dramatically increased in the colon of mice treated with DSS, peaking on day 3, and remained increased at day 7 (Fig. 2 A). ALDEFLUOR+ CD11c+ DCs were also enhanced in mesenteric LNs (MLNs) and peaked 5 d after DSS treatment (Fig. 2, A and B). We also observed an increase in ALDEFLUOR staining of non-lymphocytes in the colon (Fig. 2 B). These results show that RA production by DCs and non-lymphocytes (possibly epithelial or stromal cells) increases during intestinal inflammation and may play a role in controlling DSS-induced inflammation.

Previous studies showed that mice reared on a vitamin A–deficient diet or mice lacking RARα have altered gut homeostasis resulting from defects in T helper cell activation, goblet cell hyperplasia, and alterations in the gut microbiome (Cha et al., 2010; Hall et al., 2011a). Treatment of mice with DSS results in damage to epithelial cells in the colon, thereby compromising barrier function and leading to inflammation, characterized by loss of crypt structure and gross shortening of the colon. Treatment of mice with RA for 7 d significantly reduced the DSS-induced colon shortening when compared with mice treated with DSS alone (Fig. 2 C). RA treatment also promoted recovery from colitis, even if administered after colitis was established (Fig. 2 D). To examine the role of endogenous RA without the possible conditioning effects of rearing mice on a vitamin A–deficient diet, we treated mice with an RARi. Blocking RA signaling enhanced colon shortening induced by DSS (Fig. 2 E). Histopathological analysis revealed that mice treated with DSS had morphological changes in their ascending colon, with crypt damage and inflammatory cell infiltrate characteristic of acute colitis, and that this intestinal inflammation was reversed by treatment with RA and exacerbated by treatment with RARi (Fig. 2, F and G). RA also reversed early weight loss (Fig. 2 H), colon shortening (Fig. 2 I), and intestinal inflammation (Fig. 2, J and K) induced by infection of mice with C. rodentium. RARi treatment exacerbated intestinal damage, as determined by colon shortening and histology, induced by C. rodentium infection (Fig. 2, I–K). These findings demonstrate that treatment with RA protects against intestinal damage in two models of colitis and suggest that endogenous RA plays a role in controlling intestinal inflammation.

RA increases IL-22 production in the colon

It has been reported that RA modulates production of IL-17 and IFN-γ by CD4+ T cells, cytokines thought to promote intestinal inflammation (Mucida et al., 2007; Elias et al., 2008; DePaolo et al., 2011). We have demonstrated that RA
production by ILC3 during colitis induced by DSS treatment or C. rodentium infection (Fig. 3 D). Furthermore, RA treatment enhanced the frequency of IL-22–secreting γδ T cells (Fig. 3 E). These results suggest that treatment with RA stimulates IL-22 production by ILC3 and γδ T cells during intestinal inflammation.

IL-22 and γδ T cells mediate the protective effect of RA in intestinal inflammation

We have shown that RA enhances IL-22 production by γδ T cells and that RA protects against colon inflammation. To test whether the protective effect of RA is mediated through...
IL-22, we neutralized IL-22 in vivo. Mice treated with DSS and isotype control antibody developed colitis, and disease symptoms were reduced by treatment with RA (Fig. 4, A and B). In contrast, administration of neutralizing antibodies to IL-22 reversed the protective effect of RA on colon length (Fig. 4 A) and weight loss (Fig. 4 B). Histological analysis revealed that anti-IL-22 reversed the protective effect of RA on colon inflammation and no longer prevented crypt damage in the colons of mice with DSS-induced colitis (Fig. 4, C and D). To confirm that IL-22 plays an antiinflammatory role in DSS-induced colitis, we examined the effect of direct administration of rIL-22. Treatment of wild-type mice with rIL-22 reversed colon shortening (Fig. 4 E) to a similar degree as treatment with RA (Fig. 2 B) and protected against weight loss (Fig. 4 F). We next used TCRδ−/− mice to examine the role of γδ T cells in mediating the protective effect of RA in colitis. We did not observe protection against colon shortening in TCRδ−/− mice treated with RA, whereas RA did protect TCRδ+− littermate controls (Fig. 4 G). In contrast, treatment with rIL-22 significantly reduced colon shortening in TCRδ−/− mice (Fig. 4 G). Collectively, our study demonstrates that endogenous IL-22 is protective against DSS-induced colon inflammation and that administration of IL-22 can enhance protection. In addition, RA attenuates intestinal inflammation at least in part by enhancing IL-22 production by γδ T cells, ILC3, and possibly other cell types.
RAR binds the Il22 promoter

The molecular events controlling Il22 transcription are not well defined. We determined the effect of RA on transcription of factors known to regulate IL-22 production and found that treatment of γδ T cells with IL-1β and IL-23 enhanced Il1r, Il23r, and Rorγt expression, but addition of RA did not influence their expression (Fig. 5 B). In addition, RA did not enhance expression of the γδ TCR (not depicted). Our in vitro studies with γδ T cells were performed in the absence of a TCR stimulus, suggesting that RA acts independently of TCR signaling to enhance IL-22 production. Because RARs act as transcription factors, we examined the possibility that RARα and RARγ act directly on the Il22 locus. We performed promoter analysis and found putative binding sites for RARα and RARγ in the promoter region of Il22 (Fig. 5 A). Using chromatin immunoprecipitation with a pan-RAR antibody, we observed binding of RAR to a site containing two predicted RAR-binding motifs (−1762 bp/−1654 bp) in the Il22 promoter in γδ T cells. Importantly, binding of RAR to this site was detected in cells stimulated with IL-1β, IL-23, and RA but not with IL-1β and IL-23 alone (Fig. 5 B). We did not observe any enrichment of the RARα-binding site (−5495 bp) in the promoter region of Il22, indicating that RARs were not bound to this site under these conditions. Binding of RAR to the promoter of Hoxb3 was included as a positive control, as it is a known RAR target gene (Fig. 5 B, right). Our findings show that RAR transcription factors bind to the Il22 promoter and provide a plausible mechanism whereby RA directly promotes Il22 transcription.

In this study, we have identified RAR as novel transcriptional regulators of the Il22 promoter. We have also demonstrated a previously unidentified function for RA in enhancing...
IL-22 production by γδ T cells and ILC3 and protecting against colon inflammation by initiating the repair process in the intestine. Together these findings suggest that RA can enhance innate lymphocyte function, integrating and enhancing signals from the environment whether they are pro- or antiinflammatory to promote CD4+ effector responses. Our study also demonstrates that RA initiates tissue repair by increasing innate IL-22 production by γδ T cells and innate lymphoid cells.

MATERIALS AND METHODS

Mice. C57BL/6 mice were obtained from Harlan UK and maintained at Trinity College Dublin in a specific pathogen–free facility. TCRδ-deficient mice were obtained from the Jackson Laboratory. Animal protocols were reviewed and approved by the Trinity College Dublin animal ethics committee.

Induction and assessment of DSS colitis. Mice were given 2% DSS (molecular weight: 36,000-50,000; MP Biomedicals) in their drinking water for 7 d, and mice were weighed every 24 h. Mice were treated i.p. with 200 µg all-trans RA (Enzo Life Sciences), 400 µg RARi (BMS 493; Tocris Bioscience), or DMSO as a control every second day. Where indicated, mice were given one i.p. dose of 500 µg anti–IL-22 (clone IL22JOP; eBioscience) or 500 µg rat IgG2a isotype control (eBioscience). In some experiments, mice were treated every day i.p. with 500 ng mouse rIL-22 (R&D Systems). Sections from the ascending colon of each mouse were analyzed using hematoxylin and eosin (H&E) staining. Colitis severity was assessed by a combined score of colon cellular infiltration (0–3, according to IL-22 production by γδ T cells and ILC3 and protecting against colon inflammation by initiating the repair process in the intestine. Together these findings suggest that RA can enhance innate lymphocyte function, integrating and enhancing signals from the environment whether they are pro- or antiinflammatory to promote CD4+ effector responses. Our study also demonstrates that RA initiates tissue repair by increasing innate IL-22 production by γδ T cells and innate lymphoid cells.
to the number and localization of the inflammatory cells) and tissue disruption (0–3, according to the severity of mucosal and crypt damages) as described previously (Smith et al., 2007). The histological scoring was performed in a blinded fashion.

**Intestinal inflammation induced by C. rodentium infection.** Mice were inoculated with 2 × 10^7 CFUs of C. rodentium by oral gavage. Mice were treated i.p. with 400 µg RA-Ri (BMS 493) or 200 µg RA every second day. Mice were weighed daily and analyzed between 6 and 8 d after infection.

**Cell preparation and stimulation.** LN γδ T cells were sorted using a mouse γδ T cell isolation kit (MACS; Miltenyi Biotech). Cells were cultured in cRPMI (RPMM containing 10% fetal calf serum, 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM l-glutamine [Invitrogen], and 50 µM 2-ME [Sigma-Aldrich]) with 10 ng/ml IL-1β, 10 ng/ml IL-23, or 10 ng/ml IL-18 and 100 nM all-trans RA or 0.5 or 5.0 µM RA-Ri. IL-22 concentrations in cell supernatants were determined by ELISA (R&D Systems). Intestinal lamina propria lymphocytes (LPLs) were extracted from the small intestine. In brief, the small intestine was collected and the Peyer’s patches removed. Intestines were opened longitudinally and cut into small pieces (<5 mm). Intraepithelial cells were removed by washing with HBSS and incubating with 5 mM EDTA for 20 min at 37°C. The intestinal pieces were washed with cRPMI, and LPLs were isolated by digestion with 1 µg/ml DNase (Sigma-Aldrich) and 500 µg/ml Collagenase D (Roche) for 40 min at 37°C. The LPL fractions were purified by 40/70% Percoll (GE Healthcare) gradient. In some experiments, NCR* ILC3 (CD3^+CD19^−CD11c^−NK1.1^−NKp46^+ cells) were sorted by FACS (MoFlo; Dako). Lamina propria γδ T cells were identified by sorting CD3^+γδTCCR* LPLs.

**Flow cytometry.** Purified γδ T cells were stimulated for 48–72 h, and brefeldin A (Sigma-Aldrich) was added for the last 4 h of culture. LPLs were restimulated with IL-1β and IL-23 for 12 h in the presence of brefeldin A. Cells were stained for surface markers CD3 (clone 500A2; BD), CD8 (clone 53-6.7; eBioscience), γδ TCR (clone eBioGL3; eBioscience), NKp46 (clone 29A1.4; eBioscience), or CD11c (clone N418; eBioscience). Intracellular cytokine staining (ICS) was performed with an IntraStain kit (Dako) or with Foxp3 fixation/permeabilization concentrate and diluent buffers (eBioscience) when staining for RORγt. Antibodies for ICS include IL-22 (clone 1HBPWSR; eBioscience), IL-17A (clone eBio17B7; eBioscience), INF-γ (clone XM1G1.2; eBioscience), and RORγt (clone B2D; eBioscience). Samples were analyzed with a FACSCanito (BD) with Flowjo software (Tree Star), with isotype or unstained controls to determine gating. The presence of some cells displaying aldehyde dehydrogenase activity was determined using an ALDEFLUOR staining kit (STEMCELL Technologies) as per the manufacturer’s instructions.

**Real-time PCR.** After cell stimulation or homogenization of colon sections, RNA was extracted using an RNeasy kit (QIAGEN) per the manufacturer’s instructions. For samples from mice treated with DSS, mRNA was further purified using the Dynabeads mRNA purification kit (Invitrogen). RT was performed using high-capacity cDNA RT kit (Applied Biosystems) followed by real-time PCR using an ABI PRISM7500 Sequence Detection System (Applied Biosystems). Analysis of Il12, Il17a, Ifnγ, Fos, Fosb, Mapk14, Rarα, and Ifna and Ifnb levels was performed using commercially available primer/probe sets (Applied Biosystems). Relative levels of expression were determined by normalization to Gapdh or 18S rRNA.

**Chromatin immunoprecipitation.** Purified LN γδ T cells were stimulated for 48 h with IL-1β and IL-23 (both 10 ng/ml) in the presence or absence or RA and fixed with 1% formaldehyde. Cell lysates were sheared and immunoprecipitated with pan-RAR antibody (clone M-545; Santa Cruz Biotechnology, Inc.) or a control HA antibody (Santa Cruz Biotechnology, Inc.). Bound DNA was purified and analyzed by quantitative PCR for enrichment of predicted RAR-binding sites. Primer sequences are available on request.

**Statistical analysis.** Data were compared by two-tailed Student’s t-test, one-way ANOVA, or Mann–Whitney U test. Where significant differences were found, the Tukey-Kramer multiple comparisons test was used for identifying differences between individual groups.

We thank B. Moran for technical help with FACS.

This work was supported by a Science Foundation Ireland Strategic Research Cluster grant and a Principal Investigator Award to K.H.G. Mills. K.H.G. Mills is Co-Founder and shareholder of Opsona Therapeutics Ltd. and TriMod Therapeutics Ltd., University start-up companies involved in the development of immunotherapeutics.

Submitted: 17 July 2012
Accepted: 1 May 2013

**REFERENCES**

Cha, H.R., S.Y. Chang, J.H. Chang, J.O. Kim, J.Y.Yang, C.H. Kim, and M.N. Kweon. 2010. Downregulation of Th17 cells in the small intestine by disruption of gut flora in the absence of retinoic acid. *J. Immunol.* 184:6799–6806. http://dx.doi.org/10.4049/jimmunol.0902944

Chen, Y., K. Chou, E. Fuchs, W.L. Havran, and R. Boismenu. 2002. Protection of the intestinal mucosa by intraepithelial gamma delta T cells. *Proc. Natl. Acad. Sci. USA.* 99:14338–14343. http://dx.doi.org/10.1073/pnas. 212290499

Coombes, J.L., K.R. Siddiqui, C.V. Aranchita-Cárano, J. Hall, C.M. Sun, Y. Belkaid, and E Powrie. 2007. A functionally specialized population of mucosal CD103⁺ DCs induces Foxp3 regulatory T cells via a TGF-β and retinoic acid-dependent mechanism. *J. Exp. Med.* 204:1757–1764. http://dx.doi.org/10.1084/jem.20070590

Denning, T.L., Y.C. Wang, S.R. Patel, I.R. Williams, and B. Pulendran. 2007. Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. *Nat. Immunol.* 8:1086–1094. http://dx.doi.org/10.1038/nici1511

DePaolis, R.W., V. Abadie, F. Tang, H. Fehliger-Price, J.A. Hall, W.W. Wang, E.V. Marietta, D.D. Kasarda, T.A. Waldmann, J.A. Murray, et al. 2011. Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens. *Nature.* 471:220–224. http://dx.doi.org/10.1038/nature09849

Elia, K.M., A. Laurence, T.S. Davidson, G. Stephens, Y. Kanno, E.M. Shevach, and J.J. O’Shea. 2008. Retinoic acid inhibits Th17 polarization and enhances Foxp3 expression through a Stat-3/Stat-5 independent signaling pathway. *Blood.* 111:1013–1020. http://dx.doi.org/10.1182/blood-2007-06-096438

Geremia, A., C.V. Aranchita-Cárano, M.P. Fleming, N. Rust, B. Singh, N.J. Mortensen, S.P. Travis, and F. Powrie. 2011. IL-23–responsive innate lymphocytes are increased in inflammatory bowel disease. *J. Exp. Med.* 208:1127–1133. http://dx.doi.org/10.1084/jem.20101712

Guilliams, M., K. Crozat, S. Henri, S. Tamoutournour, P. Grenot, E. Devlard, B. de Bovis, L. Aloxopoulou, M. Dalod, and B. Mahsen. 2010. Skin-draining lymph nodes contain dermis-derived CD103⁺ dendritic cells that constitutively produce retinoic acid and induce Foxp3⁺ regulatory T cells. *Blood.* 115:1958–1968. http://dx.doi.org/10.1182/blood-2009-09-245274

Hall, J.A., J.L. Cannons, J.R. Grainger, L.M. Dos Santos, T.W. Hand, S. Naak, E.A. Wohlert, D.B. Chou, G. Oldenhove, M. Robinson, et al. 2011a. Essential role for retinoic acid in the promotion of CD4⁺ T cell effector responses via retinoic acid receptor alpha. *Immunity.* 34:435–447. http://dx.doi.org/10.1016/j.immuni.2011.03.003

Hall, J.A., J.R. Grainger, S.P. Spencer, and Y. Belkaid. 2011b. The role of retinoic acid in tolerance and immunity. *Immunity.* 35:13–22. http://dx.doi.org/10.1016/j.immuni.2011.07.002

Iwata, M., A. Hiraiyama, Y. Eshima, H. Kagetchika, C. Kato, and S.Y. Song. 2004. Retinoic acid imprints gut-homing specificity on T cells. *Immunity.* 21:527–538. http://dx.doi.org/10.1016/j.immuni.2004.08.011

Lalor, S.J., L.S. Dungan, C.E. Sutton, S.A. Basdeo, J.M. Fletcher, and K.H. Mills. 2011. Caspase-1–processed cytokines IL-1betta and IL-18 promote IL-17 production by gammacelta and CD4 T cells that mediate autoimmune. *J. Immunol.* 186:5738–5748. http://dx.doi.org/10.4049/jimmunol.1005397
Anticolitic effects of RA mediated by IL-22 | Mielke et al.

Li, Y., S. Innocentin, D.R. Withers, N.A. Roberts, A.R. Gallagher, E.F. Grigorieva, C. Wilhelm, and M. Veldhoen. 2011. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. Cell. 147:629–640. http://dx.doi.org/10.1016/j.cell.2011.09.025

Mora, J.R., M. Iwata, B. Eksteen, S.Y. Song, T. Junt, B. Semnan, K.L. Otipoby, A. Yokota, H. Takeuchi, P. Ricciardi-Castagnoli, et al. 2006. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. Science. 314:1157–1160. http://dx.doi.org/10.1126/science.1132742

Mucida, D., Y. Park, N. Satoh-Takayama, S. Dulauroy, M. Bérard, M. Kronenberg, and H. Cheroutre. 2007. Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science. 317:256–260. http://dx.doi.org/10.1126/science.1145697

Pino-Lagos, K.Y. Guo, C. Brown, M.P. Alexander, R. Elgueta, K.A. Bennett, V. De Vries, E. Nowak, R. Blomhoff, S. Sockanathan, et al. 2011. A retinoic acid–dependent checkpoint in the development of CD4+ T cell–mediated immunity. J. Exp. Med. 208:1767–1775. http://dx.doi.org/10.1084/jem.20102358

Qiu, J., J.J. Heller, X. Guo, Z.M. Chen, K. Fish, Y.X. Fu, and L. Zhou. 2012. The aryl hydrocarbon receptor regulates gut immunity through modulation of innate lymphoid cells. Immunity. 36:92–104. http://dx.doi.org/10.1016/j.immuni.2011.11.011

Sawa, S., M. Lochner, N. Satoh-Takayama, S. Dulauroy, M. Bérard, M. Kronenberg, and H. Cheroutre. 2011. RORγt+ innate lymphoid cells regulate intestinal homeostasis by integrating negative signals from the symbiotic microbiota. Nat. Immunol. 12:320–326. http://dx.doi.org/10.1038/ni.2002

Simonian, P.L., F. Wehrmann, C.L. Roark, W.K. Born, R.L. O'Brien, and A.P. Fontenot. 2010. γδ T cells protect against lung fibrosis via IL-22. J. Exp. Med. 207:2239–2253. http://dx.doi.org/10.1084/jem.20100061

Slington, D., D. Artis, M. Colonna, A. Diefenbach, J.P. Di Santo, G. Eberl, S. Koyasu, R.M. Locksley, A.N. McKenzie, R.E. Mebius, et al. 2013. Intraepithelial lymphocytes—a proposal for uniform nomenclature. Nat. Rev. Immunol. 13:145–149. http://dx.doi.org/10.1038/nri3365

Sun, C.M., J.A. Hall, R.B. Blank, N. Bouladoux, M. Oukka, J.R. Mora, and Y. Belkaid. 2007. Small intestine lumina propra dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. J. Exp. Med. 204:1775–1785. http://dx.doi.org/10.1084/jem.20070602

Sutton, C.E., S.J. Lalor, C.M. Sweeney, C.F. Berettoni, E.H. Lavelle, and K.H. Milik. 2009. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmune. Immunity. 31:331–341. http://dx.doi.org/10.1016/j.immuni.2009.08.001

Yokota, A., H. Takeuchi, N. Maeda, Y. Ohoka, C. Kato, S.Y. Song, and M. Iwata. 2009. GM-CSF and IL-4 synergistically trigger dendritic cells to acquire retinoic acid-producing capacity. Int. Immunol. 21:361–377. http://dx.doi.org/10.1093/intimm/dxp003

Zenewicz, L.A., G.D. Yancopoulos, D.M. Valenzuela, A.J. Murphy, M. Karow, and R.A. Flavell. 2007. Interleukin-22 but not interleukin-17 provides protection to hepatocytes during acute liver inflammation. Immunity. 27:647–659. http://dx.doi.org/10.1016/j.immuni.2007.07.023

Zenewicz, L.A., G.D. Yancopoulos, D.M. Valenzuela, A.J. Murphy, S. Stevens, and R.A. Flavell. 2008. Innate and adaptive interleukin-22 protects mice from inflammatory bowel disease. Immunity. 29:947–957. http://dx.doi.org/10.1016/j.immuni.2008.11.003

Zheng, Y., P.A. Valdez, D.M. Danken, Y. Hu, S.M. Sa, Q. Gong, A.R. Abbas, Z. Modrusan, N. Ghildali, F.J. de Sauvage, and W. Ouyang. 2008. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. Nat. Med. 14:282–289. http://dx.doi.org/10.1038/nm1720