



COMMENTARY

Innate B cells: oxymoron or validated concept? [v1; ref status: indexed, <http://f1000r.es/T4CAVP>]

Carl F Ware^{1*}, Chris Benedict^{2*}

¹Laboratory of Molecular Immunology, Infectious and Inflammatory Diseases Center, Sanford-Burnham Medical Research Institute, California, 92037, USA

²Division of Immune Regulation, La Jolla Institute for Allergy and Immunology, California, 92037, USA

* Equal contributors



v1 **First Published:** 02 Aug 2012, 1:8 (doi: 10.12688/f1000research.1-8.v1)
Latest Published: 02 Aug 2012, 1:8 (doi: 10.12688/f1000research.1-8.v1)

Abstract

B lymphocytes promote the initial innate interferon response to viral pathogens without the need for antigen receptor activation. B cell dependent IFN production requires the cytokine, lymphotoxin- β . The LT β pathway is well known to regulate lymphoid organogenesis and homeostasis by differentiating stromal cells and macrophages. However, in response to viral pathogens these same B cell-regulated populations rapidly produce type 1 interferons. Thus, B cells act as innate effector cells via LT β homeostatic pathways, which serve as innate host barriers to viral pathogens.

Article Status Summary

Referee Responses

Referees	1	2	3
v1 published 02 Aug 2012	 report	 report	

- Barry Rouse**, The University of Tennessee USA
- Peter Ghazal**, University of Edinburgh Medical School UK
- Mariapia Delgi-Esposti**, The University of Western Australia Australia

Latest Comments

No Comments Yet

Corresponding author: Carl F Ware (cware@sanfordburnham.org)

How to cite this article: Ware CF, Benedict C (2012) Innate B cells: oxymoron or validated concept? [v1; ref status: indexed, <http://f1000r.es/T4CAVP>] *F1000Research* 2012, 1:8 (doi: 10.12688/f1000research.1-8.v1)

Copyright: This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

Grant information: This work was supported by grants to CFW from the National Institutes of Health (AI033068 and AI048074). *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

Competing Interests: No competing interests were disclosed.

First Published: 02 Aug 2012, 1:8 (doi: 10.12688/f1000research.1-8.v1)

First Indexed: 15 Aug 2012, 1:8 (doi: 10.12688/f1000research.1-8.v1)

Lymphotoxin- β pathway and innate B cells

The B cell is an icon of the adaptive immune system, secreting a specific antibody that prevents re-infection by pathogens. Although some B cell subsets (e.g., B1 cells) show characteristics of “innate” cells (defined here as cells that do not utilize antibody or antigen receptor genes), the concept of an “innate B cell” somehow doesn’t register. However, accumulating evidence validates another view of B cells, one as an innate effector cell initiating the earliest response against viral pathogens, independently of antibody. In two studies, B cells were shown to control the initial type 1 IFN response to very different viral pathogens in lymphoid tissues, cytomegalovirus (CMV, a β -herpesvirus with a large DNA based genome)¹ and vesicular stomatitis virus (VSV, a small RNA virus that causes lympho-neurotropic pathogenicity)².

Schneider *et al.*¹ established the B cell dependence of the IFN β response to infection with CMV. This innate IFN defense mechanism was surprisingly independent of Toll-like receptor pathways, but required the Lymphotoxin (LT)- β receptor signaling pathway, part of the larger superfamily of cytokines related to TNF^{3,4}. Conditional deletion of the LT β gene in B cells, but not T cells, provided the key evidence pinpointing the involvement of LT β in B cells in the initial IFN response to CMV. The LT-IFN response occurs rapidly, initiating within a couple of hours after infection, well before adaptive immunity could contribute. Expression of the IFN β gene occurred primarily in virus-infected stromal cells in the spleen and accounted for the majority of the circulating IFN $\alpha\beta$. Blocking the LT-IFN pathway resulted in destruction of the splenic architecture and an apoptotic collapse of T and B lymphocytes⁵.

Moseman *et al.*² demonstrated the critical role of the B cell dependent LT-IFN defense pathway in response to VSV. Importantly, antibody deficient μ MT and DHLMP2a mice revealed IFN β expression in response to VSV occurred independently of B cell antigen receptor. In the absence of LT β or IFN signaling, VSV infected the lymphatic neurons and spread into the central nervous system with ensuing paralysis. These results provide strong evidence for the innate action of B cells through the LT-IFN pathway. The effectiveness of the LT-IFN pathway against two distinct pathogens suggests a more generalized role in host defense.

The architecture of host defense

The current evidence indicates the innate B cell driven LT-IFN pathway operates during infections in lymphoid tissues. A convergence of recent results may explain this observation. Mouse CMV productively infects reticular fibroblasts in the splenic marginal zone, but also subcapsular sinus macrophages in lymph nodes that express high CD169+ (SIGLEC1) (Figure 1)⁶. Interestingly, CD169+ macrophages uniquely support VSV infection in lymph nodes and provide the primary source of IFN α during the initial phase of infection with VSV⁷. Importantly, these CD169+ macrophages require the LT $\alpha\beta$ -LT β R pathway to populate the subcapsular regions in lymph nodes and the marginal sinus of the spleen^{8,9}. LT β receptor signaling regulates stromal cell expression of homeostatic chemokines (e.g., CXCL13, CCL21) that help to position CD169+ macrophages in lymph nodes and spleen. In the absence of LT β R signaling, CD169+ subcapsular macrophages no longer reside in lymph nodes, depriving the virus of a permissive cell for replication, with a

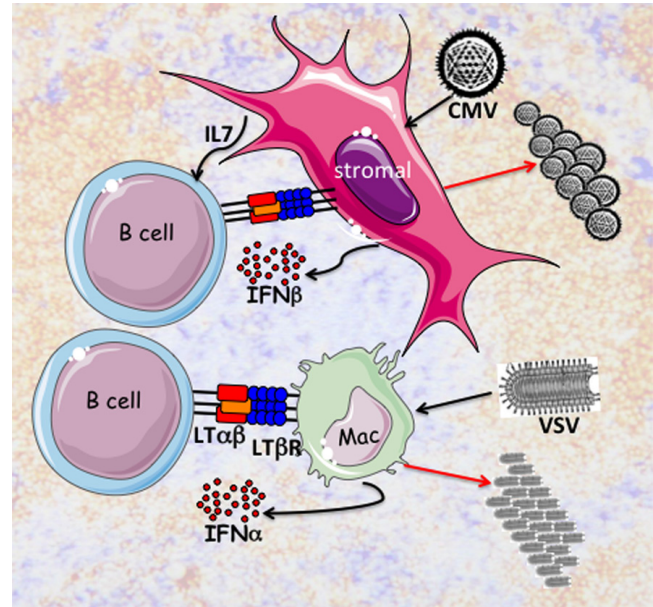


Figure 1. Innate B cells initiate production of type 1 interferons (IFN $\alpha\beta$).

commensurate loss in IFN α production. The mechanism underlying the permissiveness of the CD169+ macrophages is not entirely understood, however Khanna and Lefrancois¹⁰ point out that these macrophages have limited capacity to respond to IFN due to expression of *Usp18*¹¹ encoding an ISG15-deconjugating peptidase that destabilizes multiple antiviral proteins induced by IFN¹².

B cells express the TNF-related ligand LT $\alpha\beta$ that specifically engages the LT β R expressed in lymphoid tissue stromal cells (pink) and myeloid lineage cells including subcapsular macrophages (green). The B cell to stromal cell interaction maintains the homeostasis of lymphoid tissues through secretion of chemokines and IL7, which enhance the expression of LT $\alpha\beta$. Cytomegalovirus (CMV) infects stromal cells (ERTR7+ fibrocytes) in the splenic marginal zone from which IFN β is rapidly expressed and secreted. B cell expression of LT $\alpha\beta$ is also required for CD169+ subcapsular macrophages in lymph nodes. Vesicular stomatitis virus (VSV) infects subcapsular macrophages inducing production of IFN α . Virus replication and progeny are produced (red arrows) in the permissive stromal cells or CD169+ macrophages. IFN $\alpha\beta$ protect uninfected cells in the surrounding microenvironment.

Lymphoid organs provide the structural environment that positions key cells, such as the sinus lining macrophages, directly in the flow of lymph and blood in order to capture pathogens¹³. Yet, intentionally providing a pathogen with a source of permissive cells seems counterintuitive as a defense strategy. However, amplifying the level of viral antigens to increase presentation to adaptive immune cells could counterbalance this potential danger. Moreover, the powerful selective pressure that the IFN system places on the pathogen is relieved in the permissive macrophage, potentially limiting the emergence of mutant viruses resistant to IFN. Neighboring

cells that remain responsive to IFN signaling should be protected, corralling the pathogen within this macrophage-populated niche.

The Lymphotoxin- β pathway orchestrates the embryonic development of lymph nodes and Peyer's Patches^{14–16}. In the adult, B lymphocytes constitutively expressing LT β are the primary cells responsible for the maintenance of the microarchitecture of the spleen and lymph nodes. Thus, this LT β -dependent developmental pathway is reflected in the adult as an innate B cell host defense mechanism. Recent evidence indicates that bacterial pathogens are controlled in part by innate acting B cells utilizing pattern-recognition receptors and producing granulocyte-macrophage colony-stimulating factor¹⁷.

Together these findings validate the notion that adaptive immune cells can mediate effector functions independent of antigen receptor activation thus serving as innate effectors. Conversely, innate effector cells, NK cells display immunologic memory¹⁸, an iconic trait of adaptive immunity. These observations indicate the conventional notion of innate and adaptive cells is in need of revision.

References

- Schneider K, Loewendorf A, De Trez C, *et al.*: **Lymphotoxin-mediated crosstalk between B cells and splenic stroma promotes the initial type I interferon response to cytomegalovirus.** *Cell Host Microbe*. 2008; **3** (2): 67–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Moseman EA, Iannacone M, Bosurgi L, *et al.*: **B Cell Maintenance of Subcapsular Sinus Macrophages Protects against a Fatal Viral Infection Independent of Adaptive Immunity.** *Immunity*. 2012; **36** (3): 415–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Locksley RM, Killeen N, Lenardo MJ, *et al.*: **The TNF and TNF receptor superfamilies: Integrating mammalian biology.** *Cell*. 2001; **104**: 487–501.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ware CF: **NETWORK COMMUNICATIONS: Lymphotoxins, LIGHT, and TNF.** *Annu Rev Immunol*. 2005; **23**: 787–819.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Banks TA, Rickert S, Benedict CA, *et al.*: **A lymphotoxin-IFN-beta axis essential for lymphocyte survival revealed during cytomegalovirus infection.** *J Immunol*. 2005; **174** (11): 7217–25.
[PubMed Abstract](#)
- Hsu KM, Pratt JR, Akers WJ, *et al.*: **Murine cytomegalovirus displays selective infection of cells within hours after systemic administration.** *J Gen Virol*. 2009; **90** (Pt 1): 33–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Iannacone M, Moseman EA, Tonti E, *et al.*: **Subcapsular sinus macrophages prevent CNS invasion on peripheral infection with a neurotropic virus.** *Nature*. 2010; **465**: 1079–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Nolte MA, Arens R, Kraus M, *et al.*: **B cells are crucial for both development and maintenance of the splenic marginal zone.** *J Immunol*. 2004; **172** (6): 3620–7.
[PubMed Abstract](#)
- Matsumoto M, Fu YX, Molina H, *et al.*: **Lymphotoxin-alpha-deficient and TNF receptor-I-deficient mice define developmental and functional characteristics of germinal centers.** *Immunol Rev*. 1997; **156**: 137–44.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Khanna KM, Lefrancois L: **B cells, not just for antibody anymore.** *Immunity*. 2012; **36** (3): 315–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Honke N, Shaabani N, Cadeddu G, *et al.*: **Enforced viral replication activates adaptive immunity and is essential for the control of a cytopathic virus.** *Nat Immunol*. 2011; **13** (1): 51–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Zhang D, Zhang DE: **Interferon-stimulated gene 15 and the protein ISGylation system.** *J Interferon Cytokine Res*. 2011; **31** (1): 119–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Junt T, Scandella E, Ludewig B: **Form follows function: lymphoid tissue microarchitecture in antimicrobial immune defence.** *Nat Rev Immunol*. 2008; **8** (10): 764–75.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rennett PD, Browning JL, Mebius R, *et al.*: **Surface lymphotoxin a/b complex is required for the development of peripheral lymphoid organs.** *J Exp Med*. 1996; **184**: 1999–2006.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Mebius RE: **Organogenesis of lymphoid tissues.** *Nat Rev Immunol*. 2003; **3** (4): 292–303.
[PubMed Abstract](#) | [Publisher Full Text](#)
- De Togni P, Goellner J, Ruddle NH, *et al.*: **Abnormal development of peripheral lymphoid organs in mice deficient in lymphotoxin.** *Science*. 1994; **264**: 703–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rauch PJ, Chudnovskiy A, Robbins CS, *et al.*: **Innate response activator B cells protect against microbial sepsis.** *Science*. 2012; **335** (6068): 597–601.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Vivier E, Raulet DH, Moretta A, *et al.*: **Innate or adaptive immunity? The example of natural killer cells.** *Science*. 2011; **331** (6013): 44–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Author contributions

Both authors CFW and CB contributed equally to this article.

Competing interests

The authors declare no financial conflict of interest related to this article.

Grant information

This work was supported by grants to CFW from the National Institutes of Health (AI033068 and AI048074).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

The authors recognize the efforts of the dedicated scientists in their laboratories that contributed to the experimental work including Kirsten Schneider and Antje Rhode, and art design by Vasileios Bekiaris.

Current Referee Status:



Referee Responses for Version 1



Mariapia Delgi-Esposti, Experimental Immunology, The University of Western Australia, WA 6009, Australia

Approved: 15 August 2012

Ref Report: 15 August 2012

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



Peter Ghazal, University of Edinburgh Medical School, Edinburgh, EH16 4SB, UK

Approved: 14 August 2012

Ref Report: 14 August 2012

This commentary summarises recent findings which point to a previously under-appreciated role of B-cells acting as innate effector cells in immunity.

The authors build on the notion for a continuum of activity between the innate and adaptive arms of the immune system, integrated at the cellular level via B-cells. Accordingly, this commentary convincingly argues for reconsideration of the conventional view of the role played by innate and adaptive cells of the immune system.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



Barry Rouse, Department of Pathobiology, College of Veterinary Medicine, The University of Tennessee, Knoxville, TN, USA

Approved with reservations: 06 August 2012

Ref Report: 06 August 2012

This succinct scholarly review has an interesting story but its title could mislead.

Accordingly it gives a nice account about how B cells subserve a protective function other than by their main raison d'être (antibody production). What it does not do is to provide any evidence for contradictory terminology. Thus the primary function of B cells remains adaptive immunity with their foray into innate immunity also possible, just like countless other cell types. Cells, like us, have many activities some of which are primary and pay the bills and others minor distractions- like surfing if you happen to live in San Diego!

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.
