Dendritic cells and influenza A virus infection

Jason Waithman¹ and Justine D. Mintern²,*

¹Telethon Institute for Child Health Research; Centre for Child Health Research; The University of Western Australia; West Perth, WA Australia; ²Department of Biochemistry and Molecular Biology; The University of Melbourne; Melbourne, VIC Australia

Keywords: dendritic cells, influenza A virus, antigen presentation

Abbreviations: cDC, conventional dendritic cell; DC, dendritic cell; iBALT, inducible bronchus-associated lymphoid tissue; IAV, influenza A virus; IFNR, interferon receptor; MHC, major histocompatibility class; NS1, nonstructural protein 1; pDC, plasmacytoid dendritic cell; IFN, interferon; ssRNA, single-stranded RNA; TLR, Toll-like receptor

Influenza A virus (IAV) is a dangerous virus equipped with the potential to evoke widespread pandemic disease. The 2009 H1N1 pandemic highlights the urgency for developing effective therapeutics against IAV infection. Vaccination is a major weapon to combat IAV and efforts to improve current regimes are critically important. Here, we will review the role of dendritic cells (DCs), a pivotal cell type in the initiation of robust IAV immunity. The complexity of DC subset heterogeneity in the respiratory tract and lymph node that drains the IAV infected lung will be discussed, together with the varied and in some cases, conflicting contributions of individual DC populations to presenting IAV associated antigen to T cells.

CD8⁺ T cell immunity against pathogens, such as IAV, that do not primarily infect DCs. Therefore, DCs are a heterogeneous population of cells, with different subsets displaying specialized antigen presenting functions.

To date, the identity of the DCs involved and the exact nature of the mechanisms utilized to initiate IAV-specific T cell immunity remain controversial. There is considerable complexity in identifying subpopulations of the DC family. Developmental stages are still being defined, together with increasing numbers of lineage markers to define end-stage subpopulations. Having said this, significant progress has identified distinct DC family members that can now be readily defined. DCs are routinely subdivided into two major subsets that include plasmacytoid DCs (pDCs) and myeloid DCs, with the latter commonly referred to as conventional DCs (cDCs). pDCs are a major source of the antiviral cytokine interferon-α (IFNα). cDCs that are isolated from the lymph node that drains the lung represent a mixture of lymphoid resident DCs that do not traffic to peripheral tissues, and tissue-derived, “migratory” DCs. At least three lymphoid resident DC subsets are described and can be subcategorized based on their expression of the lymphocyte markers CD4 and CD8 (CD8⁺ DCs, CD4⁺ DCs and CD8⁻ CD4⁻ DCs). Two migratory DC subsets are defined and are subdivided based on their expression of the mucosal γδ integrin marker CD103 and myeloid marker CD11b (CD103⁺CD11b⁺ and CD103⁻CD11b⁺). In addition to cDCs and pDCs that are present in uninfected airways and lymph nodes, the inflammatory environment elicited by IAV infection recruits monocyte-derived “inflammatory DCs” to the lung parenchyma. These DCs are also referred to as tumor necrosis factor producing inducible nitric oxide synthetase-producing (TIP) DCs or interferon killer (IKDCs). Inflammatory DCs typically express CD11b and can be distinguished from conventional CD11b DCs by several specific lineage markers including Ly6C. Finally, alveolar macrophages are a dominant cell type in the pulmonary tract that are often confused with DCs, given their expression of CD11c, but can be excluded from DC populations based on their high autofluorescence¹ as well as their exclusive expression of siglec F and CD2. Therefore, many DC populations contribute to eliciting immunity to IAV both in the infected lung tissue and in the associated lymph node (Table 1).
Detection of Influenza A Virus

DCs provide a first line of defense following IAV infection. Equipped with sensors to detect viral products, DCs alert the immune system to the presence of infectious virus. Invading IAV are detected by “pattern recognition receptors” (PRR). In early studies, the molecular signature generated by IAV was considered to be double-stranded viral RNA (dsRNA) recognized by Toll-like receptor 3 (TLR3). A role for TLR3 was subsequently considered unlikely, however, given that the concentration of dsDNA generated by IAV is unlikely to be sufficient to signal TLR3. Instead, the IAV polymerase generates uncapped single-stranded RNA (ssRNA) that serves as a unique molecular signature, readily identified by the immune system as foreign. Interestingly, a growing number of cytosolic receptors that are capable of detecting viral products are being defined. These include members of the RNA helicase RIG-I-like receptor, Nod-like receptor and AIM2-like receptor families. It is becoming increasingly apparent that multiple receptors are involved in detecting IAV.

Table 1. Summary of dendritic cell subsets contributing to influenza A virus immunity

| Population      | CD11c | MHCIi | CD45RA | sirpa | CD11b | CD103 | Ly6C | CD8 |
|-----------------|-------|-------|--------|-------|-------|-------|------|-----|
| Plasmacytoid DC | int   | +     | +      | -     | -     | -     | -    | +/- |
| CD8+            | hi    | +     | -      | -     | -     | +/-   | -    | +   |
| CD8-            | hi    | +     | -      | -     | +     | -     | -    |     |

Migratory DC

| CD11b | hi    | +     | -      | +     | -     | -     | -    |     |
| CD103  | hi    | +     | -      | -     | -     | +     | -    |     |

Inflammatory DC

| hi    | +     | -      | +     | -     | +     | -     |     |
N terminus,33 it was previously considered that NS1 sequestered influenza A virus dsRNA.39 Instead, NS1 forms a complex with RIG-1.16 Finally, once IAV is cleared from the host, the inflammatory cascade must be shut down. Turning off the inflammatory response to IAV requires NLRX1, which acts to dampen RIG-1-mediated responses to IAV.36 In summary, detection of IAV by DCs (and other cell types) is a complex process with the participation of several innate immune pathways and an active counterattack by the virus itself.

Initiation of T Cell Immunity to Influenza A Virus Antigen

While it is well-documented that CD4+ and CD8+ T cell immunity is initiated in response to IAV-associated antigens, the identification of the specific DC subsets that are responsible for presenting antigen to the respective T cell populations is the subject of intense ongoing research. Analysis of individual DC subsets and their role in antigen presentation following IAV infection has mostly relied on ex vivo analysis of isolated DC populations. In particular, the DC responsible for MHCI antigen presentation of IAV antigen to CD8+ T cells is a source of great debate. There are several conflicting reports as to which DC is responsible. On the one hand, MHCI antigen presentation of IAV antigen was attributed to CD11b+ DCs,37 while in a separate study, CD103+ DCs were deemed the responsible subset.38 The divergent results could not be explained by different methodologies used to detect IAV-derived antigen in the context of H-2Kb, as both studies utilized the same TCR-like mAb. Additional studies add to the confusion where IAV antigen is presented by CD8+ DCs is also implicated in IAV MHCI antigen presentation, with one report excluding these cells ex vivo.39

Intratracheal administration of diphtheria toxin (DT) transiently depletes lung CD11c+ DCs in CD11c.DTR mice.46 In this setting, CD8+ T cell responses are impaired, implicating a requirement for migratory DCs in IAV MHCI antigen presentation.39,42 The DT system must be viewed with caution; however, as other key populations including alveolar macrophages, which can harbor infectious IAV virions can also be eliminated. DT treatment may therefore remove a potential antigen source for DCs, rather than remove critical antigen presenting cells themselves. In addition, DT treatment has the potential to impact and reduce lymphoid resident DCs. Therefore, this system needs to be interpreted with caution. Another model relies on the langerin.DTR mice,47 where DT administration specifically ablates langerin-expressing CD103+ DCs. Treatment of langerin.DTR mice with DT following IAV infection results in reduced IAV MHCI antigen presentation and impaired anti-IAV CD8+ T cell immunity.42 This implicates an important role for CD103+ DCs, although the fact that some anti-IAV CD8+ T cell effectors are primed indicates that more than one DC subset can participate in the response. Again, however, this model has its caveats. Specifically, CD103+ DC can be directly infected with IAV43 and therefore can deliver IAV antigens to other DC subsets, including the lymphoid resident DCs.41 Therefore, the loss of this population in DT-treated langerin.DTR mice could be misinterpreted as a key role in priming, rather than the provision of IAV antigen. This complexity is also applicable to the studies performed in mice lacking the chemokine receptor CCR7.48 In the absence of CCR7, lung resident CD11b+ and CD103+ DCs are unable to emigrate from the lung to the draining lymph node.49 Again, the role of CD103+ DCs as an antigen source, rather than the DC subset that initiates MHCI antigen presentation must be considered. In addition, CCR7-/- lymphoid resident DCs may be unable to migrate to the paracortex to efficiently interact with naïve CD8+ T cells. This again makes the contribution of lymphoid resident DCs difficult to exclude. Fortunately, there seems to be a consensus with regards to which DC populations are not involved in MHCI antigen presentation of IAV. pDCs do not present IAV antigens via MHCI to CD8+ T cells,39,41,42 although they are implicated in promoting anti-IAV B cell immunity.42 CD8+ lymph node resident DCs are not implicated in MHCI IAV antigen presentation.37-45 Finally, inflammatory monocyte-derived DCs do not play a crucial role in the lung-draining lymph node with only very modest CD8+ T cell priming elicited from these cells ex vivo.39

Role of Lung Resident DCs during Influenza A Virus Infection

It is becoming increasingly evident that effector CD8+ T cells continue to divide in the lung at sites of IAV pathology after their departure from the lymph nodes.50 Such an event is attributed to DCs,51 which are continually recruited to the lungs throughout the course of IAV infection.10,51,52 These include pDCs and cDCs,39,40,42 as well as inflammatory monocyte-derived DCs10,52 and IKDCs.9
The majority of the lung DC populations, with the exception of pDCs, appear to possess IAV antigens and can stimulate IAV-specific T cells ex vivo. However, to date the overall contribution and consequence of antigen presentation by these DC subsets remains unclear. Provision of local stimulation by respiratory tract DCs is required for optimal anti-IAV T cell immunity with this response being dependent on the provision of IL-15. CD8+ DCs, a subpopulation considered to reside only in the lymphoid compartment, is also reported to be present in the lungs following IAV infection. It is unclear whether DC8+ DCs precursors migrate from the blood to the infectious site, or whether the terminally differentiated cells migrate to the infected lung from the lymph node. In addition, it is unknown whether other lymphoid resident DC subsets, such as CD4+ DCs, are also present in abundant numbers at the infectious site. One possibility is that CD8+ DCs are associated with induced bronchus-associated lymphoid tissue (iBALT), but this remains to be formally demonstrated. Maintenance of iBALT structures depends on the presence of lung DCs, but the overall contribution of specific subsets within these structures and at other sites in the lung during influenza infection remains to be elucidated.

How Do Dendritic Cells Acquire Influenza A Virus Antigen?

As discussed, abundant evidence shows that respiratory tract DC traffic and present IAV-derived antigen to T cells in the lymph node that drains the IAV-infected lung. In brief, there are two major mechanisms by which this antigen can be acquired. First, DCs may capture and phagocytose infected airway cells. This has been described for human immature DCs that phagocytose apoptotic IAV-infected monocytes in vitro. In this case, the experiments were designed to exclude a role for the direct infection of DCs with the virus itself. IAV infected cells appear to undergo typical apoptosis with the display of phosphatidylserine at the infected cell surface being the most likely trigger for phagocytosis. CD36 and the αvβ5 integrin are implicated as receptors that immature DCs employ to capture and acquire apoptotic IAV infected cell cargo. Notably, excluding direct infection of DCs with IAV is not an easy undertaking. Utilizing an interesting and novel approach, Langlois et al. generated a virus containing hematopoietic-specific microRNA target sites inserted within the nucleoprotein gene. Infection with this virus results in undetectable transcription and replication in hematopoietic cells, including DCs, but intact IAV infection of epithelial cells. In this scenario, viral clearance and CD8+ T cell responses are not altered. While it is difficult to rule out whether this approach is strictly excluding IAV infection in all relevant DC populations, this study does imply that DC acquisition of viral infected cells is a significant pathway by which DCs can elicit IAV immunity.

The second major mechanism by which respiratory tract DCs acquire IAV antigen is to be directly infected with the virus itself. There are plenty of examples of IAV infection of DCs in vitro. Mouse bone marrow-derived DCs, mouse splenic DCs, human blood monocyte-derived DCs and primary human myeloid, but not plasmacytoid, DCs can be infected with IAV in vitro. Infecting DCs with IAV can result in expression of viral proteins, but does not necessarily elicit infectious virions. Whether we can extrapolate these findings to infection of pulmonary tract DCs during live IAV infection is debatable. DC subsets isolated directly from the pulmonary airways can also be infected with IAV in vitro, although this depends on the strain of virus and the specific DC subset. The CD103+ DCs is the most susceptible DCs to IAV infection, with CD11b+ DCs displaying intermediate susceptibility and pDCs being the most resistant. Isolation of DC subsets from IAV-infected mice confirms the differential infectivity of DC subsets, with the CD103+ DCs being the major subset containing infectious IAV virus. Differential infection of DC subsets correlates with their use of type I IFN receptor (IFNR) signaling, giving that ablation of IFNR signaling enhances viral replication in CD11b+ DCs. Constraining IFN signaling in CD103+ DCs to allow IAV infection may serve to promote IAV antigen presentation once CD103+ DCs arrive in the lymph node. DCs isolated from the lungs of mice infected with highly pathogenic H1N1 and H5N1 IAV strains, were productively infected and could liberate infectious virus. Infection of DCs with IAV is primarily mediated by the recognition of cell surface sialic acid (SA) that is expressed by host cell glycoproteins and glycolipids. Binding of SA by viral hemagglutinin (HA) is the primary mode of IAV attachment; however, the presence of SA is not always sufficient for cell infection. Several C-type lectins known to be expressed by DCs are implicated in IAV entry including macrophage mannose receptor (MMR), a type I integral transmembrane protein with Ca2+-dependent specificity for terminal D-mannose, N-acetyl-D-glucosamine and L-fucose; macrophage galactose type lectin (MGL), a type II transmembrane glycoprotein with Ca2+-dependent specificity for terminal galactose, Lewis-X structures and terminal GalNAc residues and DC-specific ICAM-3-grabbing nonintegrin (DC-SIGN), a tetrameric type II transmembrane glycoprotein with Ca2+-dependent lectin activity specific for high mannose. Entry of IAV into DCs via these receptors may occur through direct endocytosis of bound IAV, or alternatively may involve the transfer of virus to additional co-receptors that facilitate its entry. In an interesting study, Gonzalez et al. visualized the capture of inactivated IAV by spleen medullary CD11c+ cells. In this case, SIGN-R1, another lectin with the ability to bind mannose-rich sugars was implicated. This analysis was performed with inactivated virus in a vaccine setting and therefore the role of SIGN-R1 in live IAV infection remains to be elucidated. IAV infection of DCs can induce DCs apoptosis. As such, directly infecting DCs with IAV may be a viral mechanism to impair DC function and impede the initiation of an effective adaptive immune response. Indeed, IAV-infected human myeloid DCs are impaired in their ability to cross-present exogenous antigen via MHCI. To overcome this, DCs directly infected with IAV may transfer their antigen to uninfected, functional DCs. This mechanism of IAV antigen presentation remains to be formally demonstrated but is likely to be a mode of antigen presentation.
presentation by lymphoid resident DCs that participate in IAV T cell priming but do not access the site of infection themselves.

### Conclusion

Ultimately, studies of IAV immunity will provide the foundation for strategies to combat IAV disease. DCs are critical participants in IAV detection and importantly, process and present IAV antigens in a context that facilitates successful T cell priming but do not access the site of infection themselves. Here, we have summarized the complex roles of DCs following IAV infection of the pulmonary tract. Specific DC subsets play critical roles in both the infected lung itself and in the lymphoid organs that drain the respiratory tract. Several pathways discussed here are currently ongoing areas of intense and active research. In this case, we have attempted to discuss several studies that are often in complete disagreement, despite utilizing similar methodologies. Obviously, the complex network of DC subsets requires careful and elegant techniques for identifying and isolating purified DC populations from both the lymphoid organs and the infected pulmonary tissue. In vivo models of DC depletion are proving useful; however, they present several caveats that need to be carefully considered. All of the research discussed here has focused on studies undertaken with well-established mouse models of IAV. Moving forward, this knowledge must be considered in the context of human patients and human IAV disease.

### References

1. Mintern J, Guillonneau C, Turner SJ, Doherty PC. The immune response to influenza A viruses. In: Rappuoli R, Del Giudice G, eds. Influenza Vaccines for the Future. Springer Basel, 2011:173-98.
2. Bevan MJ. Minor H antigens introduced on H-2 different stimulating cells cross-react at the cytotoxic T cell level during in vivo priming. J Immunol 1976; 117: 2233-8; PMID:823578
3. Bevan MJ. Cross priming for a secondary cytotoxic response to minor H antigens with H-2 congenic cells which do not cross-react in the cytotoxic assay. J Exp Med 1976; 143:1283-8; PMID:1083422; http://dx.doi.org/10.1086/jem.143.5.1283
4. Heath WR, Carbone FR. Dendritic cell subsets in primary and secondary T cell responses at body surfaces. Nat Immunol 2000; 1:1237-44; PMID:19915624; http://dx.doi.org/10.1038/11822
5. Cella M, Jarrossay D, Facchetti F, Alebardi O, Hoogsteden HC, Osterhaus AD, et al. Both conventional and interstitial lung disease. J Immunol 2012; 189:946-55; PMID:22689983; http://dx.doi.org/10.4049/jimmunol.1200660
6. Vremec D, Pooley J, Hochrein H, Wu L, Shortman K. Leukocyte dendritic cell and Lung disease. J Immunol 2009; 183:4567-78; PMID:19784375; http://dx.doi.org/10.4049/jimmunol.1101307
7. Allen IC, Scull MA, Moore CB, Helli EK, McElvania-TeKippe E, Taxman DJ, et al. The NLRP3 inflammasome mediates in vivo innate immunity to influenza A virus through recognition of viral RNA. Immunity 2009; 30:556-65; PMID:19362020; http://dx.doi.org/10.1016/j.immuni.2009.02.005
8. Thomas PG, Dush P, Aldridge JR, Jr., Ellebedy AH, Reynolds C, Funk AJ, et al. The intracellular sensor NLRP3 mediates key innate and healing responses to influenza A virus via the regulation of caspase-1. Immunology 2009; 10:566-75; PMID:19362023; http://dx.doi.org/10.1016/j.immuni.2009.02.006
9. Ichinose T, Lee HK, Ogura Y, Flavell R, Iwaski A. Inflammasome recognition of influenza virus is essential for adaptive immune responses. J Exp Med 2009; 206:79-87; PMID:19139171; http://dx.doi.org/10.1084/jem.20081667
10. Ichinose T, Pang IK, Iwaski A. Influenza virus activates inflammasomes via its intracellular M2 ion channel. Nature 2010; 461:404-10; PMID:20383149; http://dx.doi.org/10.1038/nature08161
11. Diebold SS, Kaulas TI, Hennin H, Akira S, Reis e Sousa C. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. Science 2004; 305:1529-31; PMID:14976261; http://dx.doi.org/10.1126/science.1093616
12. Lind JM, Alexopoulou L, Sato A, Karow M, Adams NC, Gale NW, et al. Recognition of single-stranded RNA by Toll-like receptor 7. Proc Natl Acad Sci U S A 2004; 101:5598-603; PMID:15034168; http://dx.doi.org/10.1073/pnas.0400571101
13. Bergmann M, Garcia-Sastre A, Carrero E, Pehamberger H, Wolf K, Palese P, et al. Influenza virus NS1 protein counteracts PKR-mediated inhibition of replication. J Virol 2000; 74:6203-6; PMID:10866107; http://dx.doi.org/10.1128/JVI.74.13.6203-6206.2000

©2012 Landes Bioscience. Virulence 5
31. Li S, Min JY, Krug RM, Sen GC. Binding of the influenza A virus NS1 protein to PKR mediates the inhibition of its activation by either PACT or double-stranded RNA. Virolology 2006; 349:13-21; PMID: 16466673; http://dx.doi.org/10.1016/j.virol.2006.01.005

32. Min JY, Krug RM. The primary function of RNA helicase activity of the influenza A virus NS1 protein in infected cells: Inhibiting the 2′-5′ oligo (A) synthetase/RNase L pathway. Proc Natl Acad Sci U S A 2006; 103:710-5; PMID:16627618; http://dx.doi.org/10.1073/pnas.0602148103

33. Wang X, Li M, Zheng H, Muster T, Palese P, Bog AA, et al. Influenza A virus NS1 protein prevents activation of NF-kappab and induction of alpha/beta interferon. J Virol 2000; 74:11566-73; PMID:11090154; http://dx.doi.org/10.1128/JVI.74.24.11566-11573.2000

34. Talon J, Horvath CM, Polley R, Basler CF, Muster T, Min JY, Krug RM. The primary function of RNA helicase activity of the influenza A virus NS1 protein in infected cells: Inhibiting the 2′-5′ oligo (A) synthetase/RNase L pathway. Proc Natl Acad Sci U S A 2006; 103:710-5; PMID:16627618; http://dx.doi.org/10.1073/pnas.0602148103

35. Wang X, Li M, Zheng H, Muster T, Palese P, Bog AA, et al. Influenza A virus NS1 protein prevents activation of NF-kappab and induction of alpha/beta interferon. J Virol 2000; 74:11566-73; PMID:11090154; http://dx.doi.org/10.1128/JVI.74.24.11566-11573.2000

36. Li S, Min JY, Krug RM, Sen GC. Binding of the influenza A virus NS1 protein to PKR mediates the inhibition of its activation by either PACT or double-stranded RNA. Virolology 2006; 349:13-21; PMID: 16466673; http://dx.doi.org/10.1016/j.virol.2006.01.005

40. Ballesteros-Tato A, León B, Lund FE, Randall TD. Cutting edge: antigen presentation to CD8+ T cells after influenza virus infection. J Immunol 2008; 182:99-13; PMID:18443786; http://dx.doi.org/10.4049/jimmunol.0800897

46. Jung S, Unsunar D, Wong P, Sano G, De los Santos WR. Minimal activation of memory CD8+ T cell by abortive replication of influenza virus in interferon-deficient systems. Virology 2000; 274:9899-6; PMID:10933707; http://dx.doi.org/10.1006/viro.1998.9508

50. Mount AM, Smith CM, Kupresanin F, Stormer K, Heath WR, Bel GT. Multiple dendritic cell populations activate CD8+ T cells after viral stimulation. PLoS One 2008; 3:e1691.

57. Mount AM, Smith CM, Kupresanin F, Stormer K, Heath WR, Bel GT. Multiple dendritic cell populations activate CD8+ T cells after viral stimulation. PLoS One 2008; 3:e1691.

58. Albert ML, Saufer B, Bhandwaj N. Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. Nature 1998; 392:86-9; PMID:9617494; http://dx.doi.org/10.1038/283218a0

59. Shiratsuchi A, Kudo M, Takizawa T, Nakashima Y. Phosphatidylinositol-mediated phagocytosis of influenza A virus-infected cells by mouse peritoneal macrophages. J Virol 2000; 74:9240-4; PMID:10982371; http://dx.doi.org/10.1128/JVI.74.24.9240-9244.2000

60. Albert ML, Peacock SF, Francisco LM, Saufer B, Roy P, Silverstein RL, et al. Immature dendritic cells phagocytose apoptotic cells via alphabeta5 and CD36, and cross-present antigens to cytotoxic T lymphocytes. J Exp Med 1998; 188:1359-68; PMID:9763615; http://dx.doi.org/10.1084/jem.188.3.519

61. Langlois RA, Varble A, Chua MA, Garcia-Sastre A, Tenevteer BR. Hematopoietic-specific targeting of influenza A virus reveals replication requirements for induction of antiviral interferon responses. Proc Natl Acad Sci U S A 2006; 103:12091-5; PMID:16872965; http://dx.doi.org/10.1073/pnas.0607044103

62. Diebold SS, Montoya M, Unger H, Alexopoulou L, Roy P, Hawell LE, et al. Viral infection switches non-professional dendritic cells into high interferon-producing producers. Nature 2003; 424:324-8; PMID:12813664; http://dx.doi.org/10.1038/nature01783

63. López CB, Fernandez-Sesma A, Czeluzniak SM, Schulman JL, Moran TM. A mouse model for immunization with ex vivo influenza-dendritic cells. Cell Immunol 2000; 206:107-15; PMID:11161442; http://dx.doi.org/10.1006/cimm.2000.1736

64. Oh S, McCaffrey JM, Eichelderberger MC. Disease-dependent changes in influenza virus-infected dendritic cells result in increased allogeneic T-cell proliferation at low, but not high, doses of virus. J Virol 2000; 74:5466-9; PMID:10823850; http://dx.doi.org/10.1128/JVI.74.12.5460-5469.2000

65. Ioanidis LJ, Veity EE, Crawford S, Rockman SP, Brown LE. Abrogative replication of influenza virus in mouse dendritic cells. J Virol 2002; 76:316-24; PMID:11018204; http://dx.doi.org/10.1128/JVI.76.1.316-324.2002

66. Nonacs R, Cates J, Tollefson J, Steinman RM. Mechanisms of mouse spleen dendritic cell function in the generation of influenza-specific, cytolytic T lymphocytes. J Exp Med 1998; 188:1241-57; PMID:9617494; http://dx.doi.org/10.1084/jem.188.4.1241

67. Bender A, Albert M, Reddy A, Feldman M, Saufer B, Kaplan G, et al. The distinctive features of influenza virus infection of dendritic cells. Immunobiology 1998; 198:552-67; PMID:9561173; http://dx.doi.org/10.1016/S0171-2989(98)00788-8

68. Cella M, Salin M, Salakabira Y, Langen H, Julkunen I, Lanzavecchia A, Maturation, activation, and protection of dendritic cells induced by double-stranded RNA. J Exp Med 1999; 189:821-9; PMID:10804946; http://dx.doi.org/10.1084/jem.189.5.821

69. Osterlund P, Pirhonen J, Ikonen N, Rinikko E, Strengell M, Mäkelä SM, et al. Pandemic H1N1 2009 influenza virus induces weak cytokine responses in human macrophages and dendritic cells and is highly sensitive to the antiviral actions of interferon Virol 2010; 84:1411-22; PMID:20399392; http://dx.doi.org/10.1128/jvi.01619-09

70. Thirumalayandar A, Egering A, Elchalyawar P, Winbo-uit S, Limsalakphet A, Yongyankitvat C, et al. High susceptibility of human dendritic cells to avian influenza H5N1 virus infection and protection by IFN-alpha and TLR ligands. J Immunol 2007; 179:5220-7; PMID:17911607

©2012 Landes Bioscience. Do not distribute.