Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Modulation of dendritic cell antigen presentation by pathogens, tissue damage and secondary inflammatory signals

Javier Vega-Ramos[1], Antoine Roquilly[1,2,3], Karim Asehnoune[2,3] and Jose A Villadangos[1,4]

Antigen presentation by dendritic cells (DC) is regulated directly by pathogen-associated or cell death-associated cues, or indirectly by immunomodulatory molecules produced during infection or tissue damage. DC modulation by direct encounter of pathogen-associated compounds has been thoroughly studied; the effects of molecules associated with cell death are less well characterized; modulation by secondary signals remain poorly understood. In this review we describe recent studies on the role of these three categories of immunomodulatory compounds on DC. We conclude that characterization of the role of secondary immunomodulators is an area in dare need of further study. The outcomes of this endeavor will be new opportunities for the development of better vaccines and compounds applicable to the therapeutic immunomodulation of DC function.

Addresses
[1] Department of Microbiology and Immunology, Doherty Institute of Infection and Immunity, The University of Melbourne, Pakville, Australia
[2] Laboratoire UPRES EA 3826 ''Thérapeutiques cliniques et expérimentales des infections'', Faculte de Médecine, Université de Nantes, France
[3] Service d'Anesthésie Réanimation Chirurgicale, Hôtel Dieu, Nantes, France
[4] Department of Biochemistry and Molecular Biology, Bio21 Institute, The University of Melbourne, Parkville, Australia

Corresponding author: Villadangos, Jose A (j.villadangos@unimelb.edu.au)

Current Opinion in Pharmacology 2014, **17**:64–70

This review comes from a themed issue on **Immunomodulation**

Edited by **Massimo Triggiani**

http://dx.doi.org/10.1016/j.coph.2014.07.013

Dendritic cells (DCs) are a fundamental component of the immune system. They can detect virtually any pathogen, multiple forms of tissue damage and secondary mediators of inflammation. They are also the predominant antigen presenting cells for the maintenance of T cell tolerance and the initiation and regulation of T cell-dependent immune responses. By combining the capacity to detect environmental changes, and to communicate with T cells, DCs bridge the innate and adaptive arms of the immune system.

DC precursors constantly leave the bone marrow and seed peripheral tissues and secondary lymphoid organs, where they develop into *immature* DC [1]. In this state of differentiation DC are highly endocytic and survey their environment. Immature DC express relatively low levels of two types of molecules required for activation of naive T cells, namely Major Histocompatibility Complex (MHC) molecules, which present antigenic peptides recognized by T cell receptors (the so-called *signal 1*), and co-stimulatory molecules required for T cell activation (e.g. CD40, CD86, *signal 2*). In the absence of infection, tissue damage or inflammation, the DC that develop in secondary lymphoid organs die in the immature state, with a turn-over rate of less than a week [1]. The DC that develop in peripheral tissues constitutively migrate to lymphoid organs, where they acquire a so-called *mature* phenotype characterized by high surface expression of MHC and co-stimulatory molecules [2]. Migratory DC have a more variable but also fast turn-over rate [1]. The term *steady-state DC* is often used to refer to the DC present in the periphery and lymphoid organs in the absence of overt infection or inflammation. Steady-state DC do not secrete cytokines required for immunogenic T cell activation (the so-called called *signal 3*) and it is widely accepted that if T cells recognize antigens presented by these DCs they die, lose the capacity to become effector (immunogenic) T cells, or become regulatory T cells dedicated to dampening rather than promoting immune responses [3]. In other words, steady-state DC are *tolerogenic*. Detection of molecular cues associated with infection, tissue damage or inflammation has been generally thought to induce DC differentiation into *immunogenic* mature DC. In this review we describe recent work suggesting that this view is too simplistic, as the encounter of different types of activating stimuli can lead to generation of mature DCs with distinct capabilities. Moreover, there is evidence that the effects of infection and inflammation can extend for longer than anticipated and affect the life cycle or function of new DC produced after resolution of these events.

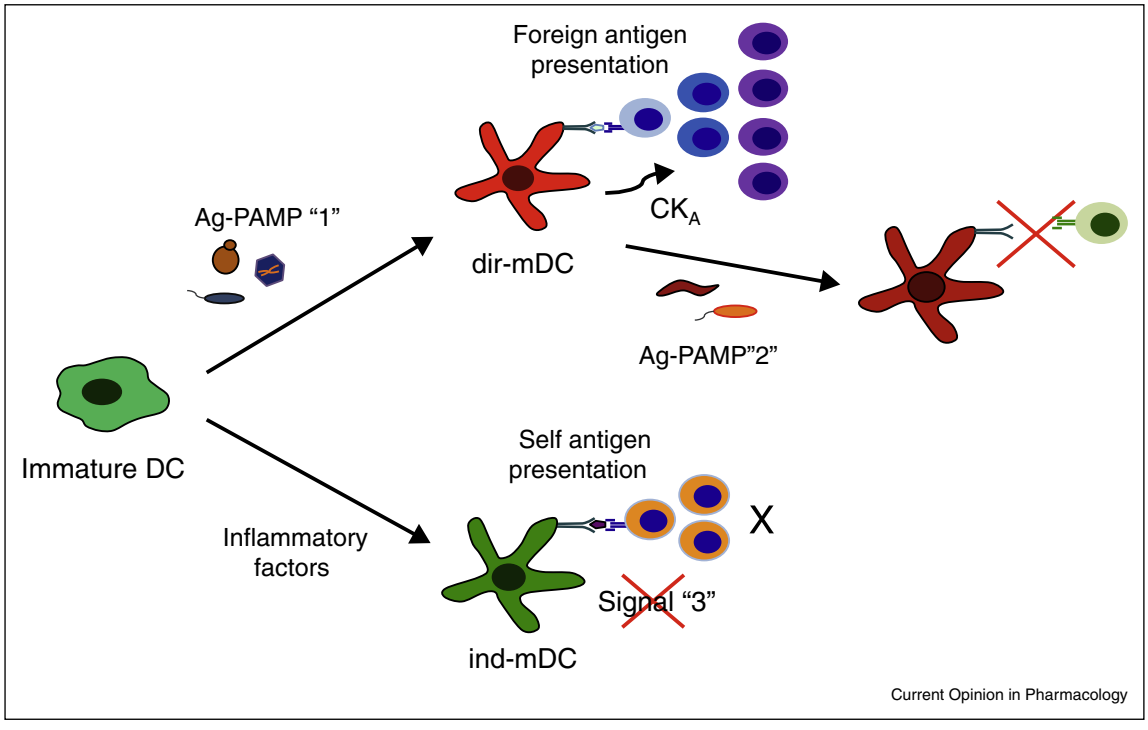
DC modulation by pathogen-associated and danger-associated molecular patterns

The best-studied mechanism of DC activation is through pattern-recognition receptors such as Toll-like receptors and the cytosolic sensors of the RIG and NOD families, which recognize lipopolysaccharide, non-eukaryotic nucleic acids and other pathogen associated molecular patterns (PAMPs). DC activated by PAMPs acquire a mature phenotype and in addition secrete signal 3 cytokines, so they are immunogenic (Figure 1). The specific suite of cytokines induced by each PAMP is tailored to promote the most adequate type of immune response to fight the agent expressing the PAMP. The process of DC activation by PAMPs has been reviewed elsewhere [4,5].

The second major family of DC modulators are the danger-associated molecular patterns (DAMPs) [6]. These are compounds that are normally only found inside cells but are released when cells undergo 'violent' death caused by infection or tissue damage (necrosis), as opposed to the non-activating cell death program that cells undergo when they reach the end of their life cycle (apoptosis). The DAMPs are not as finely characterized as the PAMPs, and neither are their receptors and functional consequences of their engagement [7]. Some examples of DAMPs are ureate, ATP, high-mobility group box 1 (HMGB1) protein or mitochondrial DNA [6]. Many are recognized by the same receptors that detect PAMPs, so it is likely that the DC modulatory activity of these two groups of compounds overlaps [7]. For simplicity, in the rest of this review we will refer to DC activated by detection of PAMPs or DAMPs as 'directly matured DC (dir-mDC)' to distinguish them from those that mature in response to secondary inflammatory signals (see below and Figure 1).

A distinctive feature of dir-mDC is that while they are highly adept at presenting a long-lived 'snapshot' of antigens acquired at the time of activation, they also lose their ability to present newly encountered antigens [8] (Figure 1). There is one exception to this general rule: antigens captured via surface molecules are efficiently presented by dir-mDC [9•,10•]. Although it is unclear whether this property contributes to natural initiation of T cell immunity, it might be exploited for clinical purposes by using artificial constructs to target antigens to surface molecules on dir-mDC [11]. Down-regulation of new antigen presentation by dir-mDC is not deleterious

Figure 1



Functional properties of directly versus indirectly activated DC. Dendritic cells can be activated directly by encounter of pathogen associated molecular patterns (PAMP), or indirectly by inflammatory mediators produced by other hematopoietic cells. Upper path: direct encounter of a pathogen (Ag-PAMP '1') activates DC, which mature (dir-mDC). The dir-mDC present the antigen to elicit activation and expansion of specific T cells, and also produce 'signal 3' cytokines which induce the differentiation of the expanded T cells. Dir-mDC down-regulate the synthesis and turn-over of MHC-II molecules, so they have a low capacity to respond to, and present, subsequently encountered antigens (Ag-PAMP '2'). Lower path: DC indirectly activated by inflammatory signals also mature (ind-mDC). As they have not captured foreign antigen, they can only present self antigens and induce proliferation of self T cells, but they do not induce full differentiation of the T cells due to a lack of 'signal 3' cytokine production.

in most scenarios of infection because normally few DC encounter the pathogen and those remaining can respond to a new infection. However, there are situations that can cause widespread local or even systemic DC activation, for example bacterial sepsis, malaria infection or pseudoinfection with PAMPs injected intravenously [12–15,16•,17••]. These events reduce or even exhaust the number of immature DC capable of capturing and presenting new antigens, impairing the ability of the immune system to mount T cell responses against model antigens or pathogens encountered subsequently [12–15,16•,17••] (Figure 1). Direct activation of an excessive number of DC by PAMPs is thus immunosuppressive. Notably, responses that depend on direct viral antigen presentation rather than on exogenous antigen (cross)presentation are unaffected or even boosted in TLR ligand-injected mice, demonstrating that the immunosuppression is due to impaired DC antigen capture and/or (cross)presentation [12,13,16•,17••]. These conclusions have been reached based primarily on mouse studies, but there is good evidence that they are also applicable to humans.

It is well established that individuals infected with the malaria parasite exhibit impaired immunity against other pathogens. The best-studied correlation is with Epstein-Barr Virus (EBV) [18], which causes Burkitt's lymphoma if the infection is not controlled by T cells. Indeed, it has been shown that anti-EBV T cells are eliminated over time in individuals exposed to recurrent malaria infections [19]. Another viral infection that correlates with malaria incidence is Hepatitis A [20•]. An association between malaria and bacteria infections has also been reported [21•], and concomitant bacterial pneumonia and bacteremia are common complications of severe malaria [22•]. Furthermore, it has long been known that vaccination responses are impaired after acute malaria [23]. Severe or systemic infections with other pathogens also cause immunosuppression [24], as does severe trauma [25,26,27••]. In fact, immunosuppression is now recognized as a key aspect of patients suffering from sepsis, severe brain injury or severe trauma [24,28,29]. Patients who died following sepsis showed clear signs of immunosuppression compared to patients who died of non-sepsis ethiologies [30]. Cytomegalovirus (CMV) and Herpes Simplex Virus (HSV) reactivation has been observed in critically ill patients [31,32], and bacterial pneumonia develops in up to 40% of patients [33].

DC dysregulation is probably not the only mechanism of immunosuppression in the above conditions, but it is likely the major contributor to impairment of T cell-dependent responses [24,29,34,35]. Induction of DC apoptosis has been observed in bacterial sepsis [36], malaria infection [37••,38••,39] and severe trauma [26]. Reduced DC numbers would obviously affect T cell priming, but we know that if DC present antigens in conditions of systemic activation T cell priming does occur [12,13], so reduced antigen presentation by dir-mDC is probably an important, if not the main mechanism of DC impairment. Drugs or vaccine constructs that promote antigen presentation by dir-mDC [9•,10•] may provide a strategy to restore DC function and T cell priming in the face of severe/systemic infections or trauma.

DC modulation by secondary regulatory molecules of inflammation

The third family of molecules that modulate DC function are the secondary pro-inflammatory and anti-inflammatory cytokines, chemokines, interferons, among others, that are released by cells of the immune system, and also by parenchymal cells, upon detection of PAMPs or DAMPs. Dissecting the specific influence of these molecules on DC function is extraordinarily difficult because of their sheer number and complexity of their activities. A compounding difficulty is that each mediator does not act on DC on its own, but in concert with other mediators, PAMPs or DAMPs, sometimes synergistically and others antagonistically. Finally, in rigor they are not only associated with infection or inflammation because they can also be produced, and modulate DC function, in the steady state. Below we describe studies pertaining the activity of some of these molecules as an illustration of their complex roles.

Recruitment of monocytes and conversion into DC is a well-known effect of infection or inflammation [40]. The growth factor csf-2 (GM-CSF) drives monocyte differentiation into DC *in vitro*, so it was long thought that it played the same role *in vivo*, but this has turned out not to be the case [41]. Csf-2 regulates homeostasis of non-monocytic DC in the steady state but is dispensable for inflammatory DC recruitment [41]. It also promotes antigen cross-presentation and the expression of DC cytokines that induce Th17 cells [42–44]. At the other end of the spectrum of secondary regulators of DC antigen presentation is IL-10, mostly secreted by T-cells and natural killer cells in order to limit tissue damage during or after inflammation [45]. IL-10 is the strongest inhibitor of DC maturation and is a well-known inducer of tolerogenic DC [46]. IL-10 also has a role in regulating the homeostasis of DC during infection, and has recently been shown to induce apoptosis of circulating DC in malaria patients [38••]. But IL-10 also plays a central role in the regulation of antigen presentation by DC. IL-10 induces the expression of MARCH1 by monocytes and DC, which in turn drives the internalization and degradation of MHC II and CD86 from the cell surface, therefore impairing their capacity to present antigens [47–50]. Both Csf-2 and IL-10 are good examples of factors that have functions in the steady-state and during inflammation, working as growth factors and as modulators of antigen presentation, exemplifying the

complexity of effects that can be mediated by secondary inflammatory factors.

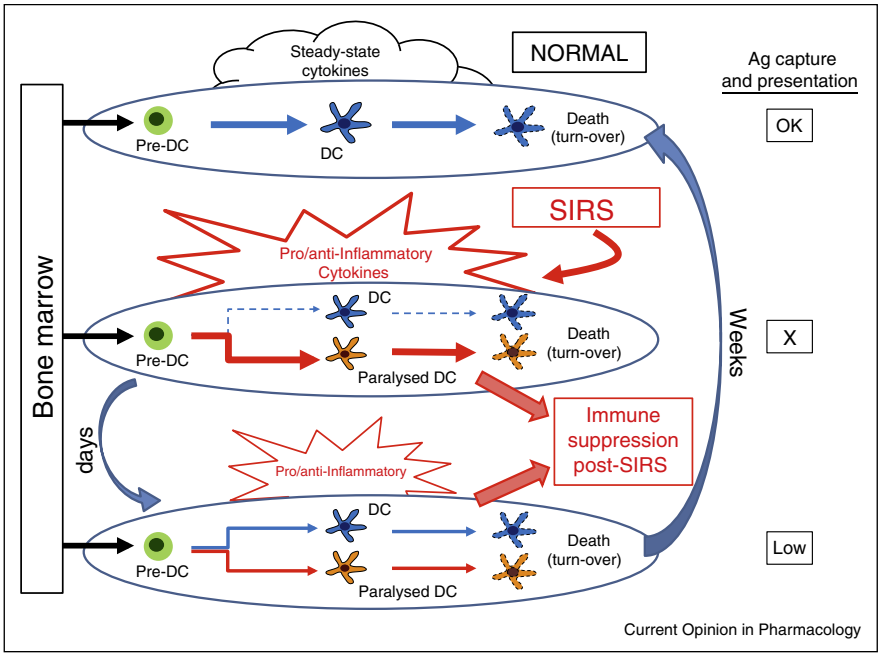
Given that the secondary regulators of inflammation can have both activating and inhibitory effects on DC antigen presentation, it is pertinent to ask what happens when these are the only molecules detected by DC in the context of an infection. Inflammatory cytokines induce acquisition of a mature phenotype in DC, with high expression of MHC II and co-stimulatory molecules. However, such DC do not secrete 'signal 3' cytokines required for full T cell priming ([51,52] and our unpublished results), so they have been termed 'semi-mature' or 'indirectly activated' DC (ind-mDC) [15,53] (Figure 1). Remarkably, ind-mDC do not down-regulate MHC II and MARCH 1 synthesis like dir-mDC do, and retain their capacity to present new antigens ([54••] and our unpublished results). The function of ind-mDC *in vivo* is not yet fully understood, but it has been proposed that they promote tolerance to self antigens during an ongoing immune response against foreign pathogens [51,52]. Indeed, human and mouse ind-mDC have been investigated as immunotherapeutic agents for tolerance induction [46,53].

Long term effects of systemic inflammation on DC functions

As described above, systemic inflammation triggered by pathogens or trauma (Systemic Inflammatory Response Syndrome, SIRS) is immunosuppressive, and this is at least in part due to induction of systemic DC maturation and the concomitant impairment of their capacity to present new antigens. It might be expected that this immunosuppression would last only until the mature DC are replaced by normal immature DC, which occurs within 3–7 days [55]. However, signs of immunosuppression are present in critically ill patients for weeks after the onset of SIRS. Again, the underlying causes of immunosuppression are probably complex [24,29], but DC impairment appears to be an important contributor.

We showed that a single injection of CpG in mice causes impaired DC function for up to 21 days [12], long after disappearance of CpG activity. In brain-injured patients suffering systemic inflammation, DC can respond to most TLR ligands (e.g. CpG or LPS), undergoing maturation and secreting cytokines, but have a decreased ability to secrete IL-12 upon TLR3 ligand stimulation for more than 10 days [56•]. The causes of the long-term impairment of DC function following systemic infection or inflammation have not been thoroughly investigated. An attractive hypothesis is that SIRS induces an altered differentiation program on DC precursors (''paralysis'') so that although their turn-over continues normally after the inflammatory trigger, the new paralysed DC do not acquire full antigen presentation functions (Figure 2). Long-term effects of bacterial sepsis, malaria infection or

Figure 2



Induction of DC paralysis following SIRS. Top: DC precursors trafficking from the bone marrow (pre-DC) continuously access peripheral tissues and lymphoid organs (oval), expand locally and their progeny becomes functional DC (blue). DC have a fast turnover rate and are constantly renewed. Local cytokines (cloud) induce high antigen (Ag) capture and presentation capacities in the developing DC. SIRS causes changes to these signals (red storm), leading to formation of paralysed DC (orange) and immune suppression. Production of paralysed DC continues for weeks until the local cytokine environment gradually returns to the normal state.

trauma on DC differentiation and function have been reported [37••,38••,57,58], and the fact that pro-inflammatory or anti-inflammatory signals affect the acquisition of antigen presentation functions in developing DC gives support to this hypothesis [42,43]. A single trigger of systemic inflammation can have lasting effects on cytokine production [27••]. An important conclusion of these studies is that DC depletion may be just one, and perhaps not the most important, mechanism of DC impairment following SIRS. They also imply that treatments aimed at increasing the production of DC [59–61] may have a limited impact on recovery of immunocompetence if the signals that promote the development of paralysed DC are not neutralized. An alternative approach might be to counteract these signals with blocking mAbs or to boost immune responsiveness with activating cytokines that promote immunity [62,63].

In summary, over the past decade there has been tremendous progress in our understanding of DC modulation by PAMPs and, to a lesser extent, by DAMPs. Our knowledge of the effects of endogenous pro-inflammatory and anti-inflammatory mediators on DC development and function remain sketchy by comparison. We anticipate important developments in this area in coming years, which will no doubt reveal new opportunities for pharmacological intervention and the development of therapeutic strategies through modulation of DC function.

Conflict of interest statement

Karim Asehnoune received fees from B-Braun, and Fresenius-Kabi.

Acknowledgements

This research has been funded by the Fundacio Pedro i Pons (JVR), the Société Française d'Anesthesie Réanimation (AR and KA), the European Society of Intensive Care Medicine (AR and KA) the association 'les gueules cassées' (AR and KA) and the National Health and Medical Research Council of Australia (JAV).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Merad M, Sathe P, Helft J, Miller J, Mortha A: **The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting**. *Annu Rev Immunol* 2013, **31**:563-604.

2. Wilson NS, Young LJ, Kupresanin F, Naik SH, Vremec D, Heath WR, Akira S, Shortman K, Boyle J, Maraskovsky E *et al.*: **Normal proportion and expression of maturation markers in migratory dendritic cells in the absence of germs or toll-like receptor signaling**. *Immunol Cell Biol* 2008, **86**: 200-205.

3. Steinman RM, Nussenzweig MC: **Avoiding horror autotoxicus: the importance of dendritic cells in peripheral t cell tolerance**. *Proc Natl Acad Sci U S A* 2002, **99**:351-358.

4. Iwasaki A, Medzhitov R: **Regulation of adaptive immunity by the innate immune system**. *Science* 2010, **327**:291-295.

5. Kawai T, Akira S: **Toll-like receptors and their crosstalk with other innate receptors in infection and immunity**. *Immunity* 2011, **34**:637-650.

6. Chen GY, Nunez G: **Sterile inflammation: sensing and reacting to damage**. *Nat Rev Immunol* 2010, **10**:826-837.

7. Zelenay S, Reis e Sousa C: **Adaptive immunity after cell death**. *Trends Immunol* 2013, **34**:329-335.

8. Wilson NS, Villadangos JA: **Regulation of antigen presentation and cross-presentation in the dendritic cell network: facts, hypothesis, and immunological implications**. *Adv Immunol* 2005, **86**:241-305.

9. • Platt CD, Ma JK, Chalouni C, Ebersold M, Bou-Reslan H, Carano RA, Mellman I, Delamarre L: **Mature dendritic cells use endocytic receptors to capture and present antigens**. *Proc Natl Acad Sci U S A* 2010, **107**:4287-4292.
Demonstrates the potential of antibody-targeted antigen delivery constructs as a strategy to harness activated DC for vaccination.

10. • Moffat JM, Segura E, Khoury G, Caminschi I, Cameron PU, Lewin SR, Villadangos JA, Mintern JD: **Targeting antigen to bone marrow stromal cell-2 expressed by conventional and plasmacytoid dendritic cells elicits efficient antigen presentation**. *Eur J Immunol* 2013.
See annotation to Ref. [9•].

11. Shortman K, Lahoud MH, Caminschi I: **Improving vaccines by targeting antigens to dendritic cells**. *Exp Mol Med* 2009, **41**: 61-66.

12. Wilson NS, Behrens GM, Lundie RJ, Smith CM, Waithman J, Young L, Forehan SP, Mount A, Steptoe RJ, Shortman KD *et al.*: **Systemic activation of dendritic cells by toll-like receptor ligands or malaria infection impairs cross-presentation and antiviral immunity**. *Nat Immunol* 2006, **7**:165-172.

13. Young L, Wilson N, Schnorrer P, Mount A, Lundie R, La Gruta N, Crabb B, Belz G, Heath W, Villadangos J: **Dendritic cell preactivation impairs mhc class ii presentation of vaccines and endogenous viral antigens**. *Proc Natl Acad Sci U S A* 2007, **104**:17753-17758.

14. Lundie RJ, Young LJ, Davey GM, Villadangos JA, Carbone FR, Heath WR, Crabb BS: **Blood-stage plasmodium berghei infection leads to short-lived parasite-associated antigen presentation by dendritic cells**. *Eur J Immunol* 2010, **40**: 1674-1681.

15. Vega-Ramos J, Villadangos JA: **Consequences of direct and indirect activation of dendritic cells on antigen presentation: Functional implications and clinical considerations**. *Mol Immunol* 2012, **55**:175-178.

16. • Sutherland RM, Londrigan SL, Brady JL, Azher H, Carrington EM, Zhan Y, Vega-Ramos J, Villadangos JA, Lew AM: **Shutdown of immunological priming and presentation after in vivo administration of adenovirus**. *Gene Ther* 2012, **19**: 1095-1100.
Shows the potentially immunosuppressive effects that may be caused by employment of vaccination vectors that induce activation of an excessive number of DC.

17. •• Ong ML, Wikstrom ME, Fleming P, Estcourt MJ, Hertzog PJ, Hill GR, Andoniou CE, Degli-Esposti MA: **Cpg pretreatment enhances antiviral t-cell immunity against cytomegalovirus**. *Blood* 2013, **122**:55-60.
An elegant demonstration that systemic activation of DC affects the induction of anti-viral immune responses mediated by cross-priming DC but not those that are initiated by infected DC capable of directly presenting the viral antigens.

18. Moormann AM, Snider CJ, Chelimo K: **The company malaria keeps: how co-infection with epstein-barr virus leads to endemic burkitt lymphoma**. *Curr Opin Infect Dis* 2011, **24**:435-441.

19. Snider CJ, Cole SR, Chelimo K, Sumba PO, Macdonald PD, John CC, Meshnick SR, Moormann AM: **Recurrent plasmodium falciparum malaria infections in kenyan children diminish t-cell immunity to epstein barr virus lytic but not latent antigens**. *PLoS One* 2012, **7**:e31753.

20. • Klein Klouwenberg P, Sasi P, Bashraheil M, Awuondo K, Bonten M, Berkley J, Marsh K, Borrmann S: **Temporal association of acute**

hepatitis a and plasmodium falciparum malaria in children. *PLoS One* 2011, **6**:e21013.
Extend the range of known opportunistic infections caused by malaria-induced immunosuppression, in which systemic impairment of DC function is a likely contributor.

21. • Scott JA, Berkley JA, Mwangi I, Ochola L, Uyoga S, Macharia A, Ndila C, Lowe BS, Mwarumba S, Bauni E *et al.*: **Relation between falciparum malaria and bacteraemia in kenyan children: a population-based, case-control study and a longitudinal study**. *Lancet* 2011, **378**:1316-1323.
See annotation to Ref. [20•].

22. • Taylor WR, Hanson J, Turner GD, White NJ, Dondorp AM: **Respiratory manifestations of malaria**. *Chest* 2012, **142**: 492-505.
See annotation to Ref. [20•].

23. Williamson WA, Greenwood BM: **Impairment of the immune response to vaccination after acute malaria**. *Lancet* 1978, **1**:1328-1329.

24. Hotchkiss RS, Monneret G, Payen D: **Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy**. *Nat Rev Immunol* 2013, **13**:862-874.

25. Roquilly A, Gautreau L, Segain JP, de Coppet P, Sebille V, Jacqueline C, Caillon J, Potel G, Lejus C, Josien R, Asehnoune K: **Cpg-odn and mpla prevent mortality in a murine model of post-hemorrhage-staphyloccocus aureus pneumonia**. *PLoS One* 2010, **5**:e13228.

26. Grimaldi D, Louis S, Pene F, Sirgo G, Rousseau C, Claessens YE, Vimeux L, Cariou A, Mira JP, Hosmalin A, Chiche JD: **Profound and persistent decrease of circulating dendritic cells is associated with icu-acquired infection in patients with septic shock**. *Intensive Care Med* 2011, **37**:1438-1446.

27. •• Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, Hayden DL, Hennessy L, Moore EE, Minei JP *et al.*: **A genomic storm in critically injured humans**. *J Exp Med* 2011, **208**:2581-2590.
A systematic analysis of the changes in cytokine levels induced by severe trauma in humans.

28. Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U: **Central nervous system injury-induced immune deficiency syndrome**. *Nat Rev Neurosci* 2005, **6**:775-786.

29. Asehnoune K, Roquilly A, Abraham E: **Innate immune dysfunction in trauma patients: from pathophysiology to treatment**. *Anesthesiology* 2012, **117**:411-416.

30. Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton AH, Bricker TL, Jarman SD 2nd, Kreisel D, Krupnick AS *et al.*: **Immunosuppression in patients who die of sepsis and multiple organ failure**. *JAMA* 2011, **306**:2594-2605.

31. Luyt CE, Combes A, Deback C, Aubriot-Lorton MH, Nieszkowska A, Trouillet JL, Capron F, Agut H, Gibert C, Chastre J: **Herpes simplex virus lung infection in patients undergoing prolonged mechanical ventilation**. *Am J Respir Crit Care Med* 2007, **175**:935-942.

32. Limaye AP, Kirby KA, Rubenfeld GD, Leisenring WM, Bulger EM, Neff MJ, Gibran NS, Huang ML, Santo Hayes TK, Corey L, Boeckh M: **Cytomegalovirus reactivation in critically ill immunocompetent patients**. *JAMA* 2008, **300**:413-422.

33. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K: **International study of the prevalence and outcomes of infection in intensive care units**. *JAMA* 2009, **302**:2323-2329.

34. Lundie RJ: **Antigen presentation in immunity to murine malaria**. *Curr Opin Immunol* 2011, **23**:119-123.

35. Wykes MN, Good MF: **What really happens to dendritic cells during malaria?** *Nat Rev Microbiol* 2008, **6**:864-870.

36. Hotchkiss RS, Tinsley KW, Swanson PE, Grayson MH, Osborne DF, Wagner TH, Cobb JP, Coopersmith C, Karl IE: **Depletion of dendritic cells, but not macrophages, in patients with sepsis**. *J Immunol* 2002, **168**:2493-2500.

37. •• Woodberry T, Minigo G, Piera KA, Amante FH, Pinzon-Charry A, Good MF, Lopez JA, Engwerda CR, McCarthy JS, Anstey NM: **Low-level plasmodium falciparum blood-stage infection causes dendritic cell apoptosis and dysfunction in healthy volunteers**. *J Infect Dis* 2012, **206**:333-340.
Demonstrate that malaria infection causes short-term and long-term deleterious effects on human DC function, probably contributing to immunosuppression.

38. •• Pinzon-Charry A, Woodberry T, Kienzle V, McPhun V, Minigo G, Lampah DA, Kenangalem E, Engwerda C, Lopez JA, Anstey NM, Good MF: **Apoptosis and dysfunction of blood dendritic cells in patients with falciparum and vivax malaria**. *J Exp Med* 2013, **210**:1635-1646.
See annotation to Ref. [37••].

39. Guermonprez P, Helft J, Claser C, Deroubaix S, Karanje H, Gazumyan A, Darasse-Jeze G, Telerman SB, Breton G, Schreiber HA *et al.*: **Inflammatory flt3l is essential to mobilize dendritic cells and for t cell responses during plasmodium infection**. *Nat Med* 2013, **19**:730-738.

40. Mildner A, Yona S, Jung S: **A close encounter of the third kind: monocyte-derived cells**. *Adv Immunol* 2013, **120**:69-103.

41. Greter M, Lelios I, Pelczar P, Hoeffel G, Price J, Leboeuf M, Kundig TM, Frei K, Ginhoux F, Merad M, Becher B: **Stroma-derived interleukin-34 controls the development and maintenance of langerhans cells and the maintenance of microglia**. *Immunity* 2012, **37**:1050-1060.

42. Zhan Y, Carrington EM, van Nieuwenhuijze A, Bedoui S, Seah S, Xu Y, Wang N, Mintern JD, Villadangos JA, Wicks IP, Lew AM: **Gm-csf increases cross-presentation and cd103 expression by mouse cd8(+) spleen dendritic cells**. *Eur J Immunol* 2011, **41**:2585-2595.

43. Sathe P, Pooley J, Vremec D, Mintern J, Jin JO, Wu L, Kwak JY, Villadangos JA, Shortman K: **The acquisition of antigen cross-presentation function by newly formed dendritic cells**. *J Immunol* 2011, **186**:5184-5192.

44. Ko HJ, Brady JL, Ryg-Cornejo V, Hansen DS, Vremec D, Shortman K, Zhan Y, Lew AM: **Gm-csf-responsive monocyte-derived dendritic cells are pivotal in th17 pathogenesis**. *J Immunol* 2014, **192**:2202-2209.

45. Banchereau J, Pascual V, O'Garra A: **From il-2 to il-37: the expanding spectrum of anti-inflammatory cytokines**. *Nat Immunol* 2012, **13**:925-931.

46. Gordon JR, Ma Y, Churchman L, Gordon SA, Dawicki W: **Regulatory dendritic cells for immunotherapy in immunologic diseases**. *Front Immunol* 2014, **5** 7.

47. Thibodeau J, Bourgeois-Daigneault MC, Huppe G, Tremblay J, Aumont A, Houde M, Bartee E, Brunet A, Gauvreau ME, de Gassart A *et al.*: **Interleukin-10-induced march1 mediates intracellular sequestration of mhc class ii in monocytes**. *Eur J Immunol* 2008, **38**:1225-1230.

48. Tze LE, Horikawa K, Domaschenz H, Howard DR, Roots CM, Rigby RJ, Way DA, Ohmura-Hoshino M, Ishido S, Andoniou CE *et al.*: **Cd83 increases mhc ii and cd86 on dendritic cells by opposing il-10-driven march1-mediated ubiquitination and degradation**. *J Exp Med* 2011, **208**:149-165.

49. Chattopadhyay G, Shevach EM: **Antigen-specific induced t regulatory cells impair dendritic cell function via an il-10/ march1-dependent mechanism**. *J Immunol* 2013, **191**: 5875-5884.

50. Moffat JM, Mintern JD, Villadangos JA: **Control of mhc ii antigen presentation by ubiquitination**. *Curr Opin Immunol* 2013, **25**: 109-114.

51. Sporri R, Reis e Sousa C: **Inflammatory mediators are insufficient for full dendritic cell activation and promote expansion of cd4+ t cell populations lacking helper function**. *Nat Immunol* 2005, **6**:163-170.

52. Joffre O, Nolte MA, Sporri R, Reis e Sousa C: **Inflammatory signals in dendritic cell activation and the induction of adaptive immunity**. *Immunol Rev* 2009, **227**:234-247.

53. Lutz MB, Schuler G: **Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity?** *Trends Immunol* 2002, **23**:445-449.

54. •• Simmons DP, Wearsch PA, Canaday DH, Meyerson HJ, Liu YC, Wang Y, Boom WH, Harding CV: **Type i ifn drives a distinctive dendritic cell maturation phenotype that allows continued class ii mhc synthesis and antigen processing**. *J Immunol* 2012, **188**:3116-3126.
A clear demonstration at the biochemical/cell biological level of the differences in maturation programs elicited by direct vs indirect activators of DC.

55. Kamath AT, Henri S, Battye F, Tough DF, Shortman K: **Developmental kinetics and lifespan of dendritic cells in mouse lymphoid organs**. *Blood* 2002, **100**:1734-1741.

56. • Roquilly A, Braudeau C, Cinotti R, Dumonte E, Motreul R, Josien R, Asehnoune K: **Impaired blood dendritic cell numbers and functions after aneurysmal subarachnoid hemorrhage**. *PLoS One* 2013, **8**:e71639.
Describes the deleterious consequences of severe trauma on DC function, a likely contributor to immunosuppression in crucially injured patients.

57. Pastille E, Didovic S, Brauckmann D, Rani M, Agrawal H, Schade FU, Zhang Y, Flohe SB: **Modulation of dendritic cell differentiation in the bone marrow mediates sustained immunosuppression after polymicrobial sepsis**. *J Immunol* 2011, **186**:977-986.

58. Pene F, Zuber B, Courtine E, Rousseau C, Ouaaz F, Toubiana J, Tazi A, Mira JP, Chiche JD: **Dendritic cells modulate lung response to pseudomonas aeruginosa in a murine model of sepsis-induced immune dysfunction**. *J Immunol* 2008, **181**:8513-8520.

59. Wysocka M, Montaner LJ, Karp CL: **Flt3 ligand treatment reverses endotoxin tolerance-related immunoparalysis**. *J Immunol* 2005, **174**:7398-7402.

60. Toliver-Kinsky TE, Cui W, Murphey ED, Lin C, Sherwood ER: **Enhancement of dendritic cell production by fms-like tyrosine kinase-3 ligand increases the resistance of mice to a burn wound infection**. *J Immunol* 2005, **174**:404-410.

61. Meisel C, Schefold JC, Pschowski R, Baumann T, Hetzger K, Gregor J, Weber-Carstens S, Hasper D, Keh D, Zuckermann H *et al.*: **Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial**. *Am J Respir Crit Care Med* 2009, **180**:640-648.

62. Lukaszewicz AC, Grienay M, Resche-Rigon M, Pirracchio R, Faivre V, Boval B, Payen D: **Monocytic hla-dr expression in intensive care patients: interest for prognosis and secondary infection prediction**. *Crit Care Med* 2009, **37**:2746-2752.

63. Roquilly A, Broquet A, Jacqueline C, Gautreau L, Segain JP, de Coppet P, Caillon J, Altare F, Josien R, Asehnoune K: **Toll-like receptor-4 agonist in post-haemorrhage pneumonia: role of dendritic and natural killer cells**. *Eur Respir J* 2013, **42**:1365-1378.