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Activation of dendritic cells by polymorphonuclear neutrophils

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1. ABSTRACT

The obsolete view describing neutrophils as innate immune cells that respond rapidly to microbial invasion and then rapidly die by apoptosis is now challenged by several data. In both human and mice, there are now evidences that neutrophils play a role in dendritic cell activation, a critical step for the outcome of the specific T cell response.

2. INTRODUCTION

Neutrophils and DCs, that are located in distinct anatomical compartments during the steady state (the blood for neutrophils and the peripheral as well as the lymphoid organs or tissues for DCs), meet at inflammatory sites during an immune response (Figure 1). Strikingly, despite this obvious observation, the question of neutrophil-DC interactions and the consequences of this cross-talk have been ignored for long time. This situation probably relates to the old view that neutrophils are inflammatory but not immune cells, whereas DCs act as professional antigen presenting cells able to initiate very efficiently T cell specific responses in the lymphoid organs. In addition, most scientists have been probably discouraged from studying neutrophil functions because these leukocytes are short lived cells that rapidly undergo spontaneous apoptosis (1-3).

However, an increasing number of recent data started to enlighten this new field of cellular interactions between neutrophils and the leukocytes that are involved in "specific immunity", leading to the breakdown of a dogma. In this article, I will focus on the interactions that take place between neutrophils and DCs and the impact of this cross-talk on DC activation.

3. DISCUSSION

3.1. Accession of DCs to the antigen presenting cell status

DCs are highly efficient in stimulating T lymphocytes and deliver signals that are critical for the further polarization of the adaptive immune response and, in this regard, are defined as professional antigen presenting cell (APC) (4). However, to perform their APC functions, DCs need to be activated.

DCs are located in almost all anatomical sites including mucosal tissues, skin and vascularized organs. In the steady state, peripheral DCs express low surface levels of major histocompatibility complex (MHC) class II and co-stimulatory molecules, and do not secrete immune cytokines. They are not efficient at stimulating T cell responses and, in this regard, they are referred to as

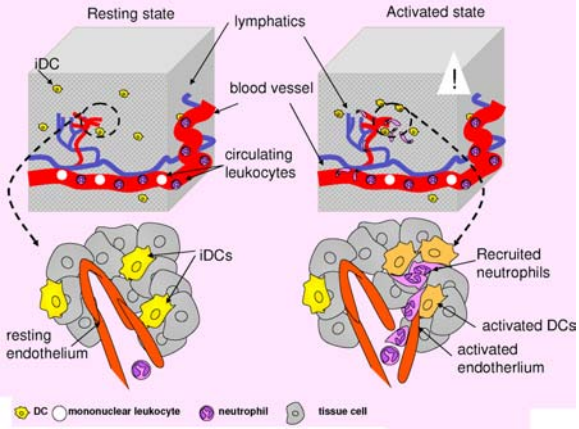

Figure 1. Neutrophils and DCs meet at inflammatory sites during an immune response. In the steady state (left part of the figure), resting DCs are seeded in peripheral organs and tissues (in grey), whereas neutrophils (purple cells) circulate in the blood and do not adhere to the resting endothelium. In an inflammatory situation (right part of the figure), endothelial cells become activated and deliver to circulating leukocytes chemotactic and adhesion signals that will further allow neutrophils to emigrate from the blood to the extravascular area. At the site of injury or infection, neutrophils and activated DCs (orange cells) encounter and interact.

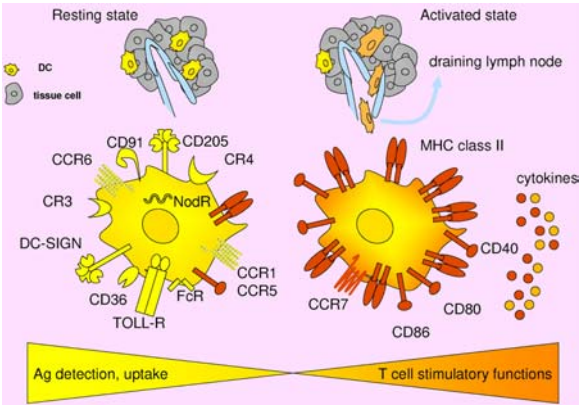

Figure 2. The DC activation/maturation process. iDCs express high levels of innate receptors including Toll, C-type lectins (DC-SIGN, CD205), complement (CR3, CR4), FcR, heat shock protein (CD91), Nod and scavenger receptors that allow them to detect microorganisms or danger signals in the microenvironment. iDCs are able to respond to locally produced inflammatory chemokines via the expression of the corresponding receptors CCR1, CCR5 and CCR6. Upon activation, DCs down-regulate the innate receptors and change their chemokine receptor profile. Activated DCs upregulate MHC class II and co-stimulatory molecules (CD80, CD86, CD40), secrete cytokines and chemokines and become competent in stimulating T cells. CCR7 expression allows activated DCs to traffic towards the lymph node.

In all illustrations, the yellow symbols represent immature DCs, whereas, those in orange/red represent activated DCs.

immature DCs (iDCs). However, in the early phase of the immune response, iDCs detect microorganisms or foreign structures *via* receptors that recognize molecular motifs expressed by a large spectrum of microorganisms called pathogen-associated-molecular pattern –PAMPs-. These pattern recognition receptors (PRRs) include Toll-like (5), C-type lectin (6) and Nod receptors (7-9). Other receptors -Fc (10-12) or complement receptors (13)- are then involved in uptake of immune complexes or opsonized microorganisms. iDCs not only detect microorganisms but also sense the tissue environment to detect endogeneous stress signals: apoptotic cells *via* expression of scavenger receptors CD36, $\alpha_v\beta_5$ or $\alpha_v\beta_3$ (14, 15) or danger-associated molecules released by injured or necrotic cells such DNA, RNA, heat shock proteins or hyaluronic acid (16-18) (Figure 2) .

Such sensitized DCs process antigens and undergo a complex and coordinated program of phenotypic, morphological and functional changes referred to as "DC activation/maturation process". This progression includes upregulation of MHC class II, CD80, CD86 and CD40 molecules, the secretion of cytokines and chemokines, the expression of chemokines and cytokines receptors (Figure 2) and the loss of phagocytic functions. Such activated DCs take part locally to the innate response by secreting inflammatory cytokines (IL-1α, TNF-α, IL-6) (19) and acquire the capacity to migrate to the draining lymph node, where they will further select and initiate the pool of naïve specific T lymphocytes.

The signals delivered by DCs to T lymphocytes are critical in directing immunity (Th1, Th2, Th17) (20-23) or tolerance (regulatory T cells) (24-28), or anergy (29) induction. The outcome of the immunological response depends on the DC status that is influenced by the stimuli to which DCs have been exposed prior to encounter T lymphocytes in the lymph nodes (17, 30). DC activation is influenced by the nature of the initial signal, i.e, bacteria, viruses, fungi, drugs, apoptotic or necrotic cells. However, DCs are sparse in peripheral tissues and surrounded by other resident professional phagocytes -such as macrophages and mast cells- or rapidly recruited inflammatory cells that might influence their response. In the case of tissue injury, neutrophils, circulating in large numbers in blood, are massively recruited to the injured site and can play a pivotal role in DC activation/maturation processes.

3.2. Neutrophils as regulator cells of the adaptive immune response

In vivo depletion of neutrophils in animal models revealed that these "phagocytic non-specific effectors" of the innate response play a significant role in induction of the T cell specific activation (31, 32). Neutrophils indeed interfere with the T cell response through the production of T cell recruiting chemokines (32, 33). They also have the potential to acquire APC functions to instruct directly CD4 (34) (32, 35-37) or CD8 lymphocytes (31), during a process called "transdifferentiation". Moreover, neutrophils can perform cross-presentation of antigens to CD8 T cells (38, 39) (Figure 3).

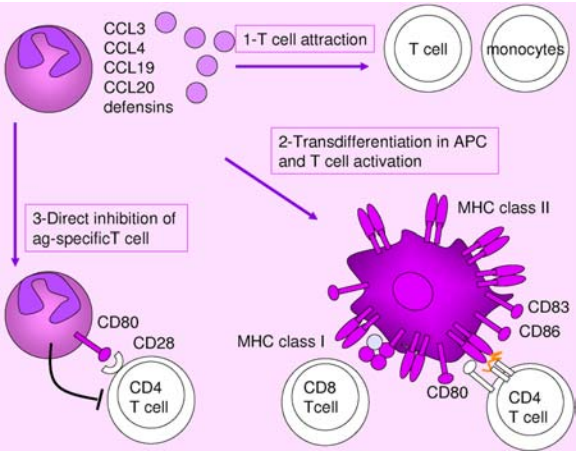

Figure 3. Neutrophils interact with T cells. Neutrophils interact with T cells through at least 3 pathways. 1) Activated neutrophils recruit T cells and monocytes via the production of CCL3, CCL4, CCL19, CCL20 and defensins; 2) Neutrophils can acquire the phenotype and the function of APCs; 3) neutrophils can deliver inhibiting signals to specific T cells through CD80/CD28 direct interaction.

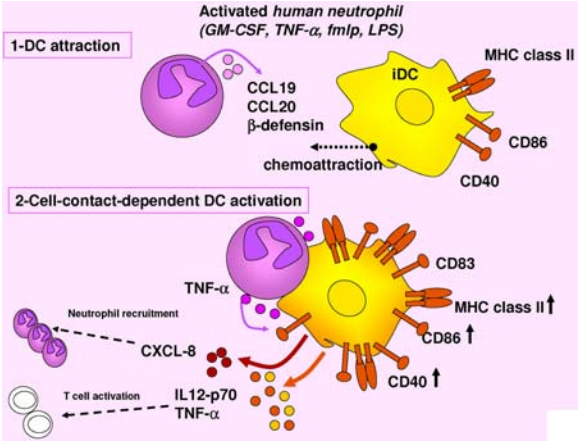

Figure 4. Human models of neutrophil-DC interaction. Activated neutrophils attract iDCs and deliver to them activation signals in a cell-contact-dependent pathway. During this interaction, TNF-α produced locally by neutrophils induces DCs to upregulate MHC class II molecules, CD80, CD86 and CD83 and secrete IL-12p70, TNF-α and CXCL-8. Neutrophil-activated DCs acquire APC functions to stimulate T cells and also play a role in attracting newly migrating neutrophils.

However, evidences obtained in both human and mouse systems, indicate that neutrophils influence adaptive immunity not only by T cell recruitment and activation but also by instructing DCs that are instrumental in directing T cell responses against exogenous as well as endogenous antigenic materials.

3.3. Neutrophils attract DCs

In vitro studies revealed that neutrophils attract DCs through the production of chemotactic factors. Human neutrophils activated by various stimuli -TNF-α , IFN-γ, bacteria, or bacterial-derived products (LPS, fMLP)-, release a large pattern of chemotactic factors including CCL19 and CCL20 chemokines (33, 40-42) and β-defensins that selectively attract iDCs (43, 44). In the mouse system, *Toxoplasma Gondii*-stimulated neutrophils secrete CCL3, CCL4, CCL5 and CCL20 chemokines (45). Interestingly, activated DCs in turn produce high amounts of CXCL-8 that mediates both recruitment and activation of neutrophils (46). Thus, in an inflammatory situation, neutrophils and DCs attract each other to favour their encounter (figures 4, 5).

Neutrophils also play a role in the replenishment of iDCs at the inflamed site, since they produce CCL2, CCL3, CCL4 and CCL20 that recruit distinct subtypes of blood DC precursors (47).

3.4. Activated neutrophils deliver both activation signals and antigen to DCs

Two independent *in vitro* studies using human neutrophils and monocyte-derived DCs showed that both cell types physically associates to form heterologous clusters within 30 minutes (48, 49). In both models, and beyond some discrepancies that probably relates to differences between these experimental systems, live activated neutrophils induce upregulation of MHC class II, CD86, CD40 or CD83 on DC surface and IL-12 production (Figure 4) *via* a cell-contact-dependent pathway. According to these results, DCs that have been exposed for less than 18 hours to neutrophils are more potent in stimulating naïve T cells in an MLR and direct the T cell response to the production of Th1 cytokines rather than Th2 (49). Similar results were obtained in the mouse system, where *Toxoplama Gondii*- or LPS-stimulated neutrophils have been shown to induce upregulation of MHC class II, CD40, CD80 and CD86 molecules on iDCs as well as IL-12 and TNF-α secretion (45, 50, 51) (Figure 5).

In human systems, we showed that live neutrophils deliver *Candida albicans* (48) to iDCs *via* a cell-contact dependent mechanism for subsequent T cell presentation. This indicates that antigenic material first captured by neutrophils and further available for uptake and presentation, can be transferred to DCs during the cellular interaction between both cell types (Figure 6).

3.5. Molecular mechanisms of neutrophil-DC communication

In human, cell-contact-dependent interactions between neutrophils and DCs are required to observe DC activation (48, 49). However, the molecular mechanisms involved differ between these two models. In the work by van Gisbergen et al. DC-specific ICAM-3-grabbing non integrin (DC-SIGN) expresses on iDCs binds neutrophil-specific glycoforms of Mac-1 (CD11b/CD18) and CEACAM1 (49, 52). The DC-SIGN ligand recognized in the Mac-1 complex is located on the α_M chain (CD11b). In contrast, we showed that direct contact between neutrophils and iDCs and the subsequent DC activation are dependent of CD18 expression on the neutrophils and did not involve DC-SIGN on the DC surface. These discrepancies could

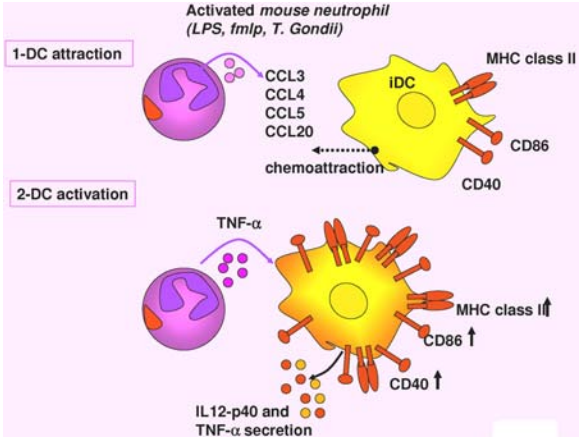

Figure 5. Mouse models of neutrophil-DC interaction. Activated neutrophils attract iDCs and deliver to them activation signals via TNF-α production. Neutrophils induce DCs to upregulate MHC class II molecules, CD40 and CD86 and to secrete IL-12p40 and TNF-α. Neutrophil-activated DCs acquire APC functions to stimulate a Th1-polarized response.

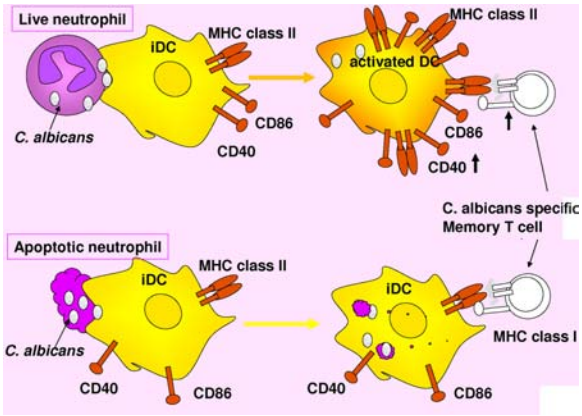

Figure 6. Neutrophils deliver antigenic molecules to DCs. Neutrophils deliver *C. albicans* to iDCs *via* a cell-contact dependent mechanism for subsequent T cell presentation. This indicates that antigenic material first captured by neutrophils and further available for uptake and presentation, can be transferred to DCs during this interaction. Although, apoptotic neutrophils deliver efficiently antigens to iDCs, they are not able to induce upregulation of DC activation markers and/or cytokine production.

however be explained by differences between the experimental approaches. First, activation of neutrophils was not performed with the same stimuli, that were LPS, fMLP or TNF-α in the van Gisbergen studies (49), and GM-CSF and IL-4 in ours (48). The nature of the stimulating signal delivered to the neutrophil may probably direct the molecular pathway further involved in neutrophil-DC communication. Secondly, although we showed that CD18 is critical for neutrophil-DC interaction, we cannot exclude involvement of CD11b in our model (48). Indeed, saturation of CD11b molecules on freshly isolated or GM-CSF-activated neutrophils was never achieved with anti-CD11b blocking antibodies (such as clones ICRF44 or IB4), even at high concentrations (25 μg/ml/10^6 cells) (data not shown), a situation that prevents inhibition of CD11b-dependent cellular interactions. Identification of CD11b as a ligand of DC-SIGN, was demonstrated using molecular and biochemical approaches (western blot, ELISA and binding experiments using immunoprecipitated neutrophil-derived proteins and recombinant DC-SIGN) instead of neutrophil-DC co-cultures with anti-CD11b inhibiting antibodies (49). Moreover, neutrophil-induced CD83 upregulation was not inhibited on DCs in the presence of anti-CD11b blocking antibodies (52). It appears, however, from both human studies that the CD11b/CD18 complex, that is involved in several neutrophil functions including cell-adhesion, transmigration, phagocytosis of microorganisms and apoptosis (53), is also required for neutrophil-DC crosstalk (Figure 7).

In both human (49) and mouse models (45, 51), the local production of TNF-α by neutrophils physically associated or close to DCs is required to induce DC activation.

3.6. Do dying neutrophils regulate DC activation?

The process of neutrophil activation is closely linked to that of cell survival (2, 54). Indeed, resting neutrophils are short lived cells, with a circulating half-life of less than 24 hrs and it is now well established that this dramatic neutrophil elimination is mediated by the constitutive activation of an apoptotic cell death program. Because the innate-immune response to infection is critical, this "naturally occurring" apoptosis can be delayed within the inflammatory environment, a process that may be advantageous for host defense. However, after they have been recruited and activated, neutrophils undergo apoptosis (or in some cases necrosis) and are cleared from the inflammated tissue by resident phagocytes (3). Uptake of dying cells, apoptotic or necrotic, by iDCs have been reported to promote antigen acquisition by DC for subsequent T cell presentation (14). In agreement with these finding, it has been shown that human apoptotic neutrophils that have phagocyted C. albicans (48)or Mycobacterium tuberculosis (55) can transfer to DCs antigens for further T cell presentation or cross presentation, respectively. Although, apoptotic neutrophils deliver efficiently antigens to iDCs (48, 55, 56), they are not able to induce upregulation of DC activation markers and/or cytokine production. This inhibitory effect could however be overcomed in the presence of proinflammatory factors such TNF-α or microorganism-derived signals.

3.7. Conclusion

The concept that neutrophils contribute directly to the adaptive immune response is now sustained by studies indicating that neutrophils associate with iDCs and deliver to them both activation signal and antigen material, allowing them to progress toward the professional APC status. In human and mouse studies, the neutrophil-DC communication have been studied using iDCs, mimicking

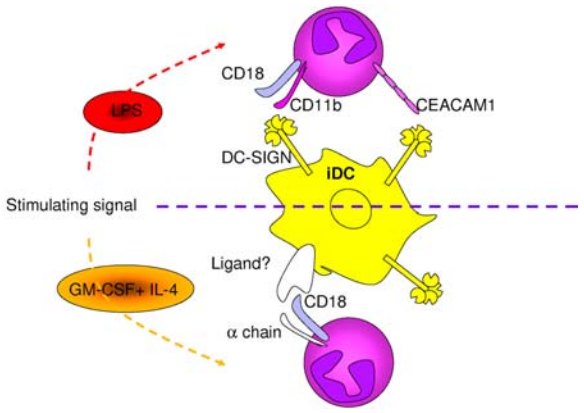

Figure 7. Molecular interactions between neutrophils and iDCs. Two independent experimental systems using human leukocytes described the molecular interactions involved in neutrophil-DC crosstalk. 1) LPS-activated neutrophils interact with iDCs via CD11b/DC-SIGN or CEACAM1/DC-SIGN interaction (52). 2) GM-CSF + IL-4 -activated neutrophils interact with iDCs via CD18 with a non-DC-SIGN ligand (48).

the *in vivo* situation in peripheral injured tissues. However, it will be of great interest to investigate the effect of neutrophil on mature DCs. Indeed, in vivo data showing that antigen-bearing neutrophils can exit the inflammated tissue to migrate into the draining lymph nodes in close contact with DC and T cells have been reported in different models (57-59). *In vitro*, it has been shown that human neutrophils are able to migrate across the endothelial barrier in a reverse direction (60). The description and the understanding of a triangular relationship between neutrophil-DC and T cells in secondary lymphoid organs will probably emerge soon and will be the next conquest of the neutrophil in the land of immunologists.

4. ACKNOWLEDGMENTS

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5. REFERENCES

1 Haslett, C., J. S. Savill & L. Meagher: The neutrophil. *Curr Opin Immunol*, 2, 10-8 (1989)

2 Haslett, C.: Resolution of acute inflammation and the role of apoptosis in the tissue fate of granulocytes. *Clin Sci (Lond)*, 83, 639-48 (1992)

3 Serhan, C. N. & J. Savill: Resolution of inflammation: the beginning programs the end. *Nat Immunol*, 6, 1191-7 (2005)

4 Steinman, R. M. & H. Hemmi: Dendritic cells: translating innate to adaptive immunity. *Curr Top Microbiol Immunol*, 311, 17-58 (2006)

5 Iwasaki, A. & R. Medzhitov: Toll-like receptor control of the adaptive immune responses. *Nat Immunol*, 5, 987-95 (2004)

6 Figdor, C. G., Y. van Kooyk & G. J. Adema: C-type lectin receptors on dendritic cells and Langerhans cells. *Nat Rev Immunol*, 2, 77-84 (2002)

7 Tada, H., S. Aiba, K. Shibata, T. Ohteki & H. Takada: Synergistic effect of Nod1 and Nod2 agonists with toll-like receptor agonists on human dendritic cells to generate interleukin-12 and T helper type 1 cells. *Infect Immun*, 73, 7967-76 (2005)

8 Fritz, J. H., S. E. Girardin, C. Fitting, C. Werts, D. Mengin-Lecreulx, M. Caroff, J. M. Cavaillon, D. J. Philpott & M. Adib-Conquy: Synergistic stimulation of human monocytes and dendritic cells by Toll-like receptor 4 and NOD1- and NOD2-activating agonists. *Eur J Immunol*, 35, 2459-70 (2005)

9 Fritz, J. H., R. L. Ferrero, D. J. Philpott & S. E. Girardin: Nod-like proteins in immunity, inflammation and disease. *Nat Immunol*, 7, 1250-7 (2006)

10 Jurgens, M., A. Wollenberg, D. Hanau, H. de la Salle & T. Bieber: Activation of human epidermal Langerhans cells by engagement of the high affinity receptor for IgE, Fc epsilon RI. *J Immunol*, 155, 5184-9 (1995)

11 Fanger, N. A., K. Wardwell, L. Shen, T. F. Tedder & P. M. Guyre: Type I (CD64) and type II (CD32) Fc gamma receptor-mediated phagocytosis by human blood dendritic cells. *J Immunol*, 157, 541-8 (1996)

12 Geissmann, F., P. Launay, B. Pasquier, Y. Lepelletier, M. Leborgne, A. Lehuen, N. Brousse & R. C. Monteiro: A subset of human dendritic cells expresses IgA Fc receptor (CD89), which mediates internalization and activation upon cross-linking by IgA complexes. *J Immunol*, 166, 346-52 (2001)

13 Bajtay, Z., E. Csomor, N. Sandor & A. Erdei: Expression and role of Fc- and complement-receptors on human dendritic cells. *Immunol Lett*, 104, 46-52 (2006)

14 Albert, M. L., S. F. Pearce, L. M. Francisco, B. Sauter, P. Roy, R. L. Silverstein & N. Bhardwaj: Immature dendritic cells phagocytose apoptotic cells via alphavbeta5 and CD36, and cross-present antigens to cytotoxic T lymphocytes. *J Exp Med*, 188, 1359-68 (1998)

15 Rubartelli, A., A. Poggi & M. R. Zocchi: The selective engulfment of apoptotic bodies by dendritic cells is mediated by the alpha (v)beta3 integrin and requires intracellular and extracellular calcium. *Eur J Immunol*, 27, 1893-900 (1997)

16 Chen, X., K. Doffek, S. L. Sugg & J. Shilyansky: Phosphatidylserine regulates the maturation of human dendritic cells. *J Immunol*, 173, 2985-94 (2004)

17 Gallucci, S., M. Lolkema & P. Matzinger: Natural adjuvants: endogenous activators of dendritic cells. *Nat Med*, 5, 1249-55 (1999)

18 Shi, Y., J. E. Evans & K. L. Rock: Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature*, 425, 516-21 (2003)

19 Foti, M., F. Granucci, M. Pelizzola, O. Beretta & P. Ricciardi-Castagnoli: Dendritic cells in pathogen recognition and induction of immune responses: a functional genomics approach. *J Leukoc Biol*, 79, 913-6 (2006)

20 Stockinger, B., C. Bourgeois & G. Kassiotis: CD4+ memory T cells: functional differentiation and homeostasis. *Immunol Rev*, 211, 39-48 (2006)

21 Gutcher, I. & B. Becher: APC-derived cytokines and T cell polarization in autoimmune inflammation. *J Clin Invest*, 117, 1119-27 (2007)

22 Gandhi, R., D. E. Anderson & H. L. Weiner: Cutting Edge: Immature human dendritic cells express latency-associated peptide and inhibit T cell activation in a TGF-beta-dependent manner. *J Immunol*, 178, 4017-21 (2007)

23 Deshpande, P., I. L. King & B. M. Segal: Cutting Edge: CNS CD11c+ cells from mice with encephalomyelitis polarize Th17 cells and support CD25+CD4+ T cell-mediated immunosuppression, suggesting dual roles in the disease process. *J Immunol*, 178, 6695-9 (2007)

24 Takahashi, T., Y. Kuniyasu, M. Toda, N. Sakaguchi, M. Itoh, M. Iwata, J. Shimizu & S. Sakaguchi: Immunologic self-tolerance maintained by CD25+CD4+ naturally anergic and suppressive T cells: induction of autoimmune disease by breaking their anergic/suppressive state. *Int Immunol*, 10, 1969-80 (1998)

25 Miyara, M. & S. Sakaguchi: Natural regulatory T cells: mechanisms of suppression. *Trends Mol Med*, 13, 108-16 (2007)

26 Groux, H., A. O'Garra, M. Bigler, M. Rouleau, S. Antonenko, J. E. de Vries & M. G. Roncarolo: A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature*, 389, 737-42 (1997)

27 Wakkach, A., N. Fournier, V. Brun, J. P. Breittmayer, F. Cottrez & H. Groux: Characterization of dendritic cells that induce tolerance and T regulatory 1 cell differentiation in vivo. *Immunity*, 18, 605-17 (2003)

28 Roncarolo, M. G., S. Gregori, M. Battaglia, R. Bacchetta, K. Fleischhauer & M. K. Levings: Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. *Immunol Rev*, 212, 28-50 (2006)

29 Choi, S. & R. H. Schwartz: Molecular mechanisms for adaptive tolerance and other T cell anergy models. *Semin Immunol*, 19, 140-52 (2007)

30 Sauter, B., M. L. Albert, L. Francisco, M. Larsson, S. Somersan & N. Bhardwaj: Consequences of cell death: exposure to necrotic tumor cells, but not primary tissue cells or apoptotic cells, induces the maturation of immunostimulatory dendritic cells. *J Exp Med*, 191, 423-34 (2000)

31 Shiratsuchi, Y., T. Iyoda, N. Tanimoto, D. Kegai, K. Nagata & Y. Kobayashi: Infiltrating neutrophils induce allospecific CTL in response to immunization with apoptotic cells via MCP-1 production. *J Leukoc Biol*, 81, 412-20 (2007)

32 Molesworth-Kenyon, S. J., J. E. Oakes & R. N. Lausch: A novel role for neutrophils as a source of T cell-recruiting chemokines IP-10 and Mig during the DTH response to HSV-1 antigen. *J Leukoc Biol*, 77, 552-9 (2005)

33 Scapini, P., J. A. Lapinet-Vera, S. Gasperini, F. Calzetti, F. Bazzoni & M. A. Cassatella: The neutrophil as a cellular source of chemokines. *Immunol Rev*, 177, 195-203 (2000)

34 Iking-Konert, C., C. Cseko, C. Wagner, S. Stegmaier, K. Andrassy & G. M. Hansch: Transdifferentiation of polymorphonuclear neutrophils: acquisition of CD83 and other functional characteristics of dendritic cells. *J Mol Med*, 79, 464-74 (2001)

35 Mencacci, A., C. Montagnoli, A. Bacci, E. Cenci, L. Pitzurra, A. Spreca, M. Kopf, A. H. Sharpe & L. Romani: CD80+Gr-1+ myeloid cells inhibit development of antifungal Th1 immunity in mice with candidiasis. *J Immunol*, 169, 3180-90 (2002)

36 Ashtekar, A. R. & B. Saha: Poly's plea: membership to the club of APCs. *Trends Immunol*, 24, 485-90 (2003)

37 Wagner, C., C. Iking-Konert, F. Hug, S. Stegmaier, V. Heppert, A. Wentzensen & G. M. Hansch: Cellular inflammatory response to persistent localized Staphylococcus aureus infection: phenotypical and functional characterization of polymorphonuclear neutrophils (PMN). *Clin Exp Immunol*, 143, 70-7 (2006)

38 Tvinnereim, A. R., S. E. Hamilton & J. T. Harty: Neutrophil involvement in cross-priming CD8+ T cell responses to bacterial antigens. *J Immunol*, 173, 1994-2002 (2004)

39 Beauvillain, C., Y. Delneste, M. Scotet, A. Peres, H. Gascan, P. Guermonprez, V. Barnaba & P. Jeannin: Neutrophils efficiently cross-prime naive T cells in vivo. *Blood* (2007)

40 Scapini, P., C. Laudanna, C. Pinardi, P. Allavena, A. Mantovani, S. Sozzani & M. A. Cassatella: Neutrophils produce biologically active macrophage inflammatory protein-3alpha (MIP-3alpha)/CCL20 and MIP-3beta/CCL19. *Eur J Immunol*, 31, 1981-8 (2001)

41 Scapini, P., L. Crepaldi, C. Pinardi, F. Calzetti & M. A. Cassatella: CCL20/macrophage inflammatory protein-

3alpha production in LPS-stimulated neutrophils is enhanced by the chemoattractant formyl-methionyl-leucyl-phenylalanine and IFN-gamma through independent mechanisms. *Eur J Immunol*, 32, 3515-24 (2002)

42 Akahoshi, T., T. Sasahara, R. Namai, T. Matsui, H. Watabe, H. Kitasato, M. Inoue & H. Kondo: Production of macrophage inflammatory protein 3alpha (MIP-3alpha) (CCL20) and MIP-3beta (CCL19) by human peripheral blood neutrophils in response to microbial pathogens. *Infect Immun*, 71, 524-6 (2003)

43 Yang, D., O. Chertov, S. N. Bykovskaia, Q. Chen, M. J. Buffo, J. Shogan, M. Anderson, J. M. Schroder, J. M. Wang, O. M. Howard & J. J. Oppenheim: Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. *Science*, 286, 525-8 (1999)

44 Yang, D., Q. Chen, O. Chertov & J. J. Oppenheim: Human neutrophil defensins selectively chemoattract naive T and immature dendritic cells. *J Leukoc Biol*, 68, 9-14 (2000)

45 Bennouna, S., S. K. Bliss, T. J. Curiel & E. Y. Denkers: Cross-talk in the innate immune system: neutrophils instruct recruitment and activation of dendritic cells during microbial infection. *J Immunol*, 171, 6052-8 (2003)

46 Scimone, M. L., V. P. Lutzky, S. I. Zittermann, P. Maffia, C. Jancic, F. Buzzola, A. C. Issekutz & H. E. Chuluyan: Migration of polymorphonuclear leucocytes is influenced by dendritic cells. *Immunology*, 114, 375-85 (2005)

47 Vanbervliet, B., B. Homey, I. Durand, C. Massacrier, S. Ait-Yahia, O. de Bouteiller, A. Vicari & C. Caux: Sequential involvement of CCR2 and CCR6 ligands for immature dendritic cell recruitment: possible role at inflamed epithelial surfaces. *Eur J Immunol*, 32, 231-42 (2002)

48 Megiovanni, A. M., F. Sanchez, M. Robledo-Sarmiento, C. Morel, J. C. Gluckman & S. Boudaly: Polymorphonuclear neutrophils deliver activation signals and antigenic molecules to dendritic cells: a new link between leukocytes upstream of T lymphocytes. *J Leukoc Biol*jlb.0905526 (2006)

49 van Gisbergen, K. P., M. Sanchez-Hernandez, T. B. Geijtenbeek & Y. van Kooyk: Neutrophils mediate immune modulation of dendritic cells through glycosylation-dependent interactions between Mac-1 and DC-SIGN. *J Exp Med*, 201, 1281-92 (2005)

50 Wan, X., P. Zheng & G. Chen: Neutrophils induce the maturation and activation of immature dendritic cells during adaptive immune responses (article in Chinese). *Zhonghua Yi Xue Za Zhi*, 86, 2761-5 (2006)

51 Xiaoxiao, W., Y. Sibiao, X. Xiaopeng, Z. Ping & C. Gang: Neutrophils induce the maturation of immature dendritic cells: a regulatory role of neutrophils in adaptive immune responses. *Immunol Invest*, 36, 337-50 (2007)

52 van Gisbergen, K. P., I. S. Ludwig, T. B. Geijtenbeek & Y. van Kooyk: Interactions of DC-SIGN with Mac-1 and CEACAM1 regulate contact between dendritic cells and neutrophils. *FEBS Lett*, 579, 6159-68 (2005)

53 Mayadas, T. N. & X. Cullere: Neutrophil beta (2) integrins: moderators of life or death decisions. *Trends Immunol*, 26, 388-95 (2005)

54 Whyte, M. K., L. C. Meagher, J. MacDermot & C. Haslett: Impairment of function in aging neutrophils is associated with apoptosis. *J Immunol*, 150, 5124-34 (1993)

55 Aleman, M., S. de la Barrera, P. Schierloh, N. Yokobori, M. Baldini, R. Musella, E. Abbate & M. Sasiain: Spontaneous or Mycobacterium tuberculosis-induced apoptotic neutrophils exert opposite effects on the dendritic cell-mediated immune response. *Eur J Immunol*, 37, 1524-37 (2007)

56 Clayton, A. R., R. L. Prue, L. Harper, M. T. Drayson & C. O. Savage: Dendritic cell uptake of human apoptotic and necrotic neutrophils inhibits CD40, CD80, and CD86 expression and reduces allogeneic T cell responses: relevance to systemic vasculitis. *Arthritis Rheum*, 48, 2362-74 (2003)

57 Abadie, V., E. Badell, P. Douillard, D. Ensergueix, P. J. Leenen, M. Tanguy, L. Fiette, S. Saeland, B. Gicquel & N. Winter: Neutrophils rapidly migrate via lymphatics after Mycobacterium bovis BCG intradermal vaccination and shuttle live bacilli to the draining lymph nodes. *Blood*, 106, 1843-50 (2005)

58 Maletto, B. A., A. S. Ropolo, D. O. Alignani, M. V. Liscovsky, R. P. Ranocchia, V. G. Moron & M. C. Pistoresi-Palencia: Presence of neutrophil-bearing antigen in lymphoid organs of immune mice. *Blood*, 108, 3094-102 (2006)

59 Bonneau, M., M. Epardaud, F. Payot, V. Niborski, M. I. Thoulouze, F. Bernex, B. Charley, S. Riffault, L. A. Guilloteau & I. Schwartz-Cornil: Migratory monocytes and granulocytes are major lymphatic carriers of Salmonella from tissue to draining lymph node. *J Leukoc Biol*, 79, 268-76 (2006)

60 Buckley, C. D., E. A. Ross, H. M. McGettrick, C. E. Osborne, O. Haworth, C. Schmutz, P. C. Stone, M. Salmon, N. M. Matharu, R. K. Vohra, G. B. Nash & G. E. Rainger: Identification of a phenotypically and functionally distinct population of long-lived neutrophils in a model of reverse endothelial migration. *J Leukoc Biol*, 79, 303-11 (2006)

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