OncoImmunology ›

Volume 1, 2012 - Issue 9

Open access

1,144 Views | 21 CrossRef citations to date | 0 Altmetric

Listen

Author's View

How imiquimod licenses plasmacytoid dendritic cells to kill tumors

Martin Holcmann, Barbara Drobits & Maria Sibilia

Pages 1661-1663 | Published online: 06 Dec 2012

Cite this article https://doi.org/10.4161/onci.22033

Abstract

We have provided evidence for a multifaceted antitumor-function of the Toll-like receptor 7 (TLR7) agonist imiquimod, which rapidly recruits plasmacytoid dendritic cells and possibly other immune cells into tumors by inducing the secretion of CCL2 by dermal cells. Imiquimod induces pDC maturation and their conversion into cytolytic killer cells, which are capable of eliminating tumors independently from the adaptive immune system.

Keywords: :

imiquimod | pDC | CCL2 | Type I IFN | cancer

One of the few success stories in the field of cancer immunotherapy has been the establishment of imiquimod as a standard therapy for the treatment of superficial skin cancers like basal cell carcinoma (BCC), actinic keratosis or preinvasive melanoma (lentigo maligna). The imidazochinoline imiquimod is topically applied to the skin as a 5% cream, and several modes of action against tumors have been suggested. Direct effects on tumor cells can be distinguished from those mediated via the immune system.[1] Imiquimod is capable of directly inducing caspase-mediated apoptosis and inhibiting adenosine signaling in transformed cells in a Toll-like receptor 7 (TLR7)-independent manner. Moreover, imiquimod act as an agonist for TLR7, which is mainly expressed by cells of the immune system, leading to activation and recruitment to the site of imiquimod application. Imiquimod-induced tumor regression is characterized by skin erythema and the presence of an inflammatory infiltrate in and around the tumor, mainly consisting—in humans as well as in mice—of different types of dendritic cells (DCs) as well as $CD4^+$ and $CD8^+$ T cells. Interestingly, B and natural killer (NK) cells have rarely been found in imiquimod-induced tumor infiltrates.[2] Commonly, $CD8^+$ T cells and NK cells need to acquire special features to kill tumor cells, such as the expression of granzyme B and perforin as well as that of tumor necrosis factor (TNF) family members like TNF-related apoptosis-inducing ligand (TRAIL). Usually, DCs are critically involved in priming NK- and T-cell dependent antitumor immune responses.[3] However, more recently DC subtypes like interferon (IFN)-producing killer DCs (IKDCs) have been characterized for their ability to directly kill tumor cells, although their true identity as DCs has recently been challenged.[4] In BCC patients receiving imiquimod, skin myeloid DCs and plasmacytoid DCs (pDCs) have been shown to express granzyme B plus perforin and TRAIL, respectively, indicating that imiquimod-stimulated DCs might not only play an important role in regulating but also in executing antitumor immune responses by directly killing malignant cells.[5]

In an orthotopic mouse model of melanoma, we investigated the mechanisms by which imiquimod recruits immune cells into the skin, with the aim to identify the effector cells that are necessary for tumor killing (Fig. 1).[6] Since imiquimod is applied topically, we assumed that the first cells responding to imiquimod would be skin-resident cells. By employing bone marrow chimeras we discovered that TLR7 expression by hematopoietic cells, but not other skin cells, is required for the antitumor effect of imiquimod. Mast cells and a few skin-resident pDCs express TLR7 and mast cells have been reported to play a critical role in the induction of adaptive immune responses upon TLR7 ligation.[7] When analyzing imiquimod-treated skins, we found increased

amounts of CCL2 and this finding correlated with a higher number of activated mast cells in the dermis (Amberg N., unpublished data). Moreover, mast cells produced CCL2 when stimulated with imiquimod (Fig. 1). Since pDCs express CCR2, the receptor for CCL2, it is likely that their recruitment to the skin is induced by CCL2 secreted by mast cells in a TLR7- and MyD88-dependent manner after imiquimod stimulation. Interestingly, CCL2 production by mast cells also relied on Type I IFN signaling (Fig. 1). Thus, it cannot be formally excluded that resident pDCs themselves produce CCL2. Mice lacking mast cells will have to be studied to clarify this issue.

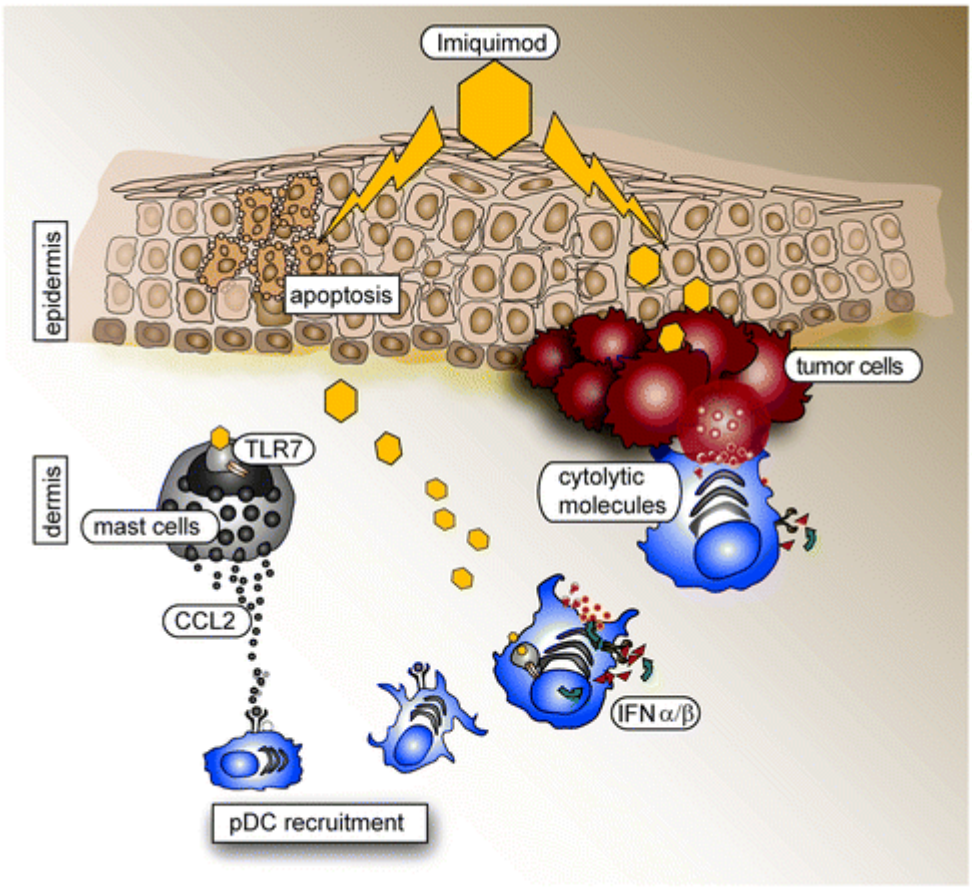
The key role of pDCs in this setting was confirmed by the finding that pDC depletion in BDCA2-DTR mice completely abolished the antitumor effect of imiquimod. The antitumor effects of imiquimod persisted in Rag2$^{-/-}$ and athymic mice, de facto excluding T and B cells as putative effector cell candidates. The same held true for NK cells: imiquimod remained active in mice subjected to NK-cell depletion. Thus, pDCs alone seem to be sufficient for tumor clearance as induced by imiquimod. The recruitment of pDCs into tumors was previously considered as a bad prognostic factor, which correlated for instance with the induction of regulatory T cells (by immature pDCs).[8] Imiquimod, however, induces the TLR7- and MyD88-dependent maturation of pDCs, resulting in the upregulation of CD8 and in the production of Type I IFN, in vitro and in vivo. CD8 and the Type I IFN receptor 1 (IFNAR1) seem to be critical for the antitumor activity of imiquimod since this was abolished by the depletion of CD8α^{+} cells. Similarly, Imiquimod was also ineffective in Ifnar1$^{-/-}$ mice.

Type I IFN may kill tumor cells either directly, in a caspase-dependent manner, or indirectly, by upregulating the expression of death-inducing factors by immune cells and/or of the respective receptors by tumor cells.[9] Blocking Type I IFN in in vitro killing assays involving imiquimod-stimulated pDCs and melanoma cells did not reduce the lysis of the latter, thus excluding a direct effect of Type I IFN. Instead, autocrine Type I IFN signaling in pDCs increased TRAIL and granzyme B production and secretion. Blocking granzyme B completely abolished the activitiy of imiquimod in vitro, whereas blocking TRAIL or its receptor DR5 was less effective. A recent study identified a similar mechanism for imiquimod-treated human pDCs.[10]

Our study confirms that only fully matured pDCs are capable of efficiently fighting tumors. Future studies will not only focus on the aforementioned mechanisms of immune-cell recruitment as induced by imiquimod but also on whether the described stimulation of pDCs is a selective feature of the imiquimod-TLR7 signaling axis or

whether other ligand-receptor pairs may provide pDCs with comparable killing activities.

Figure 1. Schematic representation of how topical imiquimod recruits and stimulates plasmacytoid dendritic cells to kill tumor cells. Toll-like receptor 7 (TLR7)-independent effects on keratinocytes are paralleled by the TLR7-dependent activation of mast cells and plasmacytoid dendritic cells (pDCs) resident in the skin. Chemokines emitted, like CCL2, recruit pDCs that secrete Type I interferon (IFN). Paracrine and autocrine IFN signaling induces the upregulation of death receptors on tumor cells and the exposure/secretion of death receptor ligands by pDCs, respectively, resulting in the enhanced killing of tumor cells.



Display full size

Related Research Data

Redefining interferon-producing killer dendritic cells as a novel intermediate in NK-cell differentiation

Source: Blood

TRAIL+ Human Plasmacytoid Dendritic Cells Kill Tumor Cells In Vitro: Mechanisms of Imiquimod- and IFN-α–Mediated Antitumor Reactivity

Source: The Journal of Immunology

Tumoricidal activity of TLR7/8-activated inflammatory dendritic cells

Source: The Journal of Experimental Medicine

Identification and Characterization of pDC-Like Cells in Normal Mouse Skin and Melanomas Treated with Imiquimod

Source: The Journal of Immunology

Mast cells are crucial for early inflammation, migration of Langerhans cells,

References

1. Schön MP, Schön M. TLR7 and TLR8 as targets in cancer therapy. Oncogene 2008; 27:190 - 9; http://dx.doi.org/10.1038/sj.onc.1210913; PMID: 18176600

   PubMed | Web of Science ® | Google Scholar

2. Palamara F, Meindl S, Holcmann M, Lührs P, Stingl G, Sibilia M. Identification and characterization of pDC-like cells in normal mouse skin and melanomas treated with imiquimod. J Immunol 2004; 173:3051 - 61; PMID: 15322165

   PubMed | Web of Science ® | Google Scholar

3. Liu C, Lou Y, Lizée G, Qin H, Liu S, Rabinovich B, et al. Plasmacytoid dendritic cells induce NK cell-dependent, tumor antigen-specific T cell cross-priming and tumor regression in mice. J Clin Invest 2008; 118:1165 - 75; PMID: 18259609

   PubMed | Web of Science ® | Google Scholar

4. Zitvogel L, Housseau F. IKDCs or B220+ NK cells are pre-mNK cells. Blood 2012; 119:4345 - 6; http://dx.doi.org/10.1182/blood-2012-03-415026; PMID: 22577157

   PubMed | Web of Science ® | Google Scholar

5. Stary G, Bangert C, Tauber M, Strohal R, Kopp T, Stingl G. Tumoricidal activity of TLR7/8-activated inflammatory dendritic cells. J Exp Med 2007; 204:1441 - 51; http://dx.doi.org/10.1084/jem.20070021; PMID: 17535975

PubMed | Web of Science ® | Google Scholar

6. Drobits B, Holcmann M, Amberg N, Swiecki M, Grundtner R, Hammer M, et al. Imiquimod clears tumors in mice independent of adaptive immunity by converting pDCs into tumor-killing effector cells. J Clin Invest 2012; 122:575 - 85; http://dx.doi.org/10.1172/JCI61034; PMID: 22251703

PubMed | Web of Science ® | Google Scholar

7. Heib V, Becker M, Warger T, Rechtsteiner G, Tertilt C, Klein M, et al. Mast cells are crucial for early inflammation, migration of Langerhans cells, and CTL responses following topical application of TLR7 ligand in mice. Blood 2007; 110:946 - 53; http://dx.doi.org/10.1182/blood-2006-07-036889; PMID: 17446350

PubMed | Web of Science ® | Google Scholar

8. Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 2004; 10:942 - 9; http://dx.doi.org/10.1038/nm1093; PMID: 15322536

PubMed | Web of Science ® | Google Scholar

9. Thyrell L, Erickson S, Zhivotovsky B, Pokrovskaja K, Sangfelt O, Castro J, et al. Mechanisms of Interferon-alpha induced apoptosis in malignant cells. Oncogene 2002; 21:1251 - 62; http://dx.doi.org/10.1038/sj.onc.1205179; PMID: 11850845

PubMed | Web of Science ® | Google Scholar

10. Kalb ML, Glaser A, Stary G, Koszik F, Stingl G. TRAIL(+) human plasmacytoid dendritic cells kill tumor cells in vitro: mechanisms of imiquimod- and IFN-α-mediated antitumor reactivity. J Immunol 2012; 188:1583 - 91; http://dx.doi.org/10.4049/jimmunol.1102437; PMID: 22231699

PubMed | Web of Science ® | Google Scholar

Download PDF

Related research

People also read | Recommended articles | Cited by 21

TLR7-based cancer immunotherapy decreases intratumoral myeloid-derived suppressor cells and blocks their immunosuppressive function

Thibaud Spinetti et al.
OncoImmunology
Published online: 4 Nov 2016

Information for

- Authors
- R&D professionals
- Editors
- Librarians
- Societies

Open access

- Overview
- Open journals
- Open Select
- Dove Medical Press
- F1000Research

Opportunities

- Reprints and e-prints
- Advertising solutions
- Accelerated publication
- Corporate access solutions

Help and information

- Help and contact
- Newsroom
- All journals
- Books

Keep up to date

Register to receive personalised research and resources by email

Sign me up

Copyright © 2026 Informa UK Limited Privacy policy

Cookies Terms & conditions Accessibility

Registered in England & Wales No. 01072954
5 Howick Place | London | SW1P 1WG