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Author's View

How imiquimod licenses plasmacytoid dendritic cells to kill tumors

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Keywords

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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
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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amounts of CCL2 and this finding correlated with a higher number of activated mast cells in the dermis (Amberg N., unpublished data).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 vi for the antitumo $CD8\alpha^+$ cells. Sir

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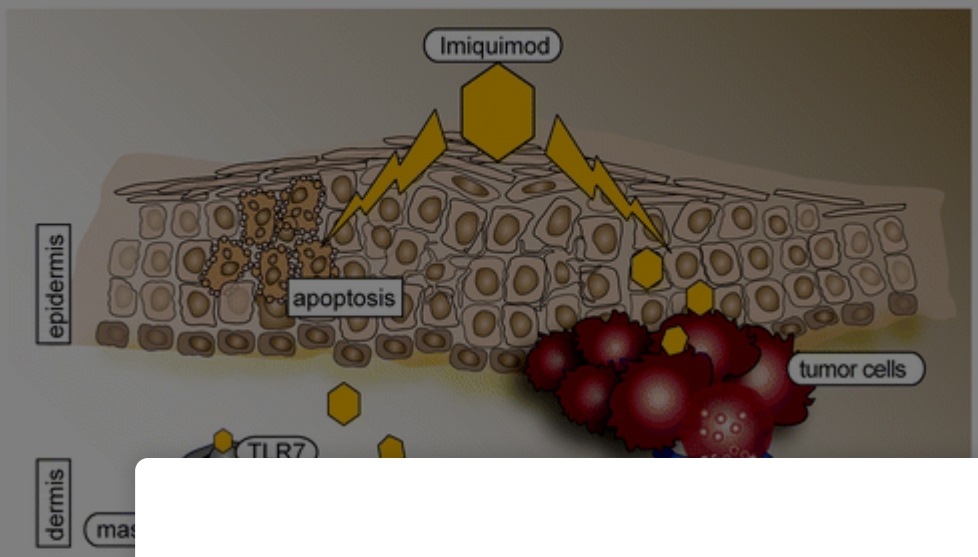
stimulation of pDCs is a selective feature of the imiquimod-TLR7 signaling axis or whether other ligand-receptor pairs may provide pDCs with comparable killing activities.

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.



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, and CTL responses following topical application of TLR7 ligand in mice

Source: Blood

Plasmacytoid dendritic cells induce NK cell–dependent, tumor antigen–specific T cell cross-priming and tumor regression in mice

Source: The Journal of Clinical Investigation

Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival

Source: Nature Medicine

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