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INSIGHTS

cDC1 dysregulation in cancer: An opportunity for intervention

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Conventional dendritic cells driven by the transcription factor Batf3 (cDC1 cells) are critical for the activation and maintenance of tumor-specific CD8⁺ T cells. In this issue of *JEM*, Lin et al. (https://doi.org/10.1084/jem.20190673) demonstrate systemic dysfunction of cDC1 cells in pancreatic cancer, which offers potential treatment strategies to expand the benefit of checkpoint blockade immunotherapy.

In the current issue of *JEM*, Lin et al. (2020) pursue an in-depth mechanistic study of the immune defects in pancreatic ductal adenocarcinoma (PDA). They found that the percentage of cDC1 cells, a key dendritic cell (DC) subset involved in T cell priming, became diminished in the pancreas and in the pancreatic-draining lymph node very early during pancreatic cancer carcinogenesis. But perhaps unexpectedly, cDC1 cells also showed diminished percentages in other lymph node regions, suggesting a systemic effect. The cDC1 cells that remained showed defective expression of several costimulatory ligands, arguing for poor DC maturation as well. These alterations in cDC1 biology were functionally important, as vaccination to induce CD8⁺ T cells against irrelevant antigens was defective in KPC tumor-bearing mice. Immunotherapeutic interventions aiming to restore cDC1 number and function were able to improve PDA tumor growth in vivo, suggesting novel strategies to consider for clinical translation.

Tumor antigen–specific CD8⁺ T cells are a critical component of the antitumor immune response and are necessary for tumor elimination with multiple immunotherapy treatment regimens. The endogenous priming and activation of CD8⁺ T cells is driven by cDC1 cells, which develop under the influence of the transcription factor Batf3 (Murphy et al., 2016). This central function of cDC1s is likely due to a heightened capability to process exogenous antigen for presentation through the class I MHC pathway (Hildner et al., 2008). Initial priming of naive CD8⁺ T cells likely occurs in tumor-draining lymph nodes, as the process depends on trafficking via CCL21 and the corresponding receptor CCR7 (Roberts et al., 2016). In addition, a population of cDC1 cells within the tumor microenvironment is required for recruitment of primed effector CD8⁺ T cells into tumor sites, as cDC1s are the chief producers of the chemokines CXCL9 and CXCL10 attracting effector T cells through the chemokine receptor CXCR3 (Spranger et al., 2017; Mikucki et al., 2015). This dynamic process of T cell priming and trafficking is critical in the generation of a T cell–inflamed tumor microenvironment, a tumor phenotype characterized by infiltration and activation of a range of immune cell subsets that includes CD8⁺ T cells (Harlin et al., 2009). Most solid tumor types have a subset of patients with a tumor microenvironment that display this phenotype, which has been shown to be a positive prognostic factor in several cancer patient populations (Galon et al., 2006; Azimi et al., 2012). This phenotype also is predictive for clinical activity with antibodies (Abs) that block PD-L1/PD-1 interactions (Ayers et al., 2017). Biologically, this is thought to be because the activated tumor-infiltrating CD8⁺ T cells are functionally held in check by negative regulatory pathways including ligation of the inhibitory receptor PD-1. Anti–PD-1/PD-L1 Abs improve the functionality of those T cells, facilitating immune-mediated tumor control and leading to improved clinical outcomes.

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Failure to spontaneously generate a T cell–inflamed tumor microenvironment, therefore, represents a major mechanism of primary resistance to anti–PD-1 Ab therapy. The driving forces involved in primary resistance are complex and likely multifactorial. Tumor cell–intrinsic oncogenic events, germline polymorphisms in immune regulatory genes, and the composition of the

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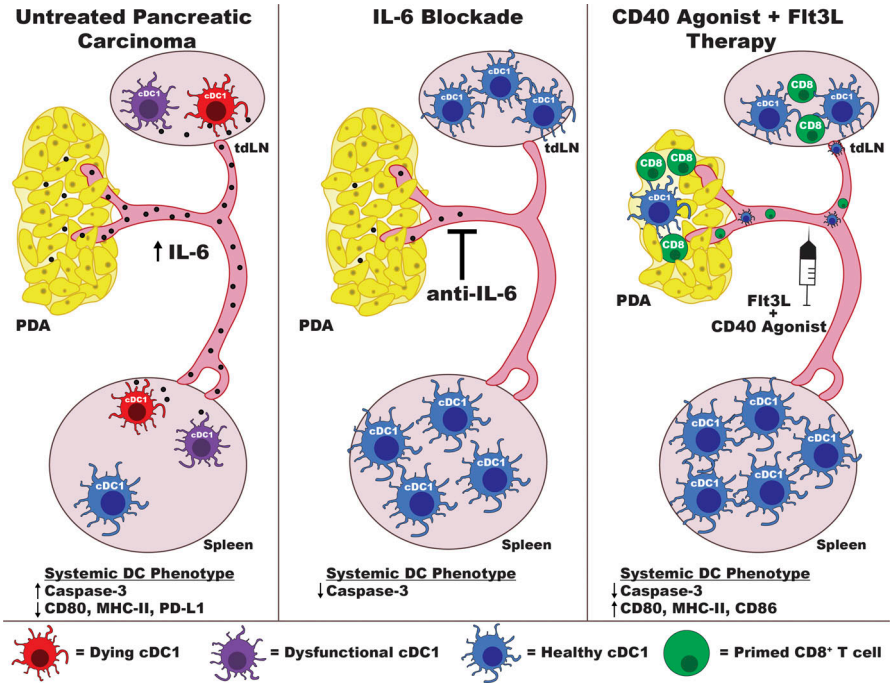

PDA has systemic effects on DC function as described by Lin et al. (2020). Production of IL-6 by PDA causes a decrease in DC survival as well as function (left). Blockade of IL-6 via intraperitoneal injection of an IL-6–depleting antibody causes a global restoration of DC survival (middle). Treatment using Flt3L and anti-CD40 agonist results in improved systemic DC survival and function as measured by CD80, CD86, and MHC-II. It also results in infiltration of PDA tumors by DCs, as well as CD8 T cells and an overall reduction in tumor burden (right).

commensal microbiota have all been demonstrated to regulate the degree of spontaneous immune priming and T cell infiltration into tumors (Lanitis et al., 2017). Of note, despite the multiplicity of mechanisms for primary resistance, a frequent observation is that non-T cell–inflamed tumors lack evidence of cDC1 cell infiltration, suggesting that absence of this key DC subset may represent a key rate-limiting step for immunotherapy efficacy (Spranger et al., 2016). In principle, failed involvement of cDC1 cells in antitumor immunity could be due to local defects within the tumor microenvironment or systemic dysregulation throughout the host. Inadequate involvement of cDC1 cells during the afferent phase of the antitumor immune response would lead to poor priming of tumor antigen–specific CD8⁺ T cells, whereas inadequate involvement late at the effector phase would lead to poor recruitment of effector T cells back into the target tissue site. Tumors in such scenarios would lack the requisite primed T cells in the tumor microenvironment for PD-1 blockade to functionally restore. Prior evidence in a genetically engineered mouse melanoma model indicated that tumor cell–intrinsic β-catenin activation was an immune-evasion oncogenic event, which mechanistically resulted in failed recruitment of cDC1 cells into the tumor site. This led to both defective T cell priming and defective trafficking of effector CD8⁺ T cells into the tumor microenvironment (Spranger et al., 2015). However, such mice could still be vaccinated against tumor antigens, and intratumoral injection of activated cDC1 cells could restore immune-mediated tumor control. These data argued for a tumor microenvironment orientation to the inadequate involvement of cDC1 cells and suggested that strategies to ensure their recruitment and activation within tumor sites could offer therapeutic utility.

Some cancer types show poor spontaneous T cell infiltration in the majority of cases, making them typically nonresponsive to anti–PD-1 and other immunotherapies. One such tumor is PDA, which only rarely responds to anti–PD-1. The commonly used genetically engineered mouse model of PDA, driven by oncogenic K-Ras and deletion of the tumor suppressor gene p53 (so-called KPC mice), recapitulates this clinical phenotype, being rich in macrophages but lacking CD8⁺ T cells. Interestingly, in the current study from Lin et al. (2020), the systemic cDC1 defect observed in the KPC model was not seen in a separate model of K-Ras/p53$^{-/-}$-driven lung cancer, indicating something relatively unique to the pancreatic cancer context. A diminished percentage of circulating cDC1 cells was also observed in patients with pancreatic cancer, and transcripts associated with cDC1 cells from PDA clinical tumor samples correlated strongly with CD8⁺ T cells markers, implying the two are linked. Mechanistically, the diminished percentage of cDC1 cells in the KPC model seemed to be a result of apoptosis, and blockade of IL-6, which is known to be elevated in PDA and has been shown to interfere with DC priming in previous studies (Brighenti et al., 2014), was able to rescue a large fraction of cDC1 from cellular death. Administration of the growth factor Flt3L also rescued from apoptosis and improved cDC1 numbers. To restore the DC maturation defect, agonistic anti-CD40 was used, and when combined with Flt3L, caused markedly improved tumor control. A schematic of these interventions is illustrated in the figure. Together, these results support the notion that restoring the number and function of cDC1 cells has potential therapeutic implications in the context of PDA.

The tools are already in hand to intervene clinically in an attempt to improve the numbers and functionality of cDC1 cells in cancer patients. Clinical grade Flt3L, anti-CD40 mAb, and anti–IL-6/IL-6R mAbs are available to explore in patients. Because anti-CD40 mAbs have not shown the same degree of activity in human cancer patients as in mouse models (Nowak et al., 2015), other strategies for DC activation/maturation should be considered, including TLR ligands and STING agonists. Systemic administration of such agents could be pursued, but in many instances, the tumor microenvironment fails to support optimal cDC1 recruitment into the tumor sites, likely because of defective local expression of the relevant chemokines. Therefore, intratumoral administration of these agents also should be considered. While not yet explored in PDA, studies of intratumoral Flt3L, the TLR3 agonist poly I:C, and local radiation

have shown remarkable evidence for T cell activation and tumor control in patients with non-Hodgkin's lymphoma (Hammerich et al., 2019). Clinical execution of these investigational protocols should involve intensive biomarker analysis to ascertain the detailed immunological effects of each component of the therapeutic approach. One might anticipate that a tremendous augmentation of $CD8^+$ T cell activation induced by such an approach would result in the up-regulation of negative regulatory immune checkpoints, such as the PD-1/PD-L1 interaction. Thus, once strategies to increase the number and function of cDC1 cells in the tumor microenvironment in patients are established, combination treatment with anti–PD-1 may be warranted. Through such interventions, it should be feasible to convert a non-T cell–inflamed tumor into one that is T cell inflamed, and expand the circle of efficacy of checkpoint blockade immunotherapy to a larger fraction of patients.

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