β-catenin-mediated inhibition of cross-priming
A new mechanism for tumors to evade immunosurveillance

Chunmei Fu and Aimin Jiang*
Department of Immunology; Roswell Park Cancer Institute; Buffalo, NY USA

Keywords: antitumor CD8+ immunity, cross-priming, DC-based vaccine, immunosuppression

Abbreviations: DC, dendritic cell; TAA, tumor-associated antigen; TADC, tumor-associated dendritic cell; OVA, ovalbumin

Cross-priming plays a major role in generating CD8+ T-cell-dependent antitumor immunity through cross-presentation. However, the cross-presentation of tumor-associated antigens by dendritic cells often promotes tolerance rather than CD8+ T-cell immunity. We have now identified a β-catenin-dependent pathway of cross-priming inhibition as a novel and potentially broad mechanism whereby neoplastic cells promote immunosuppression.

As the initiators of antigen-specific immune responses, dendritic cells (DCs) play a central role in regulating the balance between CD8+ T-cell immunity and tolerance to tumor-associated antigens (TAAs). The tumor microenvironment often recruits immunosuppressive cells and releases soluble factors that attenuate the activity of DCs, such as vascular endothelial growth factor (VEGF), indoleamine 2,3-dioxygenase 1 (IDO1), arginase, transforming growth factor β1 (TGFβ1), and prostaglandins, hence limiting the therapeutic potential of DC-based anticancer vaccines.1–3 With the exception of sipuleucel-T (Provenge®), current DC-based vaccines remain unsuccessful, and one major obstacle in this sense is the immunosuppressive activity of host DCs. Cross-priming, the process whereby DCs activate CD8+ T cells by cross-presenting TAAs on MHC class I molecules, plays a major role in generating antitumor CD8+ T-cell immunity.4,5 However, the DC compartment of tumor-bearing hosts is often defective or tolerogenic, being unable to induce productive CD8+ T-cell responses upon TAA cross-presentation.4 While some chemotherapeutic regimens are well known to promote the cross-presentation of TAAs,2,4 whether and how neoplastic cells directly interfere with cross-priming to suppress antitumor CD8+ T-cell immunity has not been elucidated until recently.

We and others have previously shown that β-catenin regulates DC-mediated CD4+ T-cell responses and promotes T-cell tolerance in murine models of autoimmune diseases,6,7 suggesting that β-catenin serves as a tolerizing signal that shifts the balance between CD4+ T-cell immunity and tolerance. Although these studies primarily examined the function of CD4+ T cells, tumors likely employ similar mechanisms to influence DC-mediated CD8+ T-cell immunity vs. tolerance. We thus wondered whether β-catenin signaling in DCs also suppresses antitumor CD8+ T-cell immunity, and—if so—how neoplastic cells might harness β-catenin to suppress antitumor CD8+ T-cell responses. We found elevated expression levels of β-catenin in DCs from mice bearing B16 melanomas.8 The tumor-mediated upregulation of β-catenin in DCs appears to be systemic, as opposed to local, since elevated β-catenin levels were observed not only in DCs isolated from tumor-draining lymph nodes, but also in splenic DCs and DCs obtained from mesenteric lymph nodes. Exposing DCs to tumor-conditioned culture media in vitro also led to upregulation of β-catenin, suggesting that this effect is due (at least in part) to the release of one or more soluble factors by malignant cells. A genetic manipulation that resulted in the constitutive activation of β-catenin in DCs (DC-β-catenininactive mice) significantly accelerated tumor growth in multiple models of neoplasia, suggesting that the activation of β-catenin in DCs negatively regulates antitumor immunity.

Both tumor-bearing and DC-β-catenininactive mice, when vaccinated with a DC-targeting monoclonal antibody (specific for lymphocyte antigen 75, LY75, best known as DEC-205) fused with model antigen ovalbumin (OVA), exhibited impaired primary and recall OVA-specific CD8+ T-cell responses, suggesting that activation of β-catenin in DCs (be it genetic or induced by tumors) negatively regulates CD8+ T-cell immunity. Both tumor-bearing and DC-β-catenininactive mice were deficient in cross-priming but not cross-presentation, as measured by antigen presentation assays in vivo. In addition, antigen-specific CD8+ T cells primed in DC-β-catenininactive and tumor-bearing mice mediated suboptimal CD8+...
memory responses when transferred into naïve wild-type mice, suggesting that deficiencies in the cross-priming phase contribute to dampened CD8+ T-cell immunity. Further studies revealed that such a deficiency in cross-priming is DC-intrinsic, as DCs isolated from immunized DC-bearing mice also exhibited impaired cross-priming when cultured with OVA-bearing mice, CD8+ immunity was restored in these mice, suggesting that the β-catenin-dependent inhibition of cross-priming can be reversed to restore impaired CD8+ T-cell immunity. As β-catenin might similarly impair the ability of DCs to activate CD8+ memory T cells during the recall phase, we reasoned that enhancing cross-priming during the recall phase might restore CD8+ memory responses. Indeed, in both DC-β-catenin-active and tumor-bearing mice, CD8+ immunity was substantially boosted upon recall with antigens that favor cross-priming. These findings indicate that strong antitumor CD8+ immunity can be achieved upon recall with agents that promote cross-priming even when the initial DC-based vaccines fail, offering a new approach to improve DC-based anticancer vaccines that elicit weak antitumor responses. Further studies are warranted to examine whether these approaches are applicable to various DC-based vaccines.

Understanding how β-catenin regulates the ability of DCs to cross-prime antigen specific CD8+ T cells requires further studies, although the maturation state of DCs and their cytokine production profile are likely involved.6,7 Interestingly, TADCs have recently been shown to express elevated levels of both β-catenin and forkhead box O3 (FOXO3). FOXO3 appears to render TADCs tolerogenic and to induce an immunosuppressive activity in tumor-specific CD8+ T cells, presumably as it influences the maturation state of DCs and their cytokine production pattern.8 An evolutionarily conserved interaction between β-catenin and FOXO3 has been shown to regulate the transcriptional activity of both FOXO3 and β-catenin/T-cell factor (TCF),9 suggesting a scenario in which the crosstalk between FOXO3 and β-catenin in DCs ultimately determines DC function (Fig. 1).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
1. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011; 480:480-9; http://dx.doi.org/10.1038/nature10673; PMID:2191302
2. Aporah L, Locher C, Ghiringhelli F, Kroemer G, Zitvogel L. Harnessing dendritic cells in cancer. Semin Immunol 2011; 23:42-9; http://dx.doi.org/10.1016/j.smim.2011.01.003; PMID:21295491
3. Shurin GV, Ouellette CE, Shurin MR. Regulatory dendritic cells in the tumor immunenvironment. Cancer Immunol Immunother 2012; 61:223-30; http://dx.doi.org/10.1007/s00262-011-1138-8; PMID:22065047
4. Melief CJ. Cancer immunotherapy by dendritic cells. Immunity 2008; 29:372-85; PMID:18799145; http://dx.doi.org/10.1016/j.immuni.2008.08.004
5. Andersen BM, Olfest JR. Increasing the efficacy of tumor cell vaccines by enhancing cross-priming. Cancer Lett 2012; 325:155-64; http://dx.doi.org/10.1016/j.canlet.2012.07.012; PMID:22809568
6. Jiang A, Bloom O, Ono S, Cui W, Unterneauer J, Jiang S, Whitney JA, Connolly J, Banchereau J, Mellman I. Disruption of E-cadherin-mediated adhesion induces a functionally distinct pathway of dendritic cell maturation. Immunity 2007; 27:610-24; PMID:17936032; http://dx.doi.org/10.1016/j.immuni.2007.08.015
7. Marinacassamy S, Reizin B, Ravindran R, Nakaya H, Salazar-Gonzalez RM, Wang YC, Puleodran B. Activation of beta-catenin in dendritic cells regulates immunity versus tolerance in the intestine. Science 2010; 329:849-53; PMID:20705860; http://dx.doi.org/10.1126/science.1188510
8. Liang X, Fu C, Cui W, Ober-Blobaum JL, Zahner SP, Shitkant PA, Clausen BE, Flavell RA, Mellman I, Jiang A. Beta-Catenin mediates tumor-induced immunosuppression by inhibiting cross-priming of CD8+ T cells. J Leukoc Biol 2013; http://dx.doi.org/10.1189/jlb.0613330; PMID:24023259
9. Watkins SK, Zha Z, Riboldi E, Shiner-Weaver KA, Stagliano KE, Sklavos MM, Ambs S, Yagita H, Hurwitz AA. FOXP3 programs tumor-associated DCs to become tolerogenic in human and murine prostate cancer. J Clin Invest 2011; 121:1361-72; http://dx.doi.org/10.1172/JCI43525; PMID:21436588
10. Hoogeboom D, Burgering BM. Should I stay or should I go: beta-catenin decides under stress. Biochim Biophys Acta 2009; 1796:63-74; http://dx.doi.org/10.1016/j.bjcan.2009.02.002; PMID:19208509