ABSTRACT Weak and ineffective antitumor cytotoxic T lymphocyte (CTL) responses can be rescued by immunomodulatory mAbs targeting PD-1 or CD137. Using Batf3−/− mice, which are defective for cross-presentation of cell-associated antigens, we show that BATF3-dependent dendritic cells (DC) are essential for the response to therapy with anti-CD137 or anti-PD-1 mAbs. Batf3−/− mice failed to prime an endogenous CTL-mediated immune response toward tumor-associated antigens, including neoantigens. As a result, the immunomodulatory mAbs could not amplify any therapeutically functional immune response in these mice. Moreover, administration of systemic sFLT3L and local poly-ICLC enhanced DC-mediated cross-priming and synergized with anti–CD137- and anti–PD-1–mediated immunostimulation in tumor therapy against B16-ovalbumin–derived melanomas, whereas this function was lost in Batf3−/− mice. These experiments show that cross-priming of tumor antigens by FLT3L- and BATF3-dependent DCs is crucial to the efficacy of immunostimulatory mAbs and represents a very attractive point of intervention to enhance their clinical antitumor effects.

SIGNIFICANCE: Immunotherapy with immunostimulatory mAbs is currently achieving durable clinical responses in different types of cancer. We show that cross-priming of tumor antigens by BATF3-dependent DCs is a key limiting factor that can be exploited to enhance the antitumor efficacy of anti–PD-1 and anti–CD137 immunostimulatory mAbs. Cancer Discov; 6(1); 71–9. ©2015 AACR.

INTRODUCTION Tumor cells are antigenic as a result of abundant mutated sequences in their exomes (1). However, they are poorly immunogenic to prime cytotoxic T lymphocyte (CTL) responses because antigen presentation takes place in the absence of appropriate co-stimulation and in a strongly immunosuppressive environment (2). The immune response to cell-associated antigens requires the interplay of specialized and professional antigen-presenting cells called dendritic cells (DC). Among the variety of DC subsets, certain DCs excel at redirecting cell-associated phagocytosed proteins to the