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Cancer therapy by resuscitating Notch immune surveillance

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The immunosuppressive tumor microenvironment perturbs numerous immune regulatory networks and usurps host antitumor immunity. We discovered that tumor interferes with host hematopoietic Notch system in lung cancer patients [1]. The resultant decrease in immune Notch signaling could be a major causative link in the inadequate induction of antitumor immunity. Interestingly, administration of the novel Delta-like ligand 1 (DLL1) multivalent cluster [1] and the FDA-approved proteasome inhibitor drug bortezomib, which also sensitizes tumors to death signals [2,3], restored the tumor-induced decrease in immune Notch. Bortezomib increased the expression of Notch target genes *Hes1* and *Hey1* in thymus, lymph node, and spleen of tumor-bearing mice. Moreover, bortezomib administration decreased the proportion of regulatory T cells and enhanced antitumor T cell production of IFN- γ . Results indicate that bortezomib-induced activation of Notch target genes *Hes1* and *Hey1* is through its inhibition of NF- κ B while its activation of *Deltex1* is mediated via PI3K. The potential of modulating antitumor Notch signaling by the prototypic DLL1 cluster in combination with bortezomib presents exciting opportunities to uncover multi-pronged immune stimulatory regimens. Therapeutic restoration of immune Notch signaling by bortezomib could provide effective treatment and recurrence-free survival in cancer patients by breaking tumor resistance, enhancing immune surveillance, and sustaining robust anti-tumor immunity.

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