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Cancer therapy by resuscitating immune surveillance

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Abstract

The immunosuppressive tumor microenvironment perturbs immune regulatory networks and usurps host antitumor immunity. We discovered that tumor interferes with host hematopoietic Notch system. The resultant decrease in immune Notch signaling could be a major causative link in the inadequate induction of antitumor immunity. Interestingly, we found that tumor-induced decrease in immune Notch could be restored therapeutically by the following two agents. Administration of a novel Delta-like ligand 1 (DLL1) multivalent cluster, and FDA-approved proteasome inhibitor drug bortezomib – which also sensitizes tumors to death signals – could activate Notch 1 signaling in lymphoid cells of tumor-bearing mice without increasing tumor cell proliferation or clonogenicity. Systemic activation of DLL1-Notch signaling could attenuate tumor vascularization as well as increase T cell infiltration in tumor, decrease proportion of regulatory T cells and enhance antitumor T cell function and memory in multiple mouse tumor models. New data also show that bortezomib affects the expression of notch receptors and ligands differentially in lymphocytes and in a wide range of solid tumor cells. Moreover, bortezomib increased the expression of Notch target Hes1 in thymus, lymph node and spleen of tumor-bearing mice, suggesting a potential synergistic action of bortezomib and DLL1 activation of Notch signaling. The potential of modulating antitumor Notch signaling by a novel prototypic agent DLL1 in combination with bortezomib presents exciting opportunities to uncover multi-pronged immune stimulatory regimens. Therapeutic restoration of immune Notch signaling could provide effective treatment and recurrence–free survival in cancer patients by breaking tumor resistance and induction of robust antitumor immunity.

Biography

Anil Shanker is an Assistant Professor in the Department of Biochemistry and Cancer Biology at Meharry Medical College. He is also a member of Vanderbilt-Ingram Comprehensive Cancer Center at Vanderbilt University. Dr. Shanker obtained his PhD from Banaras Hindu University in 1999. He performed his postdoctoral studies in tumor immunology at the CNRS/INSERM Center of Immunology, France and the National Cancer Institute, Maryland. His laboratory focuses on understanding functional cross-talk between T lymphocytes and natural killer cells and their activation signaling mechanisms in tumor models. He has over 30 research publications to his credit in cancer and immunology journals.