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Cancer immunotherapy using tumor cryoablation

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Cryoablation is gaining acceptance as a primary treatment of localized as well as salvage therapy of metastatic urologic malignancies. Anecdotal clinical reports suggest cryoablation can induce a systemic anti-tumor immune response; this phenomenon has been confirmed in animal models.To capitalize on the stimulatory effect of cryotherapy, this response must be intensified using other immunomodulatory agents to counteract the inhibitory influence of metastatic cancer on anti-tumor immunity.This intensification can be done by multiple ways. Facilitating the antigen uptake by use of monoclonal antibodies is one such method. Using antibodies specific for prostate antigens, the cryoimmune response can be augmented against the metastatic cancer.

Dendritic cell (DC) activation is another method for augmenting the immune response. Cytokines like granulocyte-macrophage colony stimulating factor promotes dendritic cell activation and migrationand provides the rationale for GM-CSF-transduced tumor cell vaccines. Another method of dendritic cell activation is intratumoral injection of unmethylatedcystosine-guanosineoligodeoxynucleotides (CpG ODNs). CpG ODNs interact with Toll-like receptor 9 (TLR9) on DC and activate innate immunity against tumors. *In situ* destruction of tumor by cryoablation combined with DC activation by CpG constitutes an "in situ DC vaccine" which can augment anti-tumor immunity for control of metastasis.

Regulatory T cells (T_{regs}) are potent suppressors of anti-tumor immunity. Cyclophosphamide has been shown to mitigate suppression of anti-tumor immunity through effects on T_{regs}. Treatment with cyclophosphamide enhances the apoptosis and decreases homeostatic proliferation of these cells. Our experiments have shown that cyclophosphamide effectively unmasks a systemic anti-tumor effect of cryoablation, resulting in prolongation of survival and even cure of half of the mice with metastatic colon cancer. Another inhibitory influence on anti-tumor immune response is presence of immune checkpoints like CTLA-4, which limit the potential for unchecked T cell activation and autoimmunity.Blockade of any of the inhibitory checkpoints could potentially enhance any pre-existent anti-tumor immunity.

We, hereby, describe the rationale and evidence behind several immunotherapy approaches that can be combined with cryoablation to devise a cryoimmunotherapeutic strategy with potential to impact the progression of metastatic disease.

Biography

Abhinav Sidana has completed his MBBS at the age of 24 years from All India Institute of Medical Sciences, New Delhi, India. He then did Post-Doctoral Fellowship at Johns Hopkins University School of Medicine, Baltimore where he worked on projects involving combination of cryotherapy with several immunomodulators. He is currently a Urology Resident at the University of Cincinnati and plans to pursue an academic career in Urologic Oncology. He has published more than 15 papers in reputed journals, presented his work at national and international forums and served as a reviewer for various journals.

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