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Contribution of muscle cells and BM-derived APCs to CD8 T cells priming upon SAM® vaccination

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SAM® vaccines are self-amplifying mRNA derived from the positive-strand alphavirus genome. They contain genes encoding non structural proteins which drive the RNA replication, but lack the viral structural proteins which are replaced by vaccine antigens.In this way; RNA amplification within the cytoplasm of transfected cells allows an increase of antigen expression. In addition, dsRNA intermediates exert an intrinsic adjuvant effect resulting in the induction of enhanced immune responses. It has been shown that SAM® vaccines are effective at eliciting both humoral and cellular antigen-specific immune responses in animal models of infectious and non-infectious diseases. However their mechanism of action has not been fully elucidated. To date, no evidence of in vivo transduction of APCs by the SAM® vectors has been produced, while the antigen expression has been shown to occur mostly in the muscle fibers. Bone marrow chimeric mice were used to assess the respective contribution of muscle cells and bone marrow derived antigen presenting cells (APCs) to CD8 T cells priming following SAM®vaccination. Our results show that bone marrow derived APCs rather than muscle cells are responsible for direct induction of Class-I restricted CD8 T cells. Nevertheless, direct transfection of APCs by SAM® vectors is it not required for CD8 T cells priming, suggesting that the antigen is expressed within muscle cells and then presentedby professional bone marrow derived APC to CD8 T cells, most likely through a cross-priming.

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Immune checkpoint inhibitor therapy for lymphomas

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Non-Hodgkin lymphomas of B-cell origin are highly immune-responsive. However, immune checkpoints in the tumor microenvironment may impair optimal antitumor immune responses. Analysis of tumor-infiltrating lymphocytes from lymphoma patients shows expression of many coinhibitory molecules, with programmed death (PD)-1 being the most highly expressed. PD-1 expression is associated with impaired T-cell function and blocking PD-1 enhances their tumor-reactivity. In a phase II clinical trial, administration of pidilizumab, an anti-PD-1 monoclonal antibody and rituximab, an anti-CD20 monoclonal antibody in patients with relapsed follicular lymphoma induced an overall response rate of 66% and a complete response rate of 52%, both of which are markedly superior to results previously reported with rituximab monotherapy. Analysis of peripheral blood and tumor samples before and after therapy with pidilizumab showed activation of both T and NK cells. In addition, predictors of clinical outcome based on the molecular features of tumor-infiltrating immune cells at baseline were identified. These results suggest that anti-PD-1 monoclonal antibody therapy is effective in follicular lymphomas and suggest that immune checkpoint inhibitor therapy is worthy of further exploration.

Biography

Sattva S Neelapu is currently a tenured Associate Professor in the Department of Lymphoma and Myeloma at The University of Texas MD Anderson Cancer Center, Houston, Texas, USA. He completed his medical school at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India and Clinical Fellowship in Medical Oncology and Postdoctoral Fellowship in Tumor Immunology and Immunotherapy at the National Cancer Institute, National Institutes of Health, Bethesda, Maryland. His research is focused on characterization of immunoregulatory mechanisms in the tumor microenvironment in patients with lymphoma and developing strategies to target them.

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