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Development of cancer vaccines targeting brachyury, a driver of the epithelial-mesenchymal transition of human carcinomas

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The phenomenon of epithelial-mesenchymal transition (EMT) has gained attention in the field of cancer biology for its potential contribution to the progression of carcinomas. Tumor EMT is a phenotypic switch that promotes the acquisition of a fibroblastoid-like morphology by epithelial tumor cells, resulting in enhanced tumor cell motility and invasiveness, increased metastatic propensity, and resistance to chemotherapy, radiation, and some certain small molecule-targeted therapies. Recently, our group identified Brachyury, a T-box transcription factor involved in the formation of mesoderm during embryonic development, as a novel driver of EMT in human carcinomas. Experiments with lung cancer xenografts have demonstrated that Brachyury is required for the dissemination of tumor cells, as Brachyury-silenced H460 cells showed a diminished ability to form spontaneous lung metastasis in nude mice. The potential role of Brachyury in human cancer progression was also suggested by the observation that Brachyury mRNA expression is predominant among high stage lung tumor tissues, with lower expression among lung tumors of stage I. We propose the use of cancer vaccine approaches that target the transcription factor Brachyury as a strategy to directly eradicate tumor cells undergoing EMT and thus to interfere with metastasis. Brachyury fulfills two major requirements for a molecule to be used as a target for vaccine approaches: (1) Brachyury is highly tumor specific, being expressed in various human carcinomas but absent in most human normal adult tissues, and (2) Brachyury-specific cytotoxic T lymphocytes can be expanded from the blood of cancer patients against an epitope of the Brachyury protein. Moreover, Brachyury-specific T cells can lyse tumor cells that express the Brachyury protein, indicating that a vaccine approach is a viable option for the generation of a long-lasting immune response against this EMT regulator. Based on these observations, a Brachyury-based cancer vaccine is currently undergoing Phase I clinical evaluation in patients with carcinomas.

Biography

Dr. Palena is an Investigator and the Head of the Immunoregulation Group in the Laboratory of Tumor Immunology and Biology, National Cancer Institute, NIH, Bethesda. Dr. Palena received her Ph.D. in Biochemistry from the National University of Rosario, Argentina, and completed a Postdoctoral Fellowship in the Laboratory of Tumor Immunology and Biology, NCI. Dr. Palena has made significant contributions to the field of cancer immunotherapy, including the identification and characterization of novel tumor-associated antigens, and the use of costimulation for optimal activation of human T-cell responses to tumor antigens. Her current research is focused on the development of novel immunotherapeutic approaches aimed at targeting critical events in tumor progression with the ultimate goal of designing vaccine(s) platform(s) and combinatorial therapies for the prevention and/or treatment of metastases in human cancer

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