Harnessing benefit from targeting tumour associated carbohydrate antigens

Thomas Kieber-Emmons
University of Arkansas for Medical Sciences, USA

Abstract

Integrating additive or synergistic antitumor effects that focus on distinct elements of tumor biology are the most rational of strategies for cancer treatment. The real challenge is to define what elements of tumor biology make the most sense to be targeted? Signal transduction (pathways) can define therapeutic strategies and approaches that might be tailored to harness benefit from sustained immunity much like that observed from natural antibodies involved in immune surveillance mechanisms. Tumor associated carbohydrate antigens (TACAs) are pan-targets on tumor cells because they play roles in initiation and metastases of cancer, and considered as common targets shared by many tumor types, and regulating a network of signaling pathways associated with cell survival. Strategies that target TACAs therefore have potential benefit as cell death therapies. We have been developing an active immunization strategy targeting TACAs using carbohydrate mimetic peptides (CMP) designed as panimmunogens. One CMP called P10s was computer designed to induce anti-GD2 and anti-LeY antibodies with the intent of inducing multiple sets of antibodies reactive with multiple TACAs when immunizing with a single agent. We have completed a Phase I clinical trial in breast cancer with a CMP, showing that this designed CMP can induce proapoptotic antibodies in humans that can sensitize tumor cells to chemotherapeutics. We have progressed to a Phase II trial in the neoadjuvant setting where we observe tumor shrinkage in combination therapy. Tumor-associated carbohydrate antigens (TACAs) support cell survival that could be interrupted by anti-TACA antibodies. Among TACAs that mediate cell survival signals are the neolactoseries antigen Lewis Y (LeY) and the ganglioside GD2. To induce sustained immunity against both LeY and GD2, we developed a carbohydrate mimicking peptide (CMP) as a surrogate pan-immunogen that mimics both. This CMP, referred to as P10s, is the N-terminal half of a peptide vaccine named P10s-PADRE, the C-terminal half of which (PADRE) is a Pan-T-cell epitope. A Phase I dose-escalation trial of P10s-PADRE plus adjuvant MONTANIDE™ ISA 51 VG was conducted in subjects with metastatic breast cancer to test 300 and 500 µg/injection in two cohorts of 3 subjects each. Doses of the P10s-PADRE vaccine were administered to research participants subcutaneously on weeks 1, 2, 3, 7 and 19. Antibody responses to P10s, GD2, and LeY were measured by ELISA. The P10s-PADRE vaccine induced antibodies specifically reactive with P10s, LeY and GD2 in all 6 subjects. Serum antibodies displayed Caspase-3-dependent apoptotic functionality against LeY or GD2 expressing breast cancer cell lines. Immunization with the P10s-PADRE vaccine was well-tolerated and induced functional antibodies, and the data suggest potential clinical benefit. For many years, immunotherapeutic approaches for cancer held more promise than actual clinical benefit for the majority of patients. However, several recent key advances in tumor immunology have now turned the tide in favor of immunotherapy for the treatment of many different cancer types. In this review, we describe four of the most effective immunotherapeutic approaches currently used in the clinic: cancer vaccines, immunostimulatory agents, adoptive T cell therapy, and immune checkpoint blockade. In addition, we discuss some of the most promising future strategies that aim to utilize multiple immunotherapies or combine them with other approaches to more effectively target cancer. Vaccines represent a strategic successful tool used to prevent or contain diseases with high morbidity and/or mortality. However, while vaccines have proven to be effective in combating pathogenic microorganisms, based on the immune recognition of these foreign antigens, vaccines aimed at inducing effective antitumor activity are still unsatisfactory. Nevertheless, the effectiveness of the two licensed cancer-preventive vaccines targeting tumor-associated viral agents (anti-HBV [hepatitis B virus], to prevent HBV-associated hepatocellular carcinoma, and anti-HPV [human papillomavirus], to prevent HPV-associated cervical carcinoma), along with the recent FDA approval of sipuleucel-T (for the therapeutic treatment of prostate cancer), represents a significant advancement in the field of cancer vaccines and a boost for new studies in the field. Specific active immunotherapies based on anticancer vaccines represent, indeed, a field in continuous evolution and expansion. Significant improvements may result from the selection of the appropriate tumor-specific target antigen (to overcome the peripheral immune tolerance) and/or the development of immunization strategies effective at inducing a protective immune response. This review aims to describe the vast spectrum of tumor antigens and strategies to develop cancer vaccines. We have previously studied the generation of immune responses after vaccination with tumor-associated carbohydrate

antigen (TACA)-containing glycopeptides from the tandem repeat (TR) sequence of MUC4, an aberrantly expressed mucin in pancreatic adenocarcinomas. A specific lead antigen from that study containing the Thomsen-Friedenreich TACA disaccharide facilitated the pursuit of a monoclonal antibody to this synthetic hapten. Initial evaluation of polyclonal antiserum resulting from immunization with a KLH conjugate of this glycopeptide into rabbits showed high titer antibodies by ELISA assays, and selective immunoreactivity with MUC4+ cells by western blot and flow cytometry techniques. Glycan microarray analysis showed an intriguing binding pattern where the antiserum showed near complete specificity for MUC4 TR glycopeptides and peptides, relative to all components on the array. Tissue staining also showed distinct tumor specificity to pancreatic tumor tissue in relation to normal pancreatic tissue, with a preference for more aggressive tumor foci. Based on this data, we produced a monoclonal antibody whose binding and reactivity profile was similar to that of the polyclonal serum, with the added benefit of being more specific for the N-terminal glycosylated peptide domain. This epitope represents a novel immunogen to potentially develop diagnostic antibodies or immunotherapies against various MUC4-positive cancers.

Note: This work was partly presented at International Conference on Glycobiology September 21-22, 2017 HOUSTON, TX, USA