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Harnessing benefit from targeting tumor associated carbohydrate antigens

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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 macrophage (TAM) phagocytic activity is emerging as a new mechanism to harness for cancer treatment. Currently, many approaches are investigated at the preclinical level and some modalities have now reached clinical trials, including the targeting of the phagocytosis inhibitor CD47. The rationale for increasing TAM phagocytic activity is to improve innate anticancer immunity, and to promote T-cell mediated adaptive immune responses. In this context, a clear understanding of the impact of TAM phagocytosis on both innate and adaptive immunity is critical. Indeed, uncertainties persist regarding the capacity of TAM to present tumor antigens to CD8 T cells by cross-presentation. This process is critical for an optimal cytotoxic T-cell immune response and can be mediated by dendritic cells but also potentially by macrophages. In addition, the engulfment of cancer cells affects TAM functionality, as apoptotic cell uptake (a process termed efferocytosis) promotes macrophage anti-inflammatory functions. Because of the abundance of TAM in most solid tumors and the common use of apoptosis inducers such as radiotherapy to treat patients with cancer, efferocytosis potentially affects the overall immune balance within the tumor microenvironment (TME)

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