Using a molecular switch to turn on cancer vaccines

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The immune system is capable of recognizing tumor growth, and naturally mounts an anti-cancer defense. Dendritic cells (DCs) can take up tumor-derived molecules (antigens) and present them to T cells, and those "primed" T cells are then able to recognize and kill tumor cells.

In recent years, researchers have attempted to capitalize upon these natural immune responses to develop new therapies- namely, by generating a pool of tumor antigen-pulsed DCs that might be used as vaccines to augment the T-cell responses of cancer patients. In clinical trials, these DC vaccines have had limited success, in part because the protocols to generate mature and active DCs in vitro are imperfect. Specifically, generation of mature DCs requires activation of Toll-Like receptors (TLRs), usually achieved by administration of lipopolysaccharide, which can cause toxic shock in humans and can promote apoptosis.

In this paper, David Spencer and colleagues, of Baylor University in Houston, Texas, addressed this problem by looking to the adaptor molecule downstream of the TLR, MyD88. They engineered a form of MyD88 that could induce downstream signaling in response to a drug, and expressed this inducible MyD88 (iMyD88) in DCs. Further, the researchers combined iMyD88 with a second pathway required for optimal activation of DCs- CD40 signaling- so that they could control both pathways with administration of a single drug. This combination improved DC-mediated tumor antigen-specific T cell responses in mouse cancer models and T cell responses to human tumor antigens. The

researchers hope that this "switch" might be broadly applicable to the design of DC vaccines.

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