

Apoptosis

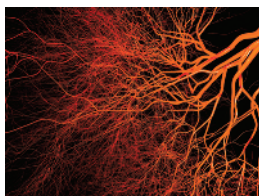
Major finding: Activation of DR5 on endothelial cells disrupts tumor vasculature and reduces tumor growth.

Mechanism: Oligomeric TRAIL selectively induced apoptosis in tumor endothelial cells expressing DR5.

Impact: Death receptor agonists may disrupt vasculature in tumors with endothelial DR5 expression.

PROAPOPTOTIC DEATH RECEPTOR AGONISTS ACT AS VASCULAR DISRUPTING AGENTS

Agonistic antibodies and recombinant ligands targeting cancer cells that express proapoptotic death receptors 4 and 5 (DR4/5) have been evaluated in clinical trials but have had limited success. Preclinical studies with these agents, which frequently do not activate murine death receptors, have mainly been performed on cultured cells or human tumor xenografts and thus have not evaluated the effects of death receptor activation on the tumor microenvironment. Wilson and colleagues therefore evaluated the effects of an oligomeric form of TRAIL (also called Apo2L), capable of engaging murine DR5, on murine tumors. Within 24 hours of treatment, severe disruption of the tumor vasculature occurred, leading to extensive tumor hemorrhage and widespread tumor cell death. Surprisingly, these effects were dependent on DR5 expression in endothelial cells in the stroma of tumor-bearing mice, as oligomeric TRAIL had no effect in DR5-deficient mice. Oligomeric TRAIL rapidly and selectively induced apoptosis in tumor-associated endothelial cells, regardless of DR5



expression in the tumor cells. Endothelial DR5 activation led to decreases in tumor vascular density and increased vascular permeability, causing hemorrhagic tumor necrosis and reducing tumor growth. To determine whether these findings might be relevant in human cancers, the authors analyzed DR5 expression in a panel of 43 primary human non-small cell lung cancers

and found that approximately 10% of the samples had regions of DR5 expression in the tumor endothelium. Because the authors did not observe DR5 expression in normal endothelium or in most other human tissues, these findings suggest that proapoptotic death receptor agonists may potentially be safely and effectively repurposed as vascular disrupting agents for anticancer therapy. ■

Wilson NS, Yang A, Yang B, Couto S, Stern H, Gogineni A, et al. Proapoptotic activation of death receptor 5 on tumor endothelial cells disrupts the vasculature and reduces tumor growth. *Cancer Cell* 2012;22:80–90.

Vaccines

Major finding: Vaccine-induced T-cell responses to multiple tumor peptides improve clinical outcome.

Concept: Reduction of T_{reg} cells in combination with vaccine IMA901 prolonged overall survival in RCC.

Impact: Monitoring of immune responses and serum biomarkers may improve cancer vaccine trials.

VACCINE-SPECIFIC IMMUNE RESPONSES CORRELATE WITH CLINICAL BENEFIT

The efficacy of cancer vaccines depends on the identification of tumor antigens that elicit a successful immune response. Walter and colleagues used an antigen discovery platform to generate the IMA901 vaccine, which is composed of multiple tumor-associated peptides (TUMAP) that were validated as naturally presented, overexpressed cancer antigens. This vaccine was then tested in clinical trials for the treatment of advanced renal cell cancer (RCC). In a phase I trial of 28 patients, the IMA901 vaccine was well tolerated and induced T-cell responses in 20 patients, as measured by *in vitro* detection of TUMAP antigen-specific T cells. Retrospective analysis showed that response to multiple TUMAPs led to an increase in disease control and that lower prevaccine numbers of regulatory T (T_{reg}) cells, which suppress T-cell-mediated immunotherapy, were correlated with this multi-peptide immune response. The role of T_{reg} cells was further evaluated in a subsequent phase II study, in which 68 patients with metastatic RCC were given IMA901 or IMA901 in combination with a single-dose pretreatment of cyclophosphamide, which inhibits T_{reg} cells. As in the

phase I trial, there was a high immune response rate, and the response to multiple TUMAPs extended patient survival time. Moreover, treatment with cyclophosphamide was associated with a prolonged median overall survival, particularly among immune responders, in which cyclophosphamide treatment led to a reduction in proliferating T_{reg} cells, suggesting that cyclophosphamide enhances the antitumor benefit of vaccine-induced immune responses. In addition, pretreatment analysis of cellular and serum biomarkers identified 2 subgroups of myeloid-derived suppressor cells and the proteins APOA1 and CCL17 as predictors of immune responses and increased overall survival in RCC. These results suggest that rational antigen discovery and validation, combined with monitoring of T-cell responses and biomarkers, may enable the development of effective cancer vaccines. ■

Walter S, Weinschenk T, Stenzl A, Zdrojowy R, Pluzanska A, Szczylik C, et al. Multi-peptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. *Nat Med* 2012;18:1254–61.