

## Rational Combination Immunotherapy: Understand the Biology

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Selecting rational treatment combinations remains a major challenge for improving immunotherapy outcomes. In this issue of *Cancer Immunology Research*, Zhang and colleagues reduced tumors by inhibiting CD47 in a lung carcinoma model, a treatment that inadvertently induced autophagy through inhibition of the Akt/mTOR pathway. By also targeting autophagy, the therapeutic response improved, highlighting the importance of understanding the biology beneath antitumor immunity. *Cancer Immunol Res*; 5(5); 355-6. ©2017 AACR.

See article by Zhang et al., p. 363.

The treatment of cancer has advanced significantly over the past decade with the advent of sophisticated immunotherapies, particularly those using mAbs to target the T-cell checkpoint pathways of CTLA-4/B7 and PD-1/PD-L1. Clinical benefit with durable responses was initially reported for select patients with melanoma and now has been extended to patients with other solid and hematologic cancers, establishing immunotherapy as an important therapeutic option to manage neoplastic disease. Combining two T-cell checkpoint inhibitors to treat melanoma can result in enhanced therapeutic responses, albeit at the risk of added toxicity. Thus, the paradigm of developing combination immunotherapy strategies has received considerable attention, and one of the most important challenges in the field is to rapidly identify rational combination approaches for clinical investigation (1).

Beyond T cells, M2 tumor-associated macrophages and myeloid-derived suppressor cells play major roles in blocking effective antitumor immunity, making their elimination and the promotion of an M1 macrophage phenotype important goals. The signal-regulatory protein (SIRP) family is a group of five glycoprotein cell surface receptors with variable amino acid sequence homology (2). SIRP $\alpha$  is the best characterized member and comprises an intracellular tail with a typical immunoreceptor tyrosine-based inhibitory motif (ITIM) and three extracellular immunoglobulin superfamily domains that include an NH<sub>2</sub>-terminal-binding site for CD47 and two C1-type IgSF domains. SIRP $\alpha$  is predominantly expressed on myeloid cells, including monocytes, macrophages, granulocytes, and myeloid CD4<sup>+</sup> dendritic cells, and can be found at variable levels on neuronal cells within the central nervous system. CD47, on the other hand, appears to be variably expressed on almost all cells, including many tumor cells. The function of CD47 was first suggested by studies in which CD47-deficient erythrocytes were infused into immunocompetent hosts and were immediately cleared by accelerated phagocytosis in the spleen. This finding established CD47 as a "don't eat me" signal that protects normal host cells from eradication by phagocytosis (2). Many tumors increase expression of CD47, suggesting the hypothesis that CD47 may provide

protection from innate immunity and that CD47/SIRP $\alpha$  interactions could be therapeutically targeted. The underlying biology of how CD47/SIRP $\alpha$  interactions block effective tumor immunity and potential strategies for combination immunotherapy are not clearly defined.

In this issue of *Cancer Immunology Research*, Zhang and colleagues have developed a CD47-targeted fusion protein designated SIRP $\alpha$ D1-Fc, which contains the first extracellular domain of human SIRP $\alpha$  and the IgG1 Fc fragment (3). SIRP $\alpha$ D1-Fc mediated antitumor activity against non-small cell lung cancer (NSCLC) xenograft tumors in mice and was associated with increased phagocytosis and macrophage cytotoxicity against NSCLC cells. They unexpectedly found that treatment was also associated with the induction of autophagy in the NSCLC cells, which was mediated by inhibition of Akt/mTOR signaling and formation of reactive oxygen species. Importantly, when SIRP $\alpha$ D1-Fc treatment was combined with inhibition of autophagy using chloroquine, antitumor activity was increased synergistically. Combination therapy increased recruitment of macrophages to the tumor microenvironment and activated both apoptotic and necrotic pathways. This suggests the potential for combining CD47/SIRP $\alpha$  and autophagy inhibition as a clinical approach.

This report also provides new insight into a previously unrecognized mechanism of immunotherapy drug resistance, induction of autophagy via inhibition of the Akt/mTOR signaling pathway. Whether this phenomenon is unique to lung cancer cells or is a more generalizable resistance mechanism remains unclear. Autophagy is an important physiologic process that mediates cell survival in the presence of many cellular stressors (4). In cancer cells, autophagy mediates resistance to chemotherapy and radiotherapy, reversible with autophagy inhibitors. Although highly specific inhibitors of autophagy are not yet available, several compounds have been used in preclinical and early-phase clinical trials for this purpose. In the current report, autophagy provided a cytoprotective effect during SIRP $\alpha$ D1-Fc treatment that could be overcome by simultaneous treatment with autophagy inhibition and immunotherapy.

Zhang and colleagues nicely demonstrate how a better understanding of the underlying biology can provide critical insights for informing clinical trial design, an approach that hastens the translation of preclinical findings to successful patient treatments.

### Disclosure of Potential Conflicts of Interest

H.L. Kaufman has received speakers bureau honoraria from Merck and is a consultant/advisory board member for Amgen, Celldex Therapeutics, Compass Therapeutics, EMD Serono, Merck, Prometheus, Sanofi, and Turnstone Biologics.

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## References

1. Ott PA, Hodi FS, Kaufman HL, Wigginton JM, Wolchok JD. Combination immunotherapy: a road map. *J Immunother Cancer* 2017;5:16.
2. Matlung HL, Szilagyfi K, Barclay NA, van den Berg TK. The CD47-SIRP $\alpha$  signaling axis as an innate immune checkpoint in cancer. *Immunol Rev* 2017;276:145–64.
3. Zhang X, Fan J, Wang S, Li Y, Wang Y, Li S, et al. Targeting CD47 and autophagy elicited enhanced anti-tumor effects in non-small cell lung cancer. *Cancer Immunol Res* 2017;5:363–75.
4. Livesy KM, Tang D, Zeh HJ, Lotze MT. Autophagy inhibition in combination cancer treatment. *Curr Opin Investig Drugs* 2009;10:1269–79.