Immunotherapy

Major finding: SIRPα variants with high CD47 affinity enhance the antitumor activity of therapeutic antibodies.

Concept: Blockade of antiphagocytic CD47 signaling lowers the threshold for macrophage activation.

Impact: High-affinity SIRPα monomers may act as universal adjuvants for tumor-specific antibodies.

HIGH-AFFINITY SIRPα VARIANTS POTENTIATE ANTIBODY THERAPY EFFICACY

Cancer cells can evade detection by the immune system by co-opting normal self-tolerance mechanisms. For example, many cancers avoid macrophage detection by expressing high levels of CD47, which binds to a macrophage inhibitory receptor, signal-regulatory protein alpha (SIRPα), and prevents phagocytosis. Blockade of the interaction between CD47 and SIRPα is therefore being investigated as a way to increase phagocytosis of cancer cells by macrophages. Weiskopf and colleagues sought to use the SIRPα binding domain as a CD47 antagonist, but it had poor activity due to the weak affinity of the native CD47–SIRPα interaction. The authors therefore created mutant libraries of the SIRPα binding domain and used yeast surface display to identify SIRPα variants with increased affinity for CD47. These variants maintained a highly similar structure and CD47 binding mode as wild-type SIRPα but with an approximately 50,000-fold increase in CD47 affinity. The high-affinity SIRPα variants bound and blocked CD47 expressed on cancer cells but did not increase phagocytosis of cancer cells *in vitro* unless the prophagocytic stimulus of an antibody Fc chain was present. However, these molecules caused red blood cell destruction and anemia, prompting the authors to evaluate the ability of SIRPα variants to increase phagocytosis of cancer cells when combined with tumor-specific antibodies. In several tumor models, high-affinity SIRPα variant monomers synergized with all clinically available therapeutic antibodies tested, including rituximab, alemtuzumab, and trastuzumab, to induce significant tumor regression in association with increased macrophage infiltration. Moreover, the antitumor effects persisted even after treatment cessation and were not toxic. Lowering the threshold for macrophage activation by blocking CD47 signaling with high-affinity SIRPα variant may be a universally effective approach for potentiating the efficacy of tumor-specific antibodies. ■

Weiskopf K, Ring AM, Ho CC, Volkmer JP, Levin AM, Volkmer AK, et al. Engineered SIRPα variants as immunotherapeutic adjuvants to anticancer antibodies. Science 2013 May 30 [Epub ahead of print].

Metabolism

Major finding: Internalization and degradation of extracellular protein supplies cancer cells with amino acids.

Concept: Macropinocytosed proteins serve as a source of glutamine for *RAS*-mutant cancer cells.

Impact: A subset of cancers may be sensitive to inhibition of macropinocytosis.

MACROPINOCYTOSIS SUPPORTS CANCER CELL METABOLISM

Overexpression of some oncogenes has been observed to induce macropinocytosis, a type of endocytosis in which extracellular fluid and its contents are internalized by large vesicles, but the physiologic relevance of macropinocytosis and its role in cancer are unclear. Commisso and colleagues show that increased macropinocytosis is a hallmark of cancer cells endogenously expressing mutant RAS proteins both *in vitro* and *in vivo* and that high levels of macropinocytosis are dependent on oncogenic RAS signaling. Given that proteins account for the majority of soluble compounds in extracellular fluid, it is possible that internalization and subsequent degradation of extracellular proteins might serve as a source of amino acids in RAS-transformed cells. Indeed, serum albumin, the most abundant extracellular protein, was internalized and intracellularly degraded, which led to an increase in intracellular levels of glutamate and α-ketoglutarate, metabolites of the amino acid glutamine. Carbon tracing experiments indicated that extracellular protein–derived amino acids entered multiple metabolic pathways, suggesting that internalization and degradation of extracellular protein is necessary to meet the metabolic demands of *RAS*-mutant cells, particularly their increased dependence on glutamine. Consistent with this possibility, albumin supplementation rescued the inhibitory effects of glutamine deprivation on *RAS*-mutant cell growth, which could be reversed by pharmacologic inhibition of macropinocytosis with 5-(*N*-ethyl-*N*-isopropyl)amiloride (EIPA). Importantly, administration of EIPA slowed the growth of *RAS*-mutant xenografts *in vivo*, in some cases even inducing regression, providing further evidence that macropinocytic nutrient uptake is essential for the survival of RAS-driven tumors. Of note, an oncogenic SRC mutant was also found to induce macropinocytosis of albumin to augment intracellular glutamine levels, suggesting that this phenomenon is not only a consequence of mutant RAS activity. Induction of macropinocytosis by oncogenic signaling pathways may therefore create a potential therapeutic target in a subset of human cancers. ■

Commisso C, Davidson SM, Soydaner-Azeloglu RG, Parker SJ, Kamphorst JJ, Hackett S, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature 2013;497:633–7.