Targeting Akt in cell transfer immunotherapy for cancer

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Pharmacologic inhibitors of the serine/threonine kinase Akt, initially aimed at deranged oncogenic pathways in tumors, have recently been shown to act as immunomodulators that markedly enhance the antitumor properties of T cells. Repurposing Akt inhibitors to improve antitumor immunity may be viewed as a manifestation of a larger paradigmatic shift in which hallmark characteristics of cancer (e.g., immune evasion), rather than merely causal features (e.g., somatic mutations) can be exploited for therapeutic benefit.

Cancer Therapy: A Play in Three AKTs

The predominant focus of cancer research since the origin of the somatic mutation theory in the early 1900s has been to identify causes of cancer, currently perceived as driver mutations that result in excessive growth. The therapeutic durability of inhibiting putative driver mutations, however, has largely been disappointing. Here, we discuss how therapeutic approaches resulting from an expanding concept of cancer—that now includes a central role for the immune system—are showing promise for the treatment of patients with advanced cancer. In particular, pharmacologic inhibitors of Akt that were initially developed to target cancer cells may also show therapeutic potential by augmenting the antitumor efficacy of the immune system.

The Set Up: AKT in Carcinogenesis

The serine/threonine kinase Akt, also known as protein kinase B (PKB), was initially discovered within a transforming retrovirus called AKT8 isolated from mice (arbitrarily designated AKR mice) that were highly prone to developing spontaneous thymomas.1 Two human homologues—AKT1 and AKT2—were subsequently described, and in a survey of 225 human tumors one gastric adenocarcinoma was found to have 20-fold amplification of AKT1, thereby establishing the first association between Akt and human cancer.2

Confrontation: Direct Targeting of AKT in Cancer

The principle biological effects of Akt activation of its downstream substrates, particularly as they relate to tumorigenesis, include promotion of cell survival, proliferation, and growth. Although mutations in Akt genes are rarely found in human cancers, amplification of Akt has been observed in cancers of the pancreas, ovary, stomach, and breast, suggesting that Akt inhibitors might have therapeutic efficacy in these histologies.1

Although there are several clinically relevant Akt inhibitors, including MK-2206, RX-0201, and PBI-05204, perifosine has been most highly scrutinized in Phase I/II studies3. Despite a central role for Akt in the biologic function of nearly all cell types, dose-limiting toxicities of systemically administered perifosine are surprisingly manageable and include vomiting, diarrhea, gout, arthralgias, and gastrointestinal bleeding. Therapeutic efficacy, however, has been poor; for example, in treatment of 10 patients with advanced pancreatic adenocarcinoma there were no responses and 3 deaths during therapy. No objective response was observed with perifosine in 14 patients with metastatic melanoma or in 19 patients with advanced head and neck cancers.3

Increasing appreciation of the heterogeneity of the mutational landscape in cancer makes targeting of a single deranged oncogene less clinically attractive. Figure 1 illustrates the potential for Darwinian outgrowth of cancer after treatment with Akt inhibitor. One way to address this therapeutically is to exploit and strengthen the adaptive immune response, which may be capable of recognizing a dynamic and evolving landscape of mutated antigens.

Resolution: AKT Inhibition of T Cells Promotes Antitumor Immunity

A hallmark feature of the new and expanding concept of cancer includes its
capacity to evade the immune system. In this view, tumors are not merely sheets of malignant cells, but vascularized organs with a host of at least 28 types of tumor-infiltrating immune cells. The importance of memory and cytotoxic T cells has been particularly well described. In colorectal cancer, for example, the presence of tumor-infiltrating lymphocytes is a favorable prognostic indicator and more accurately predicts survival than the standard TNM system of cancer staging. Accordingly, in some cases patients with advanced cancers who receive immunotherapies relying on endogenous T cells—whether checkpoint inhibitors or cell-transfer therapy—have demonstrated curative eradication of their disease.

Among 98 patients with metastatic melanoma who received cell-transfer therapy using autologous tumor-infiltrating lymphocytes, 52 (56%) had an objective response and 20 (22%) had a complete and durable response to therapy. Interestingly, correlates with favorable response include the capacity of T cells to persist for long periods after adoptive transfer, telomere length of T cells, and expression of CD27, suggesting that transferred T cells with features of immunological memory have superior efficacy. The notion that memory-like T cells have superior antitumor immunity has also been corroborated extensively in preclinical animal models. However, because therapeutic T cells isolated from the tumor microenvironment are characteristically exhausted and senescent, there is a great therapeutic interest in methods to rejuvenate their capacity for long-term persistence and potent antitumor function.

Mounting evidence shows that canonical metabolic pathways such as the phosphatidylinositol-3-kinase–Akt pathway regulate the fate and function of cytotoxic T cells. Excessive Akt activity can drive cytotoxic T cells to a state of short-lived and terminal differentiation. In an effort to minimize effector differentiation of therapeutic T cells prior to adoptive transfer, it has recently been shown that culture with a pharmacologic inhibitor of Akt promotes phenotypic, metabolic, and functional features of immunological memory in antitumor T cells. Consistent with these findings, T cells treated with an Akt inhibitor demonstrated superior persistence and enhanced antitumor immunity in mouse models of cell-transfer therapy.

Although results in preclinical animal models are promising, it remains to be seen whether this approach will enhance the efficacy of T cell-based therapy in patients with advanced cancer. The third act, so to speak, is not yet fully played out. And so we look forward to translation of this approach to the clinic. Pharmacologic inhibitors of Akt that were initially developed to directly target cancer cells may also show therapeutic potential by augmenting the antitumor efficacy of the immune system.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
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