CHEMOTHERAPY

Conventional chemotherapy boosts the effect of cancer vaccines

Therapeutic cancer vaccines have been developed as an alternative treatment option to conventional chemotherapy and radiotherapy. However, evidence has indicated that therapeutic cancer vaccines given as a single agent may not produce substantial clinical benefits. Recent data suggest that the benefit of cancer immunotherapies can be improved when combined with conventional methods of treatment. To date, however, the mechanisms involved in this occurrence have remained unknown.

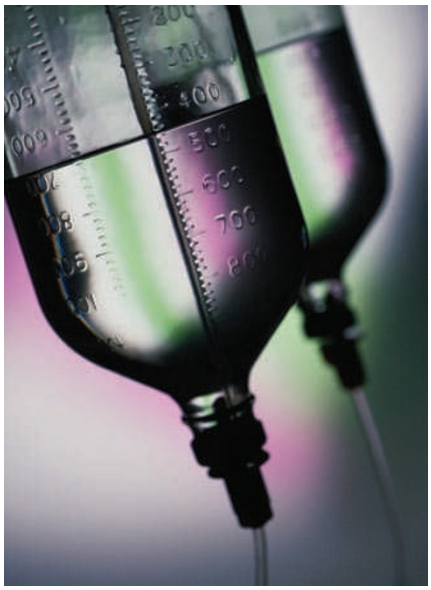
Now, a mechanism by which cancer immunotherapies mediate a potent antitumor effect when combined with conventional chemotherapeutics has been uncovered in mice by a team of researchers led by Dmitry Gabrilovich at the H. Lee Moffitt Cancer Center and Research Institute, Tampa, USA. "We have found that chemotherapy synergized with immunotherapy in the killing of tumor cells," says Gabrilovich.

The aim of cancer immunotherapy is to induce an immune response through the production of cytotoxic T lymphocytes (CTLs) that target specific tumor antigens and kill tumor cells. Chemotherapy is usually associated with immunosuppressive effects; thus, conventional chemotherapy was not previously considered as an attractive adjunct to cancer immunotherapy. However, high rates of clinical responses have been reported in several clinical trials using various combinations of chemotherapy regimens and cancer vaccines in patients with a wide range of cancers. "This observation suggested that there is a common mechanism underlying this potentially important phenomenon," Gabrilovich explains. His team, therefore, decided to move from the bedside back to the bench to identify the mechanism involved.

Gabrilovich and colleagues tested the effects of two types of cancer immunotherapy (cancer vaccine and adoptive T-cell therapy), and three different drugs (paclitaxel, cisplatin, and doxorubicin) in several different tumor models *in vivo* and *in vitro* in mouse cells and *in vitro* in human cells. Each of the drugs used have different mechanisms of action: paclitaxel induces apoptosis by interfering with the normal function of microtubule breakdown; cisplatin induces apoptosis by binding to and causing crosslinking of DNA; doxorubicin interferes with DNA and prevents replication.

All three chemotherapeutic drugs sensitized the tumor cells, making them more susceptible to attack from CTLs. Of note, the researchers observed that in the absence of chemotherapy, the CTLs were only able to target tumor cells expressing specific antigens. By contrast, following chemotherapy, the CTLs were also able to exert their cytotoxic effects on tumor cells that did not express specific antigens. "This effect was mediated by increased penetration of granzyme B released by CTLs into tumor cells in [a] perforin-independent manner," Gabrilovich comments.

Granzyme B is a critical mediator of cell apoptosis by CTLs in cell-mediated immune response. The chemotherapeutic drugs increased the permeability of tumor cell membranes to granzyme B, which can penetrate neighboring tumor cells that do not express the specific antigen that the CTLs target. These cells in turn release granzyme B, which the investigators suggest is responsible for increasing the sensitivity of the cells to CTLs generated by cancer immunotherapies. Activated CTLs were, therefore, able to kill neighboring tumor cells without coming into direct contact with them. Gabrilovich suggests that this effect could dramatically increase the potency of the antitumor activity of CTLs, adding "this effect is mediated via upregulation



of mannose–6–phosphate receptor on tumor cells induced by chemotherapy". Thus, nonspecific toxic effects associated with conventional chemotherapy should not be increased as the enhanced antitumor effect of combined treatment is limited to those cells that are sensitive to chemotherapeutic agents.

This study has uncovered a potentially novel therapeutic approach for the treatment of advanced-stage cancer. "The main implication for future research is that cancer immunotherapy can be tried as frontline treatment in combination with conventional chemotherapy in patients with advanced cancers," describes Gabrilovich. "The overall concept needs to be confirmed in detailed studies in patient's samples, the time of intervention needs to be worked out as well as the mechanism of mannose–6–phospate up-regulation," he concludes.

Lisa Richards

Original article Ramakrishnan, R. *et al.* Chemotherapy enhances tumor cell susceptibility to CTL-mediated killing during cancer immunotherapy in mice. *J. Clin. Invest.* **120**, 1111–1124 (2010)