New hope for tumor vaccines

The way a tumor cell dies determines its immune-stimulating capacity, according to a study by Casares and colleagues on page 1691. Tumor cells that die from exposure to the chemotherapy drug doxorubicin, they show, become highly immunogenic and induce the regression of established tumors when injected into mice.

Inactivated tumor cells have long been considered to be attractive vaccine immunogens, in part because whole-cell vaccines would allow each patient to be immunized against his or her own tumor. But this approach has met with limited success, probably because traditional ways of inducing tumor cell death—by irradiation or freeze-thawing—somehow strip the cells of their immunogenicity.

Many vaccine strategists have instead turned to T cell-inducing dendritic cell (DC) vaccines, in which DCs are grown from a patient’s blood, pulsed with tumor antigens, and reinserted. But the new data by Casares and colleagues might help revive interest in the simpler whole-cell approach.

Casares et al. show that tumor cells treated with doxorubicin, but not those treated with the chemotherapy drug mitomycin, elicit a tumor-specific T cell response in mice. Although both treatments induced apoptosis of the injected tumor cells, only the doxorubicin-treated cells were taken up by DCs, which then activated specific T cells. The immune-stimulating effect of doxorubicin required the activity of the death-inducing caspase enzymes in the tumor cells, although the relevant caspase targets were not identified.

The authors are now trying to pinpoint the doxorubicin-induced changes on the dying tumor cells that render them more palatable to DCs. In the meantime, they suggest that this approach—should it work in humans—might provide a more practical alternative to anticancer vaccine strategies that require the labor-intensive cultivation of autologous DCs. JEM

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A toxic gas eases IBD

A study on page 1703 might help explain why active smokers rarely suffer from an inflammatory bowel disease (IBD) known as ulcerative colitis. Hegazi and colleagues show that carbon monoxide (CO) gas, a component of cigarette smoke, shuts down the production of a disease-promoting cytokine, thus easing chronic bowel inflammation in mice.

CO is both a toxic air pollutant and a normal byproduct of cellular heme metabolism. Although CO’s asphyxiant properties have earned it a bad reputation, the ubiquitous tissue expression of the natural CO-producing enzyme heme oxygenase-1 (HO-1) suggests that the effects of CO must not be all bad.

Indeed, recent studies have shown that CO, at least at low concentrations, has a redeeming quality: it acts as an antiinflammatory agent. Low dose inhaled CO is therapeutic in many acute disease models including bacterial sepsis, organ transplantation, and vascular injury. Normally, HO-1 expression (and thus CO production) is induced under conditions of cellular stress, such as infection or oxygen deprivation, probably to limit the adverse effects of stress-induced inflammation.

The effects of CO on chronic inflammation, however, had not been studied. Here, Hegazi and colleagues show that CO exposure also inhibits chronic intestinal inflammation in mice. Exogenous CO treatment induced the expression of HO-1, either directly or indirectly, which in turn limited the intestinal production of the inflammation-promoting cytokine interleukin (IL)-12. In macrophages, HO-1 inhibited the expression of the transcription factor IRF-8 (interferon regulatory factor-8), which normally drives the synthesis of IL-12 in response to bacterial lipopolysaccharide and interferon-γ—a situation that mimics

the stimulation of these cells in the inflamed intestine.

Although the induction of HO-1 is required for the therapeutic effects of CO in most disease models, this is the first study to identify IRF-8 as a target of HO-1–induced inhibition. How HO-1 represses IRF-8 expression remains to be determined.

Based on these results, the authors suggest that inhaled CO or agents that increase endogenous HO-1 activity might be therapeutic in patients with ulcerative colitis. However, nonsmokers with IBD shouldn’t necessarily break out the Marlboros, as cigarette smoking is a risk factor not only for heart disease and cancer but also for Crohn’s disease, another form of IBD. JEM