Immune response to cancer stem cells may dictate cancer's course

26 March 2007

Although stem cells hold incredible promise in the fight against certain diseases, in cancer they're anything but helpful. In fact, mounting evidence is showing that a tumor's growth and spread may depend on "cancer stem cells," which comprise only a very small subset of the tumor. Now, a new study by Rockefeller University scientists shows that immunity to cancer stem cells may help protect people with a precancerous condition from developing the full-blown disease, and that these cells could be an important target for cancer vaccines.

About three percent of adults over 40 test positive for a condition known as monoclonal gammopathy of undetermined significance, or MGUS. MGUS itself is relatively benign, but in a small number of cases it progresses into multiple myeloma, a cancer of blood plasma cells. Yet despite the fact that MGUS and myeloma cells are genetically quite similar, researchers had been unable to figure out why most MGUS patients never develop the cancer. In research published in the March 26 issue of the Journal of Experimental Medicine, Madhav Dhodapkar, associate professor and head of Rockefeller's Laboratory of Tumor Immunology and Immunotherapy, shows that MGUS patients who naturally develop an immune response to an embryonic stem cell protein, called SOX2, appear to be protected against the development of myeloma.

Dhodapkar and his colleagues tracked patients with early plasma cell tumors — which are present in both MGUS and early myeloma — for as long as three years, then filtered their results depending on whether the subjects had an immune reaction against SOX2. Thirteen patients showed immunity to the protein and, by the end of the study, none of the 13 had tumors that progressed. But of the 18 patients who did not have an immune reaction to SOX2, 70 percent developed progressive myeloma. "So a person's immunity to this antigen, SOX2 — which is thought to be very important to embryonal stem cells and is also expressed in cancer — appears to predict the outcome in people with premalignancy or early myeloma," Dhodapkar says. "This shows that the biology of stem cell genes is going to be very important in the context of cancer biology. Because when you get an immune response against these genes the outcome is quite different than when you don't."

This immune response, which correlates so closely with clinical outcome, appears to be targeting the cancer stem cells rather than the bulk tumor cells in myeloma — something that gives researchers hope for a completely new approach. "In immunology for the longest time, we've tried to focus on targeting bulk tumors. But maybe we should be targeting stem cells," Dhodapkar says. "You need to target the roots to really kill the tree, but what we've been doing is trimming the branches and it hasn't worked."

Not only does this study give Dhodapkar a potential target for cancer vaccines, it also shows him that the immune systems of the people with the precancerous MGUS didn't just react to SOX2; they reacted to a completely different set of antigens than did the immune systems of patients with the fully developed cancer. Scientists have known for decades that cancer cells carry antigens, mutant proteins that can be recognized by the immune system. So they've concentrated on trying to identify tumor antigens and induce the immune system to attack them. The new research, however, also implies that researchers might be better off studying which antigens the immune system attacks before the cancer takes hold. "It's becoming clearer that the immune system in cancer is really a two-edged sword," Dhodapkar says. "Certain aspects, particularly inflammation, can promote cancer. But it's really important for us to figure out what parts of the immune system help prevent, or help target, cancer in a beneficial manner."

Because the immune systems of MGUS and

myeloma patients respond to such different antigens, Dhodapkar also envisions these differences being used to screen for onset of disease in people who otherwise show no sign of disease. And this method could be used not just for myeloma but also for any tumor preceded by precancerous lesions. "You could use immune response as a way of screening for all kinds of cancers, because it recognizes cancer at a stage where it can't be seen by any other method," he says.

Dhodapkar notes that the study is preliminary and must be confirmed in larger numbers of patients. "This raises more questions than it answers right now," he says, "but these studies provide new targets which we can develop vaccines and drugs against."

Source: Rockefeller University