More Antioxidant Criticism?

Keith I. Block, MD

Scientists from Cold Spring Harbor Laboratory are criticizing antioxidants again. As you may recall, about 18 months ago, Nobel Prize winner James Watson published a paper saying antioxidants are bad for cancer patients, and that antioxidant-rich blueberries amount to nothing more than a natural "junk food" that are OK to eat because they taste good, but not because they are healthy for you.

Last week Dr David Tuveson, deputy director of Cold Spring Harbor Laboratory, along with Navdeep Chandel of Northwestern University, published an article in the New England Journal of Medicine on the promise and perils of antioxidants for cancer patients – emphasizing the perils. They discussed basic research about the function of reactive oxygen species (abbreviated ROS, also called free radicals) with the cell, in normal cells,and in cancer cells. ROS do have specific functions in healthy cells. Healthy cells make low levels of ROS in their mitochondria. These ROS run various functions involving cell survival, multiplication, differentiation and metabolism. In cancer cells, however, the mitochondria ramp up their production of ROS so that they can survive, even though they are abnormal, multiply much faster than their normal counterparts, de-differentiate and use new metabolic pathways that produce cancer-fostering molecular fuel. But this high level of ROS also exposes cancer cells to danger: we now know that cell death and apoptosis (cellular suicide) can be caused by ROS. This is one mechanism that helps chemotherapy and radiation therapy, both of which generate ROS in the body, kill cancer cells. So the cancer cells also start producing internal antioxidants, glutathione and thioredoxin. These antioxidants can heal the damage from ROS and prevent cell death, while allowing the ROS to work their other mischief in the survival, multiplication and metabolism of the cancer cells.

Tuveson actually poses a rather interesting mechanism for dealing with the ROS mischief: find some antioxidants that stop the production of ROS in the mitochondria in the first place. This is a legitimate target for drug discovery, and might lead to some interesting new drugs in the future. But the other message of Tuveson's paper, and a message that certainly seems to be picked up and even exaggerated in press coverage of the publication, is that dietary antioxidants are BAD for you. This is because Tuveson and Chandel assert that dietary antioxidants have tumor-accelerating properties because they interfere with the ROS that can cause apoptosis and cell death.

What is the evidence that they cite for the harmful effects of antioxidants? The main human study that they cite is the notorious study of alpha-tocopherol (one type of vitamin E) and beta-carotene conducted in smokers in Finland, in which study participants taking antioxidants wound up with higher rates of cancer, rather than the expected lower rates. A lot has been said over the years about this study, but let us point out once again that this study used high doses of a *synthetic* version of beta-carotene, which seems to have an unusually negative reaction with smoking. The vitamin E used in the trial is only one of 8 forms of natural vitamin E

that is found in our food, and it drives down blood levels of the other vitamins, which make crucial contributions to our health. They also mention findings that taking one or a few types of antioxidant vitamins does not prevent cancer, a hypothesis that I've long thought was a waste of time to study in the first place. Cancer is an incredibly multifaceted disease, depending on disorders of oxidation, inflammation, glycemia, immune deficits, stress hormones, blood coagulation, genetics and a network of other hallmarks. Thinking that you can protect someone from this complex of a disease by giving a single vitamin is just silly. Both preventing and fighting cancer demand a full-scale revision of potentially carcinogenic life patterns.

While Tuveson and Chandel cite the Finnish study, they don't cite any of a host of other articles they could have brought to the attention of their readers on the *protective* effects of (antioxidant-rich) vegetables and fruits. Just for one quick example of a recently published paper: women in Poland who ate the most vegetables were 63% less likely to get breast cancer than vegetable-shunning controls, while those who ate the most fruits, possibly even including blueberries, were 53% less likely to get cancer; this relationship was especially true for those who didn't exercise much (interestingly, there was no relationship of total carbohydrate intake to cancer risk, but high intake of sugary sweets and desserts raised risk by an eye-popping 350%!). And there are a lot of other studies that point to the healthful and cancer-reducing properties of vegetables and fruits. So don't stop your weekly trips to the farmers' market just yet!

But Tuveson and Chandel are also overlooking some interesting properties of antioxidants that are known among researchers in the area of natural products. This is the selective pro-oxidant properties of many natural antioxidants. These antioxidants have healthful effects on normal cells, but in cancer cells they are well known to cause apoptosis. And why is this? It's because when these antioxidants are put into cancer cells, sometimes only at particular dosages, they turn into prooxidants. In cancer cells, this prooxidant activity causes apoptosis, as well as triggering many other effects that actually stop cancer growth.

The best known prooxidant antioxidant at this time is intravenous high-dose vitamin C. While vitamin C at regular oral doses has an antioxidant effect just like any other antioxidant, if it is given in high doses – like 50 grams a day, much more than you can take in supplements – it turns into a prooxidant, and appears to kill cancer cells. The prooxidant activity is triggered because of iron and other metals that are abundant in tumor tissues. When vitamin C interacts with these metals, it starts to behave like a prooxidant. The cancer-killing properties of high-dose vitamin C have been validated in laboratory studies, and there are many small studies and case reports on its apparently beneficial effects in cancer patients. A formal study is now being conducted at the University of Kansas, but in the meantime, the treatment is available at many other centers, including the Block Center. Note that you can't use oral vitamin C supplements for this effect. Even if you felt like taking dozens and dozens of vitamin C tablets daily, your body closely regulates how much vitamin C can be absorbed through the digestive system. Vitamin C must be administered intravenously, bypassing your digestion, in order to reach prooxidant levels.

Many well-known supplemental antioxidants come from plants. These include curcumin from turmeric, resveratrol from grape skins, epigallocatechin gallate (EGCG) from green tea, flavonoids like quercetin and luteolin, and many others. We recently reviewed a large body of literature that indicates that many plant-based and even animal-based antioxidants cause prooxidant effects in cancer cells, without harming normal cells. Researchers at the Karmanos Institute in Michigan have been the most active in exploring this phenomenon. They have discovered that this activity occurs when the plant antioxidants interact with metal ions, usually copper ions, not unlike the interaction of vitamin C with iron in cancer cells. When these antioxidants are added to cancer cells, we can demonstrate that they cause the production of ROS inside of the cells. Cancer cells have higher levels of copper than normal cells, since it forms part of many enzymes that signal cancer cells to grow uncontrollably.

In addition, it appears that metabolic disruptions often seen in cancer cells, mentioned above, pry copper away from some of the structures that hold it in the cell. This frees it to interact with the plant antioxidants, and generate intracellular ROS – resulting in apoptosis for the cancer cells. Because normal cells have less copper, and because their metabolism is normal and leaves copper chemically bound up, the antioxidants do not damage normal cells.

In effect, then, the antioxidants act as targeted drugs to produce ROS and cause apoptosis in cancer cells, but not in normal cells. Since chemotherapy and radiotherapy act by killing cancer cells with ROS, perhaps we should, in fact, consider giving these antioxidants with chemotherapy. Does this actually work? There is very interesting evidence suggesting that it does. For instance, researchers in China gave breast cancer patients going through radiation high doses of EGCG (1200 mg per day). They then compared blood samples from the patients to samples from radiation patients who did not get EGCG. The blood of the EGCG patients had much lower levels of VEGF, which promotes formation of tumor blood vessels, and also had lower levels of MMP-9, which stimulates metastasis. The EGCG patients also had an increased rate of breast cancer cell apoptosis over that of patients with radiation alone.

Giving plant antioxidants along with chemotherapy to tumor-bearing animals is another way to test the proposition that these antioxidants may support the activity of chemotherapy, possibly through demonstrated prooxidant activity. Curcumin is well known to improve the activity of many chemotherapy drugs in animals, and there are numerous studies on its ability to boost the anticancer effects of both chemotherapy and radiation. Here are a few of the other prooxidant-antioxidants that we found both to produce intracellular ROS and to support the actions of chemotherapy drugs in tumor-bearing animals:

Antioxidant	Type of chemotherapy	Type of cancer
Alpha-lipoic acid	Adriamycin	Leukemia
Apigenin	Gemzar	Pancreatic
EGCG	Adriamycin	Prostate
EGCG	Adriamycin	Liver cancer
Genistein	Platinol, Taxotere, Gemzar	Ovarian

Gamma tocotrienol Xeloda Gastric

These are just a few of the prooxidant-producing antioxidants that we found that increase the effectiveness of chemotherapy treatment in animals. This activity actually seems to be quite widespread among natural antioxidants. It's been observed for melatonin, lycopene and even vitamin D (did you know that vitamin D is an antioxidant!?). Interestingly, we did not find evidence of this effect for beta-carotene and alpha-tocopherol, the two antioxidants that have given rise to problematic results in previous clinical trials.

While we applaud innovative efforts to discover new anticancer drugs, as the Cold Spring Harbor scientists appear to be doing, we think they, and members of the press, should stop criticizing natural antioxidants, a helpful class of compounds about which we are gaining new insights every month. We also think you should continue to consume fruits and vegetables, including blueberries. And – particularly if you have been through or will be going through an antioxidant-destroying treatment like radiation or chemotherapy, consider having terrain tests done at the Block Center to determine whether your levels of specific antioxidants are low, and then implementing a balanced diet and supplement regimen to bring them up to appropriate levels. Vitamins do have many other functions in a healthy body besides participating in cancer cell apoptosis, and we don't think you should allow yourself to experience nutritional deficiencies. We also don't suggest that you start mega-dosing yourself on a single vitamin or other type of supplement in hopes of curing or preventing cancer. Nutrition and supplementation in the case of cancer demand expert advice and multifaceted solutions that take your unique situation into account, and it's essential to seek out such advice before beginning any supplement program.