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wo forms of skin and brain cancer respond very poorly to chemotherapy and radiation: melanoma and glioblastoma multiforme brain cancer. Both are the focus of an intensive effort in the Department of Nutritional Sciences at The University of Arizona to find natural, biologically active compounds that will sensitize the cancerous tumors to therapy without damaging normal tissue. By using the compounds in conjunction with conventional treatment, the researchers hope patient survival rates will ultimately increase.

The incidence of melanoma, an aggressive and often fatal form of skin cancer, is increasing at the rate of 3 percent annually, according to the American Cancer Society, which predicted more than 63,000 new cases and more than 8,000 deaths for 2008 in the United States alone.

Dacarbazine, the standard chemotherapeutic drug for melanoma for decades, has been ineffective when used alone. To improve its performance, Randy Burd, assistant professor of nutritional sciences and member of the UA's BIO5 Institute, has been testing the drug and its new analog Temozolomide in combination with various bioactive compounds to gain greater response rates on melanoma tumors in cell cultures.

"After working with COX-2 inhibitors—Celebrex and Vioxx that were ultimately taken off the market—we started looking at quinones, which occur in nature as pigments, vitamin biochemical backbones and plant compounds and then we analyzed the enzymes involved in their activation," Burd says.

Quercetin, a polyphenol found in apples, onions, green tea and other plant-based foods, is a quinone that has shown an interesting effect on melanoma tumors. In low concentrations quercetin behaves as an antioxidant, yet at high concentrations it becomes a cell-damaging pro-oxidant. Burd's group is exploiting the pro-oxidant attribute of quercetin, using tyrosinase, which is the highly expressed enzyme responsible for the pigment formation in human skin cells that grow out of control in melanoma.

"The quercetin is similar to precursors of melanin," Burd says. "The tyrosinase actually recognizes and activates quercetin to a pro-oxidant rather than an antioxidant." When tested together in melanoma tumor cell cultures the result is tumor cell death—the melanoma enzyme is tricked into activating so much quercetin that it turns around and sensitizes the melanoma cells to the chemotherapy drug and they die.

Quercetin is an example of a biological response modifier (BRM), a drug or a compound that changes the function of tumor cells so they will be more responsive to chemotherapy or radiation, according to Burd. Key members of his research group

responsible for moving this work forward include nutritional sciences research associates Sittadjody Sivanandane and Thilakavathy Thangasamy, and graduate research associate Erin Mendoza.

The team is now screening a library of bioactive food and plant compounds to find out if they kill tumor cells for different cancers, and if they do, what genes or proteins are involved in their activity. The research is supported through a combination of pharmaceutical sponsors, private grants and government funding.

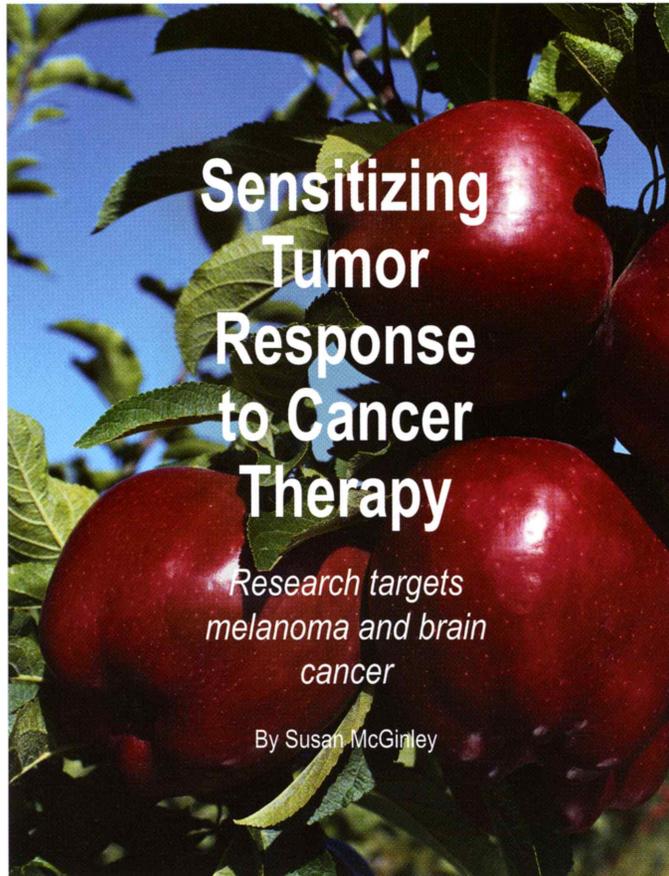
For successful compounds like the quercetin used in the melanoma study, the researchers need to modify them into deliverable pharmaceutical drugs, making the compound more potent, and then put them into repeated clinical trials.

"We're also looking at which enzymes are expressed in different tumors so we can design a specific therapy," Burd says. In the case of glioblastoma multiforme brain cancer, the focus is on finding and screening quinones that could be used in the brain to reverse the radiation-resistance of tumors, and then using those compounds in conjunction with radiation treatment. The approach is new, and the potential slate of possible bioactive compounds that could be used for different types of cancer is vast.

Burd is ultimately interested in developing and training students in nutrigenomics, the study of molecular relationships between nutrition and the response of people's genes for disease prevention and intervention. A new program in nutrigenomics has been created through a partnership between investigators at The University of Arizona, researchers Adam P.

Dicker and Susan Lanza-Jacoby at Thomas Jefferson University in Philadelphia, and Marc S. Halfon at the University at Buffalo in New York. Down the line, it may be possible to develop individualized diets based on someone's cancer risk.

"For example, we would want to know how products like quinones are going to interact with the genes and enzymes in your precancerous cells and cancerous cells," Burd suggests. "Then we would check which foods you should be eating with your particular gene or protein profile to inhibit or treat cancers. Nutrigenomics is limited right now, but it's an emerging field." ★



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