

Resveratrol May Be a Powerful Cancer-Fighting Ally

Newspapers and magazines regularly contain headlines about studies that show that average consumption of wine, beer, and spirits may—or may not—convey health benefits. Results from ongoing studies have been mixed, but in the case of red wine, one key constituent found in high concentrations in grapes and grape skins may prove to be an ally in cancer prevention and treatment.

Resveratrol, an antioxidant and antifungal, is sold over the counter in the United States as a nutritional supplement and is found in raspberries, blueberries, peanuts, and some pine trees. It is one of a number of naturally occurring polyphenols that are under investigation for their potential antioxidant and anticancer properties. Experiments also suggest that resveratrol can help control atherosclerosis, heart disease, arthritis, and autoimmune disorders.

Scores of researchers have looked at the cellular and biochemical mechanisms of resveratrol in cell lines and animal models—enough to raise the possibility that the compound could block cancer progression. Resveratrol appears to reduce the activation of the protein NF-kappa B (NF- κ B), which directs crucial cellular processes.

This summer, a team of biochemists from the University of Virginia mapped the role of resveratrol in NF- κ B activation. The group discovered that non-small-cell lung cancer cells treated with resveratrol died because of disruption to the normal functioning of NF- κ B. In cancer cells, NF- κ B interference essentially induces apoptosis, or programmed cell death. The reason: resveratrol enhances sensitivity to the substance known as tumor necrosis factor alpha, or TNF- α , a “biological response” modifier known to induce cancer cell death.

“Resveratrol doesn’t affect ‘upstream’ pathway signaling,” said Marty Mayo, Ph.D., assistant professor of biochemistry and molecular genetics at the University of Virginia who oversaw the team that identified the apoptosis mechanism. “It affects NF- κ B directly.

Ultimately it’s a way of marking a protein [for death].” Their results were published in June in *The EMBO Journal*.

Another key player in the entire process is SIRT1, a protein that is one of seven sirtuin enzymes active in the human body and vital to some healthy metabolic functions. The Virginia team pinpointed how resveratrol triggers SIRT1 to physically interact with a subunit of the NF- κ B molecule to inhibit genetic transcription and thus boost cell sensitivity to TNF- α -induced apoptosis.

Sirtuins are receiving intense scrutiny because of their suspected role in encouraging longevity and overall cell vitality, including resistance to



Resveratrol, an antioxidant found in high concentrations in grapes and grape skins—and, therefore, wine—is under investigation for its potential anticancer properties.

cancer. As enzymes capable of counteracting the damaging effects of oxygen in tissues, sirtuins seem to mediate the effects of aging. As such, it may also be possible to invoke resveratrol’s anticancer effects as an aid to boost human longevity.

Animal models have supported the view of resveratrol as a sirtuin enabler. A 2003 Harvard Medical School study, for example, found that yeast cells treated with resveratrol lived 60% to 80% longer than expected. Roundworms fed a diet rich in resveratrol lived 14% longer than a control group of worms that did not receive the compound, and the lifespans of fruit flies receiving resveratrol were extended by 29%.

“We think sirtuins buy cells time to repair damage,” said molecular biologist David Sinclair, Ph.D., assistant profes-

sor of pathology at Harvard Medical School. “There is a growing realization from the aging field that blocking cell death—as long as it doesn’t lead to cancer—extends life span.”

Resveratrol could prove its mettle against a broad array of cancers. A 2002 German study conducted at the University of Saarland Medical School indicated some benefit against the HCT116 colon carcinoma cell line and a derivative. Another investigation, conducted jointly by the Northwestern University Medical School and the University of Texas Health Science Center, included resveratrol among a large group of antioxidants that may play a role in inhibiting the growth of T47D, one type of breast cancer cell line.

So far, the data in humans derive largely from epidemiologic studies. Danish scientists studying alcohol as a risk factor for oropharyngeal and esophageal cancers found that drinking one or more glasses of wine a week may be associated with a lower risk of developing upper digestive tract cancer compared with drinking a similar amount of beer or spirits. Previous epidemiologic studies conducted in the United States and abroad have demonstrated resveratrol’s benefit in preventing or mitigating diseases of the circulatory, cardiac, and immune systems.

“[Resveratrol] has some benefit for people with atherosclerosis and heart disease,” Mayo said. “That was one of the issues associated with the French Paradox.” The French Paradox refers to the fact that the French, despite a diet rich in saturated fats, nevertheless experience a relatively low incidence of coronary heart disease. Several researchers have proposed that resveratrol is the protective compound behind the paradox.

Regardless, it would be a mistake to see resveratrol as a magic anticancer bullet, said Roy Frye, M.D., Ph.D., a pathologist at the University of Pittsburgh. “People have to keep in mind it’s not known how specific resveratrol is,” Frye said. “Is resveratrol acting on all

seven SIR proteins [in humans]? It would be nice to have a more potent and more targeted compound to achieve more surety in how and where it's acting."

Exactly what form resveratrol should assume to be of maximum physiological effect remains at issue. An August 2004 study conducted by the Medical University of South Carolina and published in *Drug Metabolism and Disposition* raised questions about how



Dr. Marty Mayo

well the body can absorb and process artificial resveratrol-containing supplements. Other investigations, including one conducted by German and British

scientists in 2000 on a rat model, indicate that more experiments need to be conducted to pinpoint the most effective means of resveratrol delivery within the human digestive tract. At this stage, natural resveratrol sources such as red wine appear to be the most effective. Otherwise, absorption may prove inadequate to reach the *in vivo* concentrations necessary to spur meaningful biologic activity.

Aside from resveratrol's specific anticancer activity, an array of other NF- κ B inhibitors hold the prospect of escalating the effectiveness of existing cancer therapies, Mayo said. Clinical trials using this approach in patients are showing encouraging results, Mayo pointed out, and subsequent research may lead to additional means of expanding the effectiveness of combined therapies.

"[Resveratrol] is one inhibitor. If we can find more and get them to work together, it will have a dramatic effect," he said. "People talk about cancer therapy and wonder why HIV [therapies have] been so successful. The bottom line is a multipronged approach. You have to take multiple steps to inhibit cancer."

—James Schultz