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FILE: ▪ Lung Cancer
▪Plant Extracts

HC 040255-298

Date: February 15, 2006

RE: Molecular Mechanisms Involved in Killing Cancer Cells

Ancuceanu RV, Istudor V. Pharmacologically active natural compounds for lung cancer. *Alt Med Rev.* 2004; 9(4):402–419.

Although lung cancer is the second most common cancer in men (prostate cancer is first) and the third most common cancer in women (breast and colorectal are first and second, respectively), it is the most deadly. According to data cited by the authors, "lung cancer continues to account for the highest number of cancer deaths in the United States (32% men; 25% women)." Once diagnosed with cancer, 80% of patients die within one year; only 5–15% survive for five years. This article describes the molecular mechanisms involved in killing cancer cells and in vitro and in vivo research, mostly on experimental animals, into the cancer-killing potential of plants.

In contrast to healthy cells, cancerous cells exhibit immortality and uncontrolled cell division. The biology and biochemistry of cellular replication provide five targets for therapies. These are microtubule interference (interrupting the molecular scaffolding that holds a cell together in its three-dimensional structure); three inhibit the ability of DNA to replicate, which is a necessary step in cell division (topoisomerase poisoning or topoisomerase catalytic inhibition, DNA alkylation, and DNA inhibition); protein synthesis inhibition; immune mechanisms (stimulating the immune system to attack the cancer cells); and lipoxygenase inhibition (one of the enzymes responsible for producing inflammatory chemical signals, which is important in the growth and spread of cancer).

Microtubule interfering substances

A range of plant extracts that interfere with microtubule assembly are already being used clinically. These include vinblastine and vincristine from Madagascar or rosy periwinkle (*Catharanthus roseus*) and especially the second generation vinorelbine, colchicine from the autumn crocus (*Colchicum autumnale*), and the taxanes paclitaxel and docetaxel derived from a constituent of the bark of the Pacific yew tree (*Taxus brevifolia*). A methanol leaf

extract of rough cocklebur (*Xanthium strumarium*) has most recently been tested on experimental lung cancer cells in vitro and has shown promise at stopping cellular division.

Topoisomerase poisons

Two semisynthetic alkaloids are currently used as topoisomerase poisons in cancer treatment. These are topotecan and irinotecan, both derived from camptothecin, which was isolated from *Camptotheca acuminate*. According to the authors, "the most important topoisomerase II poison is etoposide, a semisynthetic derivative of a natural lignan (podophyllotoxin) found in Podophyllum species." Topoisomerase I poisons cleave single DNA strands, while topoisomerase II poisons cleave both DNA strands).

Other plant alkaloids that are currently being studied are: lycobetaine from *Lycoris radiata*, and nitidine from shiny-leaf prickly ash (*Zanthoxylum nitidum*).

The annonaceous acetogenins, polyketide-derived fatty acids demonstrate a brood range of biological activities, including antitumor and cytotoxic effects, some of them being shown to act as topoisomerase poisons. Annonacin, the most active of these acetogenins acts through apoptotic mechanisms. Other acetogenins like bullatacin (*Annona atemoys, A. reticulata*) also activate apoptosis. However, the authors of this review point out that apoptosis is not a distinct mechanism of activity, but rather the end result of a variety of mechanisms targeting different cell components. Experimental evidence suggests that the primary mechanism could be that of topoisomerase poisons – annonacin (from *A. murricata, A. reticulata, Goniothalamus giganteus*) and rolliniastatin–1(an acetogenin from *Rollinia* spp.) having such properties. *Annona* spp. (*A. montana*, *A. atemoya*, *A. reticulata*, and *A. murricata*), *Goniothalamus giganteus*, and *Rollinia* spp. A flavonoid, baicalein, extracted from Baikal skullcap (*Scutellaria baicalensis*) also appears to inhibit topoisomerase.

DNA alkylating agents

Plant-derived alkylating agents "have not been well investigated." The authors review data from studies of just one compound, 4–ipomeanol, derived from the sweet potato (*Ipomoea batatas*) infected with the fungus *Fusarium solani*. Unfortunately, "in clinical settings the results were very unsatisfactory with no objective antitumor responses and toxicity concerns." Contrary to what preclinical studies had suggested, 4-ipomeanol was mainly toxic at the hepatocellular rather than the pulmonary level.

DNA synthesis inhibitors

This is the largest category of anti-cancer mechanisms reviewed in this article. Unlike the other categories where the way in which therapeutic agent works is understood, "if a substance is found to inhibit DNA synthesis, the mechanism of activity is not necessarily completely understood." The polyphenol resveratrol, found in grapes (*Vitis vinifera*), peanuts (*Arachis hypogaea*), and mulberries (*Morus* spp.), is a phytoallexin, a chemical produced in response to an injury, such as damage by ultraviolet radiation or attacks by fungi. Resveratrol

reduced the tumor volume and tumor weight (42% and 44%, respectively) in mice with lung cancer.

Other DNA synthesis inhibitors include indirubin (isoindigotin, indigo red) from indigo (*Indigofera tinctoria*), and the leaves of *Strobilanthes cusia* syn. *Baphicacanthus cusia*, polygonum indigo (*Polygonum tinctorium*), isatis (*Isatis indigotica*), and anil indigo (*Indigofera suffrutticosa*). Grape seed extract (*V. vinifera*) contain "natural antioxidants with a broad spectrum of chemoprotective properties." Chemotherapy is frequently toxic to both the cancerous and healthy cells. Grape seed extract "had the advantage of favoring the growth and viability of normal cells" in vitro.

α-Hederin (kalopanaxsaponin A), identified as the active antitumor compound from a fraction of an ethanolic extract from *Nigella sativa* seed, exhibited a dose-dependent antitumor activity more potent than cyclophosphamide. beta-Hederin, more active than the alpha isomer against the A549 cell line, may be an even more promising agent.

The authors also describe anti-cancer experimental data using extracts of *Physocarpus intermedius*, whose constituents 3-O-caffeoyloleanolic acid, betulinic acid, and the methyl ester of euscaphic acid were all active against cancer in vitro. Ursolic acid, isolated from *Polylepis racemosa* and *Oldenlandia diffusa* also show promising in vitro activity. Additionally, *O. diffusa* appears to have the added benefit of stimulating the immune system to attack tumor cells.

Protein synthesis inhibitors

Lignans, lectins from mistletoe (*Viscum album*), some alkaloids (pretazettine, lycorine, homoharringtonine, antofine, tubulosine) and some quassoinoids (bruceantin isolated from *Brucea antidysenteria*) all exhibit the ability to inhibit protein synthesis in cancer cells in vitro. Rocaglamide-type lignans are isolated from the stem of *Aglaia elliptica*, which was cytostatic but not cytotoxic in vitro. Other lignans isolated from the stem bark of theFormosan plant (*Aglaia formosana*) exhibited tumoricidal activity in vitro.

Compounds acting via immune modulation

These compounds are all derived from fungi, which are known to stimulate the immune system. They include PSK (Polysaccharide Kureha; Polysaccharide K; krestin) and PSP (polysaccharide P), which are isolated from coriolus (*Coriolus versicolor*) and maitake mushroom (*Grifolia frondosa*) D fraction. Clinical trials using PSK increased two- and five-year survival times in lung cancer patients who received PSK plus radiotherapy compared to those receiving radiotherapy alone. According to this review article, "Two-year survival rates of patients older than 70 years were 55 percent for patients who received PSK and 22 percent for patients who did not receive PSK. After five years, survival rates were 23 percent and 7 percent, respectively." The maitake D-fraction has also been used in clinical trials and resulted in "symptomatic improvement or regression" in two studies.

Lipoxygenase inhibitors

Flavonoids, which are excellent free-radical scavengers, have been studied on various cancer cell lines in vitro, including gastric, pancreatic, human breast, and prostate cancers. The flavonoids investigated were baicalein, wogonin, their glucopyranosiduronides baicalin and wogonoside, and skullcapflavoine II (neopbaicalein) isolated from the root of Baikal skullcap.

Conclusion

Mortality for lung cancer is high, and the search for novel agents for its treatment continues. Many current cancer therapies have their origins in plant extracts, and plants continue to be important resources for cancer research. Most of the studies on natural anticancer therapies reviewed in this article were conducted in vitro or on animals. While results from many of these studies are promising, clinical trials must verify the efficacy of these potential plant-derived chemotherapies.

—John Neustadt, ND

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