New Therapies for Melanoma

More than 68,000 individuals were diagnosed with melanoma in the United States in 2010, and 8,700 people will die as a result of the disease, according to estimates by the National Cancer Institute. However, the outlook for patients may be about to change. In March of this year, the Food and Drug Administration (FDA) approved the drug ipilimumab (Yervoy) for the treatment of advanced melanoma. The drug—developed by Bristol-Myers Squibb and Medarex—works by blocking a molecule called CTLA-4, which interferes with the ability of T cells to fight off foreign invaders, including abnormal cancer cells. The FDA approval was based on results of a phase III clinical trial (Hodi et al. N Engl J Med 2010;363:711–23) showing that the drug increased median overall survival compared to gp-100, an investigational cancer vaccine which was used as an active control. Ipilimumab is the first drug the FDA has approved for advanced melanoma in more than a decade—and is the first of a series of potential new drugs in the pipeline. Biovex is currently testing its drug OncoVEX$^{GM\text{-}CSF}$ in phase III trials in thousands of patients with advanced melanoma. This drug uses a modified version of the herpes virus to specifically produce granulocyte macrophage colony-stimulating factor (GM-CSF) inside tumor cells; GM-CSF then stimulates immune cells to mount an attack on the tumor. The MAGE-A3 vaccine developed by GlaxoSmithKline is also being tested in a phase III trial of advanced melanoma. In addition, numerous companies are developing targeted therapies against the BRAF protein; the gene encoding this protein is mutated in many cases of melanoma. In recent phase II trials, a BRAF inhibitor being developed by Roche (RG7204) extended progression-free survival of patients with advanced melanoma whose tumors had the BRAF mutation. GlaxoSmithKline has also started late-stage trials of 2 new BRAF inhibitors for advanced stage melanoma in patients with the BRAF mutation. ■

Diabetes–Cancer Link

Eating a healthful diet and exercising can decrease the likelihood of developing diabetes and various related illnesses—cancer among them. A growing body of evidence now suggests that diabetes and conditions that predispose to it, such as high blood pressure and obesity, increase the risk of cancer. One of the most recent and largest studies to date examining this link, the National Institutes of Health–American Association of Retired Persons Diet and Health Study, has revealed that women with diabetes had an 8% increased risk of developing cancer compared to nondiabetic women, whereas for men the increase was 9%, as long as the rates of prostate cancer were excluded from the calculation. (Diabetic men have lower prostate cancer risk possibly because diabetes decreases testosterone levels.)

The researchers based these results, presented at this year's American Association for Cancer Research annual meeting in Orlando, Florida, on diet, lifestyle, and medical health data collected from more than 500,000 individuals over an 11-year period. Although the results didn't differentiate between type 1 and type 2 diabetes, type 2 is by far the most common form among Americans and is typically linked to obesity. In a related study presented at the same meeting, researchers reported that metabolic syndrome—a group of conditions including raised blood pressure, elevated waist circumference, and low "good" cholesterol—not only increases the risk of heart disease and diabetes, but may also increase the risk of the two most common types of liver cancer. Liver cancer incidence is on the rise in the United States. The study suggests that this increase may be linked to a rising incidence of metabolic syndrome, which today affects as many as 25% of Americans. ■

One Medicine Doesn't Fit All

Even as a tumor is shrinking in response to a drug, some tumor cells may be undeterred by the drug's effects, eventually causing the tumor to grow back. By analyzing tumors of patients who have relapsed, researchers have discovered that tumors harbor different populations of cells carrying distinct therapy-escaping mutations, and that these vary from tumor to tumor and—even within a single tumor—can change over time. Eradicating tumors may therefore require combinations of drugs tailored to their changing mix of cells.

Recent research has focused on lung cancer, a leading cause of death globally that has been difficult to treat. Some types of lung cancer are driven by an overly active epidermal growth factor receptor (EGFR) and respond dramatically to drugs such as erlotinib (Tarceva; OSI Pharmaceuticals) and gefitinib (Iressa; AstraZeneca) that bind to EGFR and block its function. However, the response to these targeted therapies is, in most cases, short lived. Several studies have shown that about half of tumors that become resistant to erlotinib and gefitinib contain in their mix cells in which EGFR has a mutation (T790M) that prevents the drugs from binding properly. In other patients, some cells have turned on a different growth receptor, called MET, to allow them to grow when EGFR is blocked. Yet other cells use other mechanisms to escape treatment.

The picture beginning to emerge is that treating a cancer with a drug targeted to one type of cancer-causing mutation may impact the growth of the majority of cells, as intended, but also allows populations of cells with additional mutations, which may only have been present in small numbers in the original tumor, to grow and take over. Depending on the type of drug used in treatment, different cell populations will dominate. "There is a competition among populations of cells," says Jeffrey Engelman of Harvard Medical School. By taking biopsies of a patient's tumor before, during, and after treatment, Engelman's group has shown that the cellular landscape of the cancer looks much different depending on the stage of treatment. "The implication is that we may have to continuously reassess a tumor," he says. Researchers are now starting to test combinations of drugs that can target not only the mutation driving cancer growth, but also the tumor's potential resistance mechanisms, all at once. The idea of using combination therapy is not new, but now that researchers know many of the molecular drivers of cancer and of resistance, they can select drug combinations in a more rational way, according to William Pao, professor at Vanderbilt-Ingram Cancer Center in Nashville. The results of several clinical trials for combination therapies should start to become available this summer. ■