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Targeting tumor behavior may lead to new liver cancer drugs

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Ohio State University cancer researchers have used computational and genomic methods to identify possible anti-cancer agents that may block a particular kind of tumor behavior. The agents target multiple genes associated with that behavior at one time.

The researchers wanted to find agents that might reverse the gene changes associated with invasive liver cancer and perhaps stop liver tumors from spreading in the body. Such therapy could greatly improve patient survival, the researchers say.

The findings are published online in the journal *Cancer*.

"This is an exciting new way to find potentially useful anti-cancer agents," says principal investigator Dr. Tushar Patel, director of hepatology and a researcher with Ohio State's Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute.

"For nearly two decades, cancer drug discovery has sought agents that block a single molecular target or pathway," he says. "Our approach identifies agents that could potentially block tumor progression by striking multiple genes that are associated with a particular cancer-related behavior."

New drugs for liver cancer are needed because the disease is widespread worldwide. The most common type of liver cancer, hepatocellular carcinoma, causes 630,000 deaths every year worldwide, and the

incidence is rising in many countries, including the United States.

Only one drug is presently approved for treating advanced liver cancer, Patel says. He notes that several new agents are in development for the disease, but each affects just one or another of the many processes that are altered in liver cancer cells.

"We believe that targeting a certain type of tumor behavior might be helpful for liver cancer because many different biochemical pathways in tumor cells can be involved. Most targeted agents affect only one pathway, so a combination of drugs may be needed. Alternatively, new agents that hit multiple targets simultaneously could be used," he says.

Patel and his colleagues began their study by identifying the gene changes present in liver cancers that had invaded neighboring blood vessels.

The researchers then looked for agents that could reverse these changes as a group. They did this using a database called the connectivity map, a collection of data sets that offers a way to compare gene changes caused by a disease with gene changes caused by different chemicals or drugs.

"We queried the gene changes present in invasive liver cancer cells against the connectivity map and looked for compounds that had an opposite effect on these changes," Patel says. "If genes 'A, B and C' were increased in our tumor cells, we wanted to find an agent that decreased genes 'A, B and C'," he says.

Their search identified two compounds: Resveratol, a component of red wine that recently and coincidentally was shown by others to inhibit the ability of liver cancer cells to invade tissues and metastasize, and 17-allylamino-geldanamycin (17-AAG), which has shown anticancer activity in some solid tumors but has not been tested in liver cancer.

Last, the researchers used laboratory tests to verify that the two compounds actually did alter the invasive ability of liver cancer cells.

"This approach is exciting because it can be applied to any well-defined disease behavior," Patel says. "It might also improve the approach to drug discovery and design if some agents were modified to select for a particular genomic profile rather than a single chemical target.

"Overall," he says, "this could be a more relevant way of looking at cancer because we want to block certain disease changes and specific effects such as invasion, metastasis or chemotherapy resistance."

Source: Ohio State University Medical Center