Tumor mutations can predict chemo success

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(PhysOrg.com) -- New work by MIT cancer biologists shows that the interplay between two key genes that are often defective in tumors determines how cancer cells respond to chemotherapy.

The findings should have an immediate impact on cancer treatment, say Michael Hemann and Michael Yaffe, the two MIT biology professors who led the study. The work could help doctors predict what types of chemotherapy will be effective in a particular tumor, which would help tailor treatments to each patient.

"This isn't something that's going to take five years to do," says Yaffe, who, along with Hemann is a member of the David H. Koch Institute for Integrative Cancer Research at MIT. "You could begin doing this tomorrow."

The work could also guide the development of new chemotherapy drugs targeted to tumors with specific genetic mutations.

Hemann, Yaffe, and their colleagues report their results in the Aug. 15 issue of the journal *Genes and Development*. Koch Institute postdoctoral associates Hai Jiang and H. Christian Reinhardt are lead authors of the study, which the researchers say is one of the first examples of how genetic profiling of tumors can translate to improvements in patient treatment.

"There's a huge amount of genetic information available, but it hasn't made its way into clinical practice yet," says Hemann.

Genetic mystery

The research team focused on two proteins often involved in cancer, p53 and ATM. One of the first tumor suppressor genes discovered, p53 serves a watchdog function over a cell's genome, activating repair systems when DNA is damaged and initiating cell death if the damage is irreparable.

ATM is also involved in controlling the cell's response to DNA damage and is known to help regulate p53.

Mutations in p53, ATM or both are often seen in tumor cells. (ATM mutations occur in about 15 percent of cancers, and p53 is mutated in about 30 percent.)

Scientists have long tried to pin down a relationship between mutations in these genes and the effectiveness of DNA-damaging chemotherapy agents, but published studies have produced conflicting reports.

"It's been unclear whether the loss of p53 made tumors easier to treat or harder to treat. You could find examples of either case in the clinical literature," says Yaffe, adding that the same holds true for ATM.

The new study, conducted with human cancer cells, shows that tumors in which both p53 and ATM are defective are highly susceptible to chemotherapy agents that damage DNA. The double mutation prevents tumor cells from being able to repair DNA, and the cells commit suicide.

However, in cells where p53 is mutated but ATM is not, that type of chemotherapy is less effective. Remarkably, tumors where ATM is mutated but p53 is not turn out to be highly resistant to those types of chemotherapy.

With this new information, doctors could choose chemotherapy treatments based on the status of the p53 and ATM genes in a patient's tumor. Traditional DNA-damaging chemotherapy would be a good option for patients with both p53 and ATM mutations, but not for those with normal p53 and mutated ATM.

For patients who have normal ATM and mutated p53, other options might be better: New drugs that inhibit ATM, now in clinical trials, could improve tumors' susceptibility to chemotherapy in those patients.

The study shows the importance of studying cancer genes as a network, rather than trying to predict outcomes based on the status of single genes such as p53, says Robert Abraham, director of the cancer drug discovery program at Wyeth Pharmaceuticals.

Once ATM inhibitors are approved, "understanding the combined status of ATM and p53 should allow physicians to identify patients who should be treated with ATM inhibitors and chemotherapy and those for whom such a therapy could potentially be harmful," Abraham says.

In patients with normal p53 and mutated ATM, doctors could use drugs that target alternative DNA repair pathways. In their Genes and Development paper, the MIT researchers showed that treating such tumors with a drug that targets DNA-PK, another protein involved in DNA repair, renders them vulnerable to chemotherapy.

Source: Massachusetts Institute of Technology (news : web)