Why cancer drugs lose their power:
Platinum-based cancer drugs destroy tumor
cells by binding to DNA strands
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A 3-D model of a cisplatin molecule.

(PhysOrg.com) -- For 30 years, the chemotherapy
drug cisplatin has been one of doctors' first lines of
defense against tumors, especially those of the
lung, ovary and testes. While cisplatin is often
effective when first given, it has a major drawback:
Tumors can become resistant to the drug and start
growing again.

Now, MIT cancer biologists have shown how that
resistance arises, a finding that could help
researchers design new drugs that overcome
cisplatin resistance. The team, led by Tyler Jacks,
director of the David H. Koch Institute for
Integrative Cancer Research at MIT, reports the
results in the April 15 issue of the journal Genes
and Development.

Cisplatin and other platinum-based cancer drugs
destroy tumor cells by binding to DNA strands,
interfering with DNA replication. That activates the
cell's DNA repair mechanisms, but if the damage
is too extensive to be repaired, the cell undergoes
programmed suicide.

Eventually, cancer cells learn to fight back. The
new study shows that tumor cells treated with
cisplatin ramp up their DNA repair pathways,
allowing them to evade cell death, says Trudy
Oliver, a postdoctoral fellow in Jacks' lab and lead
author of the paper.

Previous studies had suggested several possible
mechanisms for resistance development, including
enhancement of DNA repair pathways,
detoxification of the drug, and changes in how the
drug is imported into or exported out of the cell.
However, those studies were done in cancer cells
grown in the lab, not in living animals (in vivo).

"Many mechanisms have been identified but it's
not clear what happens in vivo because the in vivo
environment is so much more complicated than in
cell lines," says Oliver.

Oliver and her colleagues set out to study cisplatin
resistance in mice with a mutation in a gene called
Kras, which leads the animals to develop lung
cancer. About 30 percent of human lung cancer
patients have mutations in Kras. Some of the mice
also had defective versions of the tumor suppressor
gene p53, which is mutated in about half of human
lung cancers.

The researchers found that cisplatin was effective
against lung tumors in both sets of mice, though it
was more potent in mice that still had functional
p53. In those mice, tumors actually shrunk, while
the drug only slowed tumor growth in mice with
defective p53. Those results are consistent with
findings in human patients.

After four doses of cisplatin, mice with normal p53
developed resistance to the drug, and tumors
started growing faster. To figure out why, the researchers analyzed which genes were being transcribed more as resistance developed, and identified several that are involved in DNA repair pathways.

One gene that particularly caught the researchers’ attention is PIDD (p53-induced protein with a death domain), which is turned on by p53 and has been implicated in programmed cell death, though its exact function is not known. When PIDD levels are artificially increased in human lung cancer cells, they become more resistant to cisplatin. Oliver is now studying tumors in which the PIDD gene has been knocked out, to see if its absence hinders drug resistance.

It is likely that PIDD is just one of many genes, in many pathways, involved in the drug resistance process, says Oliver. “It’s not a simple phenomenon,” she says.

The work was funded by the National Institutes of Health and the National Cancer Institute.

This study represents an important step toward better understanding of how cisplatin resistance arises, says Thomas Helleday, professor of radiation oncology at the University of Oxford, who was not involved in the research. Helleday describes the work as a “landmark” paper that “has important implications in the design of new drugs, which should be targeted to stop the repair that is activated in cisplatin-resistant tumors.”
