Drug kills cancer cells by restoring faulty tumor suppressor

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A new study describes a compound that selectively kills cancer cells by restoring the structure and function of one of the most commonly mutated proteins in human cancer, the "tumor suppressor" p53. The research, published by Cell Press in the May 15th issue of the journal *Cancer Cell*, uses a novel, computer based strategy to identify potential anti-cancer drugs, including one that targets the third most common p53 mutation in human cancer, p53-R175H. The number of new cancer patients harboring this mutation in the United States who would potentially benefit from this drug is estimated to be 30,000 annually.

P53 recognizes cellular stress and either puts the brakes on cell proliferation, or kills the cell if the damage is irreparable. The gene encoding p53 is mutated in over half of human cancers, and loss of p53 function has been linked to many aspects of cancer including aggressiveness, metastasis and poor response to chemotherapy and radiation. "Restoring the function of mutant p53 with a drug has long been recognized as an attractive cancer therapeutic strategy," explains senior study author, Dr. Darren R. Carpizo, from The Cancer Institute of New Jersey. "However, it has proven difficult to find compounds that restore the lost function of a defective tumor-suppressor."

Dr. Alexei Vazquez, a co-author of the study, developed a computer based screening method to identify compounds that target tumor cells with p53 mutations, but not cells with normal p53. The screening method was unique because it involved cancer cells with diverse genetic backgrounds, a model that recapitulates what is seen in actual human

cancers. This method identified several compounds that killed cancer cells containing mutant p53. One of the compounds did so by restoring the structure and function of the p53-R175H mutant. The researchers went on describe the details of the reactivation mechanism and showed that normal cells were not impacted by the compound.

In addition to identifying a compound for selectively restoring the function of the p53-R175H mutant, the findings also support the development of rationally targeted cancer therapies. "Anti-cancer drug development is moving in the direction of "personalized medicine" in which the drugs are chosen based on the molecular pathways that are deranged in an individual patient's tumor," concludes Dr. Carpizo. "Our findings support the growing trend in developmental therapeutics in which the efficacy of future cancer drugs will depend upon the knowledge of the patient's tumor genotype."

More information: Yu et al.: "Allele Specific p53 Mutant Reactivation." DOI:10.1016/j.ccr.2012.03.042

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