How do cancers become resistant to chemotherapy?

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Genetic mutations in cancer cells can lead to resistance to treatment, thereby potentially resulting in relapse. However, a new article, published April 3 in the magazine section of the online, open-access journal *PLoS Biology*, suggests that the converse may also happen. Steven Frank from the University of California, Irvine, and Marsha Rosner from the University of Chicago, propose that it may often be the case that a few cells become resistant before any genetic change, and then later acquire the genes to stabilize that resistance.

Why does it matter whether resistance comes before genetic mutations, or vice versa? Because the effectiveness of treatment depends primarily on preventing resistance. If, as is the current view, genetic mutations occur first and then spread to cause resistance, then treatment protocols must focus on preventing the origination of cancer cells with the particular set of mutations that cause this resistance. Widely used combination therapies are designed specifically to limit the chance that a cancer cell can develop the suite of mutations necessary for resistance.

Frank and Rosner argue that a few cells may often become resistant before they get specific genetic mutations. Such non-genetic resistance may occur through the random variation in cellular characteristics that has been widely observed among genetically identical cells. Alternatively, non-genetic resistance may occur when cells change (essentially reprogram) their characteristics in response to the stress of moving into new tissues, or dealing with toxic drugs. Cells are known to have many flexible programs of expression in response to a change in

their environment. If cells first become resistant by either non-genetic randomness or flexibility, then those resistant cells can later acquire genetic changes to stabilize their resistance. Such a progression that starts with non-genetic resistance necessarily alters one's ideas as to how to design combinations of drugs aimed at preventing relapse.

The idea that non-genetic resistance comes first is not entirely new. But the small amount of existing evidence has not led to a change in how people view the issue. This new article aims to bring this perspective to a wider group of researchers by combining the evidence from prior studies with a clear understanding of the evolutionary theory by which populations adapt to extreme challenges. New studies, designed in the light of how evolution might occur in cancers, will show whether alternative approaches to treatment can improve outcomes.

More information: Frank SA, Rosner MR (2012) Nonheritable Cellular Variability Accelerates the Evolutionary Processes of Cancer. PLoS Biol 10(4): e1001296. doi:10.1371/journal.pbio.1001296

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