Distinguishing Friend from Foe in the Battle Against Cancer

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The latest generation of cancer chemotherapeutic drugs specifically targets mutant enzymes or “oncoproteins” that have run amok and now promote uncontrolled cell growth. As promising as these drugs are, cancer cells with their backs against the wall have the tendency to fight back. A major goal of cancer research is to frustrate these acts of cellular desperation.

In a forthcoming issue of *Cancer Cell*, investigators at the Salk Institute for Biological Studies uncover one means cancer cells use to stay alive and in doing so suggest a strategy to overcome their recalcitrance. The study, led by Tony Hunter, Ph.D., in collaboration with Inder Verma, Ph.D., shows that resistance to the chemotherapeutic drug rapamycin is mediated by the survival factor NF-kB.

Rapamycin, like the pharmaceutical superstar Gleevec, which revolutionized the treatment of chronic myelogenous leukemia, is a so-called signal transduction inhibitor or STI, a small molecule that stifles inappropriate growth signals sent by mutant proteins in cancer cells. STIs may look like overnight successes, but they are actually the result of decades of hard work.

“We have been working for 35 years looking at mechanisms underlying formation of cancer cells,” says Hunter, an American Cancer Society professor in the Molecular and Cell Biology Laboratory. “We've made huge progress identifying specific events that change normal proteins into proteins that cause cancer and developing drugs that target those

proteins. This work provides another potential direct target for development of cancer drugs."

The Hunter lab previously showed that mouse cells lacking tumor suppressors known as TSC genes are more susceptible to the lethal effects of chemotherapeutic agents than are normal cells. Why cells from these TSC null mice were so poorly equipped to survive was not entirely clear.

Co-lead authors Sourav Ghosh, Ph.D., and Vinay Tergaonkar, Ph.D., postdoctoral fellows in the respective Hunter and Verma labs moved those mouse studies to the next level by tinkering with TSC activity in human cancer cells. Says Ghosh, "We were able to extend this model based on TSC null cells to different human cancer cell lines, where we knocked down TSC expression and showed that the same pattern held true."

Specifically, the team found that human cells lacking TSC genes were vulnerable to chemotherapeutic attack because they couldn't activate a major line of defense mediated by the Nuclear Factor kappa B, known as NF-kB, which triggers both inflammatory and survival responses by inducing transcription of specific genes.

Not only did this explain why TSC null cells are vulnerable to insult, but it also provided biochemical evidence that there is crosstalk between two survival mechanisms. Explains Tergaonkar, who is now an assistant professor at the Institute for Molecular and Cell Biology (IMCB) in Singapore, "Our findings show for the first time that the TSC complex can regulate the NF-kB signaling cascade."

The experiments also explained a paradox: TSC null cells treated with rapamycin actually survived cellular insult better than untreated cells-a highly inauspicious outcome if the goal is to kill cancer cells. The Hunter

and Verma team found that rapamycin did that by increasing NF-kB activity in the TSC null cells when they were exposed to chemotherapeutic drugs.

Rapamycin, an immunosuppressant used to block organ rejection after transplants, also inactivates proteins stimulating cell division and in clinical trials has been combined with other drugs to halt cancer cell growth.

But to cancer cells, rapamycin is both friend and foe. “Rapamycin is not as successful as initially expected in treating cancer,” explains Ghosh. “Instead of killing cells, you end up triggering a survival response in them.” This study, however, suggests that taking NF-kB out of the game would make rapamycin less “friendly.”

“A major problem of chemotherapy is that sooner or later cancer cells develop resistance, which requires higher and higher doses of chemotherapeutics,” observes Verma, who is also an American Cancer Society professor in Salk's Laboratory of Genetics. “Rapamycin-mediated killing of cancer cells could be increased by inhibiting the function of NF-kB proteins. Our studies provide the basis for arriving at this very important conclusion, which has enormous bearing on cancer treatment.”

Tergaonkar concurs. “Our studies suggest the potential use of NF-kB signaling inhibitors as adjuvants to maximize the effect of rapamycin-based therapeutics. These findings will have a significant impact on human health.”

Also contributing to the study are Salk postdoctoral fellows Carla Rothlin, Ph.D., Ricardo Correa, Ph.D., and Virginie Bottero, Ph.D., and Pradeep Bist, Ph.D., an IMCB postdoctoral fellow in Singapore.

Source: Salk Institute for Biological Studies