New cancer drug screening technique more closely mirrors reality

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Improving on traditional screening tests for potential anti-cancer drugs, scientists at Dana-Farber Cancer Institute have developed a laboratory technique that more closely simulates the real-world conditions in which tumor cells mingle with the body's normal cells.

Because these neighboring cells - key components of what is known as the "tumor microenvironment" - can alter the effectiveness of anti-cancer drugs, the new technique may help researchers narrow the field of possible therapies more quickly and identify the most promising candidates more readily. The technique, described in a study published online today by the journal *Nature Medicine,* can be used to study a wide variety of cancer cells that infiltrate an equally wide range of normal tissues, the authors say.

"Despite their often impressive results in the laboratory, for every 100 potential anti-cancer therapies administered in patients in clinical trials, only about eight prove safe and effective enough to receive Food and Drug Administration approval," says the study's senior author, Constantine Mitsiades, MD, PhD, of Dana-Farber. "This success rate is clearly not as high as we would like it to be, and one reason may be that so far we haven't had a good way to account, at the earliest stages of laboratory testing, for the impact of the tumor microenvironment on these drugs."

In conventional drug screenings, different types of cancer cells are exposed to hundreds or thousands of compounds under laboratory

conditions in which only tumor cells are present. The compounds that prove best at killing tumor cells are then earmarked for further study.

A shortcoming of this approach, Mitsiades says, is that "in the human body, tumor cells don't grow in isolation, but come in contact with a wide variety of non-malignant cells. Many of these 'accessory' cells support one another through direct contact or by producing substances known as growth factors. Tumor cells can take advantage of these signals to fuel their own growth."

Evidence from a variety of studies suggests that these otherwise normal elements of the tumor microenvironment can impede the effectiveness of anti-cancer drugs and allow cancer to become resistant to different therapies - one of the biggest challenges in oncology.

To get a better understanding of this phenomenon and develop treatments to address it, Mitsiades and his colleagues developed a technique in which tumor and normal cells are "co-cultured" - that is, grown together - and exposed to hundreds or thousands of compounds in large-scale screening tests. In the technique, dubbed "cell-specific in vitro bioluminescence imaging," or CS-BLI, the cancer cells in each sample are equipped with a gene that makes them glow - a process unaffected by the normal cells nearby. By measuring the amount of light emitted by each sample after treatment, investigators can determine which compounds are most proficient at killing tumor cells, and whether this effectiveness changes when normal cells are around the tumor. (To make sure the candidate drugs aren't also killing normal cells, researchers can do a "counter-screen," in which they measure the effect of each compound on the normal cells.)

While there are other techniques for screening drug activity in co-cultures of malignant and normal cells, they either involve radioactivity or entail a time-consuming process of data capture and analysis,

rendering them too cumbersome for large-scale studies, Mitsiades remarks.

With CS-BLI, Mitsiades and his colleagues have identified numerous compounds that acted powerfully against isolated samples of tumor cells but were significantly less effective against the same types of tumor cells co-cultured with non-malignant cells. Perhaps surprisingly, they also identified some compounds which are more effective against tumor cells mixed with non-malignant cells than against tumor cells alone.

In this latter category, researchers found a particular compound that was more active against myeloma tumor cells, both in laboratory cultures and mice, when the cells were in contact with healthy cells of the bone marrow - their usual location in patients. The compound also prevented the myeloma cells from responding to growth signals produced by the bone marrow cells. With conventional techniques, candidate drugs such as this one would have gone completely unnoticed, Mitsiades observes.

He emphasizes that CS-BLI is not a technique for predicting which anti-cancer agents will be effective in individual patients, but can help researchers identify which agents are the best prospects for additional investigation.

"It will be of use in prioritizing candidate drugs for further rigorous study of their properties before embarking on clinical trials," he remarks. "This technique may show that the classical methods of studying candidate cancer drugs in laboratory conditions have overestimated the effectiveness of some agents, and underestimated others.

"The technique also provides a powerful tool for determining which biological mechanisms allow cancers to become resistant to certain treatments and which new therapies can neutralize those mechanisms.

Hopefully, combining such new therapies with other, established or investigational, treatments may contribute to improved success rates of clinical trials."

Provided by Dana-Farber Cancer Institute