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How chemo kills tumours: research to reduce side effects

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(PhysOrg.com) -- University of Manchester researchers are investigating exactly how chemotherapy drugs kill cancerous tumours in a bid to reduce side effects and test the effectiveness of safer new agents.

Dr Stephen Taylor and Karen Gascoigne at the University's Faculty of Life Sciences have taken a new systematic approach to studying anti-mitotic drugs, which are used extensively for breast or ovarian cancer in the UK.

This class of drugs, which includes the agent taxol, has been used clinically for many years because they are highly effective. However, as in all chemotherapy, there are side effects. In the case of taxol these include peripheral neuropathies which can lead to permanent nerve damage and loss of sensation in fingers.

In addition little is known about how anti-mitotic drugs work, despite a lot of research on them, because many studies were population-based approaches that were indirect and led to vague and confusing interpretations.

Dr Taylor said: "To bypass the neurotoxicity, new anti-mitotics are being generated. Early clinical studies show that these drugs do not result in significant neurotoxicity. The big question now is whether they will have anti-tumour effects.

"To help determine this, we need to know which types of tumours are

likely to be sensitive to these new agents, and which ones are likely to be resistant. This would allow clinicians to better design the clinical trials, i.e. you only recruit patients who are likely to respond. In addition, if the drugs show promise, then it would pave the way for patient stratification in the future, again allowing oncologists to identify which patients are likely to benefit from these drugs in advance of treatment.

“To predict which types of tumours are likely to respond, we first need to know how anti-mitotic drugs work, both the classical drugs and these new agents.”

He and Ms Gascoigne, whose findings are published in the journal Cancer Cell (August 2008), have shown how different tumours respond to the anti-mitotic drugs – which target the mitotic spindle (the structure that separates the chromosomes during cell division) – and revealed that the variation in cell behaviour was far greater than previously recognized.

They used a high throughput automated time-lapse light microscopy approach to systematically analyze over 10,000 single cells from 15 cell lines in response to three different classes of anti-mitotic drug. This revealed the large variation in cell behavior with cells within any given line exhibiting multiple fates.

Dr Taylor explained: “We know that anti-mitotic drugs block the final stage of the cell division process, mitosis. How the cells then die is a mystery.

“We embarked on a fresh, more direct approach that is actually quite simple. Basically, we just watched the cells using time-lapse microscopy; this allowed us to track the behaviour of individual cells and determine their fate when exposed to different anti-mitotic drugs.

“The first thing we realised was that the picture was much more complicated that we originally thought; the range of different behaviours was profound. Not only did cells from different cell lines behave differently, but cells within the same line also behaved differently.

“The level of complexity was at first overwhelming. However, as we slowly made our way through the data, patterns began to emerge. This allowed us to formulate a new hypothesis. We were then able to design more experiments to test this hypothesis.

“In essence, it turns out that when cells are exposed to these drugs they arrest in mitosis. Then a race starts between two competing cellular signalling networks. One network is trying to kill the cell, the other is trying to cause the cell to exit mitosis and thus allow the cell to survive. The winner of the race decides the fate of the cell; death or survival.

“The factors influencing the race not only vary from cell line to cell line, but also within cells from the same line, explaining why there is so much complexity.

“What we want to do now is figure out how we can help the cell death pathway win the race more often; this would hopefully mean that the anti-mitotic drugs would be better at killing cancer cells. First we want to test this idea in the lab but hopefully in the longer run this will mean that these drugs can be used more effectively in the clinic.”

He added: “Karen, a talented graduate student, worked very hard on this study and the work was only possible because the Faculty recently bought a fully automated microscope that allowed us to analyse such large numbers of cells. We acquired this state-of-the-art microscope thanks to the University’s Strategic Research Fund, which demonstrates the University’s commitment to cancer research.

“Our systematic, single-cell-based approach to describe how different tumour cells respond to these drugs has given a data set that provides an invaluable resource and an intellectual framework for dissecting how anti-mitotic agents kill tumour cells.”

Provided by University of Manchester