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Jan 18th 2007

From The Economist print edition

An old observation about cancer cells may lead to a new treatment

CANCER cells manage their energy production in a most peculiar way. A healthy cell relies on its mitochondria (descendants of bacteria that took up residence in the single-celled ancestors of animals and plants about 2 billion years ago) to oxidise sugar molecules and release useful energy. Most cancer cells, however, use a less efficient mechanism called glycolysis to power themselves. They thus cut their mitochondria out of the loop.

That cancer cells often rely on glycolysis was discovered by Otto Warburg in 1930. But until recently the Warburg effect, as it has come to be known, was little more than a curiosity—and a contentious one at that. Now, it looks a lot more interesting, for Evangelos Michelakis and his colleagues at the University of Alberta, in Canada, are testing a drug called dichloroacetate that suppresses the Warburg effect and reactivates the mitochondria. The result shows why mitochondrial suppression is so important to tumours: when they are unsuppressed, the tumour they are in stops growing.

At first sight, this is all terribly paradoxical. Cancer cells multiply rapidly—and such multiplication requires a lot of energy. Normally, glycolysis is merely the prelude to energy production. It breaks glucose down into molecules called pyruvate that are fed to the mitochondria for processing. This breakdown yields some energy, but not much. However, it does not require oxygen—a substance that cancer cells are frequently deprived of, as tumours often fail to develop the blood vessels needed to supply it.

Cancer cells seem to adjust so well to glycolysis that even if blood vessels do grow into a tumour and the oxygen thus returns, they stick with it. From the cancer's point of view that is a very good choice, as one of the other jobs of the mitochondria is to kill a cell if it goes bad—a process known as apoptosis.

The role of dichloroacetate is to re-activate the mitochondria by stimulating an enzyme that feeds pyruvate into their energy-generating cycle. (The drug is already tested and approved for the treatment of certain mitochondrial diseases.) It seems this reactivation also allows the mitochondria to stimulate apoptosis.

At least, that is what Dr Michelakis thinks is going on. His results are certainly reminiscent of those obtained last year by Valeria Fantin and Philip Leder of Harvard Medical School. Dr Fantin and Dr Leder used a trick called RNA interference to modify glycolysis in the tumours of some specially bred laboratory mice.

If too much pyruvate is being made, the surplus is normally turned into lactic acid. (Athletes whose muscles demand more energy than their mitochondria can deliver suffer from a build-up of lactic acid as their glycolytic pathways go into overdrive. It is this build-up that causes cramp.) The RNA interference employed by Dr Fantin and Dr Leder stops the conversion of pyruvate into lactic acid, causing it to build up. Their hope was that, overwhelmed with pyruvate, the mitochondria would be forced to respond.

And respond they did. Apoptosis shot up in the treated animals. Dr Fantin and Dr Leder also observed a marked decline in tumour growth rates. The survival rate of animals went up, too. None of the members of an untreated control group survived the four-month period over which the experiment was conducted. By contrast, 80% of the treated animals survived.

RNA interference is the subject of eager investigation among pharmaceutical companies, but so far it has yet to yield a drug approved by the regulators. Dichloroacetate, by contrast, is already employed for other purposes. That does not mean it will work as an anti-cancer agent in the real world, of course. But it does give it a head start. And even if dichloroacetate itself does not work, Dr Michelakis's study points towards a new approach to stopping cancer in its tracks.

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