Tea: a rich brew of anti-cancer magic bullets?

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Recent research has demonstrated that several of the polyphenols found in black tea are able to selectively destroy cancer cells. One compound in particular has been singled out as having outstanding potential for future therapeutic development. Kuang Yu Chen (Rutgers University, Piscataway, NJ, USA) told delegates at the *222nd National Meeting of the American Chemical Society* (27–29 August 2001, Chicago, IL, USA) that *in vitro* experiments had demonstrated TF-2, which is a mixture of theaflavin-3-monogallate and theaflavin-3′-monogallate, inhibited the growth of virally-transformed human lung cells and cancer cells from a colon-cancer cell line. However, the compound had no effect on normal, non-cancerous cells, even at high concentrations[1].

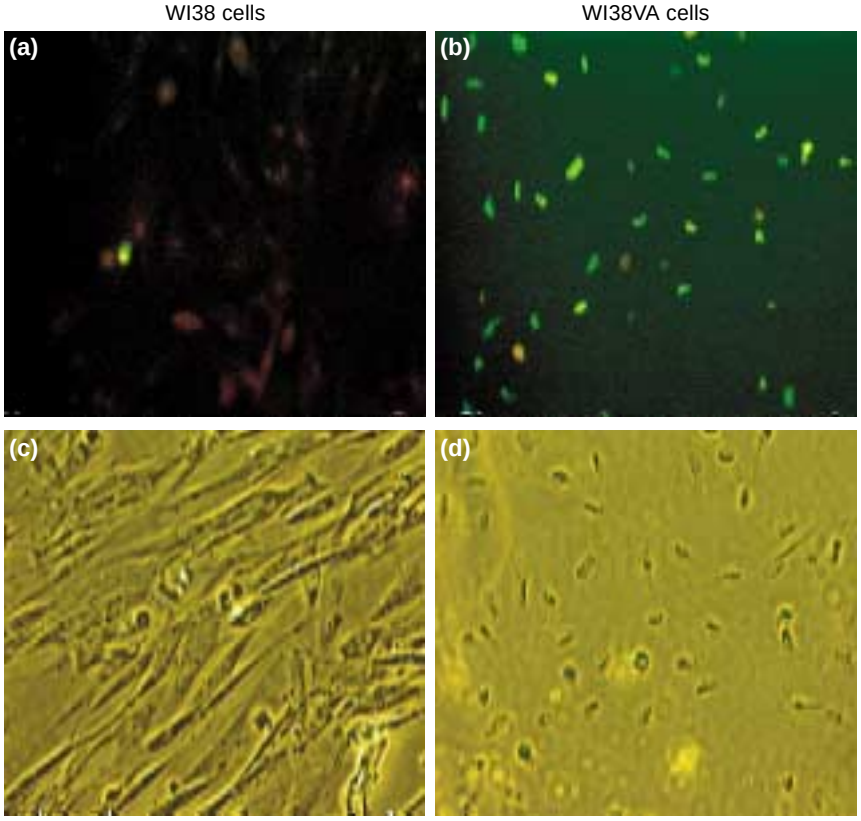

Figure 1. This experiment illustrates the TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling) assay of the effect of TF-2 on apoptosis. **(a)** and **(b)** are normal human cells (WI38) treated with TF-2 (100 μM) for 18 h. **(a)** shows apoptotic cells (green fluorescence caused by incorporation of fluorescein-12-dUTP) and **(b)** shows the phase contrast microscopic picture of the identical field of normal cells. **(c)** and **(d)** show transformed human cells (WI38VA cells) after the treatment of TF-2. Both **(c)** and **(d)** are of the same microscopic field. The contrast of differential apoptotic effect is clear [**(c)** versus **(a)**].

But why tea?

'We did not start out to study tea specifically', explains Chen, 'even though epidemiological studies and animal studies do suggest strongly that green and black tea can lower the risk of various forms of cancer.' Instead the research of Chen and colleagues involved an intensive search for food components that can kill cancer cells but not their normal counterparts. Screening hundreds of food substances revealed that black and green tea were both rich sources of some very interesting compounds. 'Among them, we have green tea epigallocatechin gallate (EGCG) and black tea theaflavin-3'-monogallates (TF-2), which both inhibit human cancer-cell growth while having little or no effect on normal human cells at the same or even higher dosage,' explains Chen. Such compounds, and their synthetic derivatives, have molecular scaffolds to which the human body has been exposed for thousands of years and Chen predicts that they could be far less toxic than many of the chemotherapeutic agents in use today.

TF-2 and its anti-inflammatory potential

TF-2 caused inhibition of growth in transformed and cancerous cells partly by inducing apoptosis (Fig. 1). The exact mechanism involved is still the subject of current research but, because TF-2 did not induce any apoptosis in normal cells, it seems probable that TF-2 could target components involved only in the apoptotic pathways in cancerous cells. 'TF-2

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also inhibits expression of the *COX-2* gene[2]; the connection between *COX-2* gene activation and certain cancers, particularly colon cancer, is well-established[3] and this gene is also known to play an important role in the pathology of inflammation,' points out Chen. He predicts that the identification of this and other anti-inflammatory components in food substances could lead to the design of a rational diet for dealing with inflammation-related diseases. These compounds are also good starting points from which to design more effective anti-inflammatory drugs for treating inflammation-related diseases. As Chen points out, the market for non-steroidal anti-inflammatory drugs is huge (worth US$1.9 billion in 1997 in the USA), which is why Wall Street estimated that the worldwide sale of the first licensed *COX-2* inhibitors could reach US$1–3 billion annually[4].

Chemotherapy and chemoprevention

In addition to its possible anti-inflammatory action, TF-2 could have the potential as a chemopreventive agent for use in high risk groups, or to prevent secondary cancers. It would be particularly attractive to consider the compounds that show anti-*COX-2* activity as potential treatments for colon cancer. A direct link between *COX-2* expression and colon cancer has been demonstrated in APC knockout mice[5], suggesting that expression of this gene is one of the steps involved in colon cancer formation. Surgery is currently the main treatment for colon cancer but is curative in only 50% of patients. This 50% tend to have localized disease, whereas patients who have developed metastasis receive follow-up chemotherapy and radiotherapy, which is where drugs based on TF-2 could be targeted.

Zhen-Yu Chen of the Department of Biochemistry at the Chinese University of Hong Kong (Hong Kong, China), whose group has been investigating the antioxidant properties of black tea theaflavins[6], says that the work of the Rutgers group is highly regarded. 'The data from cancer cell lines and animal experiments are very consistent, showing that both green tea catechin and black tea TFs (a mixture of TF-1, TF-2A, TF-2B, and TF-3) have an inhibitory effect on tumour cells,' he says. However, he agrees with Kuang Yu Chen that much work, including well-planned clinical trials, is required to show that TF-2 might prevent cancers.

Kuang Yu Chen reports that plans are already in place for a future collaborative project with Steven Shiff, Director of the Unilever Center for the Study of Diet and Nutrition in the prevention of Chronic Disease (The Cancer Institute of New Jersey, New Brunswick, NJ, USA). In the meantime, the group is continuing the necessary preclinical work. 'For TF-2, we have initiated global gene screening to examine which genes are targeted by TF-2 in the transformed cell. We are also studying the mechanism by which TF-2 suppresses *COX-2* gene expression, but these studies are still at a preliminary stage,' says Chen.

From tea leaves to grape skins and beyond

Kuang Yu Chen's group has also investigated the properties of reserveratrol, a trihydroxystilbene found in the skin of black grapes, and also in peanuts and pine nuts. 'The potential of reserveratrol was there, but we felt it could be improved upon, so, using this as a prototype, we synthesized several polyhydroxy- and polymethoxy-stilbenes and tested their anti-proliferative effect in normal and transformed human cells,' reports Chen. One of the analogues, 3,4,5,4′-tetrahydroxystilbene (R-4) differentially inhibited the growth of SV40-transformed lung fibroblast cells, by inducing them to apoptose[7]. 'R-4 appears to cause apoptosis by a p53-dependent pathway; transformed cells treated with R-4 showed a significant increase in *p53* gene expression and also in expression of *Bax*, a pro-apoptotic gene,' explains Chen. Also, like TF-2, R-4 suppressed the expression of the *COX-2* gene in the transformed cells[7].

Looking to the future, Chen hopes that the most promising compounds will eventually enter clinical trials. 'A major problem that we need to start solving now is the need to produce large quantities of these compounds – clinical trials will not be possible until we can do that, no matter how good the results of our preclinical work,' says Chen.

References

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