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Editorial Comment

One of the most interesting areas of current research in human molecular oncology is the mechanisms by which cells die in a process called apoptosis. Alterations in these pathways represent a crucial hallmark of many malignant tumours.

While basic research efforts are targeted at trying to elucidate different cell death pathways and at the identification and characterisation of the pro-apoptotic and anti-apoptotic proteins, there are attempts to exploit this knowledge for therapeutic purposes.

One of the most interesting pro-apoptotic proteins recently identified is the TNF-related apoptosis-inducing ligand (TRAIL). This protein is a member of the tumour necrosis factor (TNF) superfamily and appears to selectively induce cancer cells, but not normal cells, to undergo apoptosis. This selective activity has been observed in cancer cells growing in culture and also in preclinical animal systems. There is thus great interest in this molecule and early clinical investigations are now underway.

Since the precise determinants of the sensitivity to TRAIL are not yet fully elucidated, much of the current research is aimed at understanding whether and when TRAIL can be potentially effective against cancer. The induction of apoptosis can be of relevance in determining the clinical response to chemotherapy. Therefore, it seems logical to question whether the activity of TRAIL can synergise with the activity of other cytotoxic agents by increasing the amount of apoptosis.

In this issue, two papers provide experimental preclinical evidence that supports the potential therapeutic value of this approach. Mizutani and colleagues report that TRAIL shows a synergistic activity with 5-fluorouracil (5-FU) in the renal carcinoma cell line Caki-1. Moreover, even more interestingly, they found that TRAIL treatment could counteract the resistance of freshly isolated human renal carcinoma cells to 5-FU. In the second report, Vignati and colleagues show that some human ovarian cancer cells are intrinsically sensitive to TRAIL, whereas others are not. However, of note, they showed in cell lines in which TRAIL alone was not effective that the addition of TRAIL was able to increase the sensitivity of these cells to paclitaxel and cisplatin treatments by enhancing the apoptotic response.

If this sensitivity of cancer cells to TRAIL observed in preclinical systems is confirmed in clinical studies, the possibility of significantly increasing the efficacy of cancer chemotherapy by combining TRAIL with anticancer drugs appears to be a very attractive strategy, particularly for resistant tumours.

However, experienced cancer pharmacologists know how difficult it is to successfully translate results obtained in preclinical experimental models into clinical practice. In this issue, Zuzak and colleagues indicate that in childhood primitive neuroectodermal brain tumours (PTEN), the TRAIL pathway may not lead to apoptosis because of the loss of *caspase 8* gene expression, due to aberrant promoter methylation. This reminds us of the need to focus on specific, well characterised neoplastic diseases which provide the molecular features required for the response.

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