Urol Res (1999) 27:1–2


INVITED EDITORIAL

Christine M. Chresta · John A. Hickman

# Apoptosis: its relevance to carcinogenesis and anti-tumour drug sensitivity

Received: 3 July 1997 / Accepted: 11 June 1998

## Apoptosis: one of the "A" words

Why are the fields of apoptosis and angiogenesis so hot at present? Because both address absolutely fundamental aspects of tumour development. Understanding how cells can survive with a damaged genome, without undergoing apoptosis, and how they develop a new blood supply, goes to the heart of the disease. Progress towards selective therapies will only be made when drugs are selectively targeted to fundamental events which underlie the pathology of a tumour. The relevance of apoptosis to both carcinogenesis and chemotherapy is that in both there is a failure to delete damaged cells; in carcinogenesis after genomic damage, in chemotherapy after a variety of perturbations, including genomic damage. Apoptosis, a type of "programmed cell death", is a cellular *response* to damage. Deletion of a damaged cell may be preferential to allowing it to survive with the potential for further divisions, amplifying the damaged population. Interestingly, different cell types have different thresholds for the engagement of this response to damage: some cells die more readily than others after the same amounts of genomic damage. Understanding the molecular determinants of these thresholds lies at the centre of understanding how to kill tumours selectively. Not surprisingly, there are a number of players involved in promoting cell survival and suppressing apoptosis. How many is not certain. Is it a handful of players or is it well into double figures? This is an important question for which we need an answer. It has become dogma that there need only be a limited number of events to initiate a tumour: one of these has to be that making it permissive to survive the progressive genomic damage characteristic of tumour progression.

C. M. Chresta (✉) · J. A. Hickman
Cancer Research Campaign Molecular and Cellular Chemotherapy Group, School of Biological Sciences, G.38, Stopford Building, The University of Manchester, Manchester M13 9PT, U.K.

## Thresholds

In an excellent recent review of the role of the aspartate proteases (caspases) in the biochemistry of apoptosis, Salvesen and Dixit [6] proposed the existence of an "apostat", a conceptual organelle-like complex in which cellular decisions of life and death were taken. Signals would be received by the apopstat from sensors of cellular damage, such as p53 from DNA damage, as well as signals promoting survival, such as those coming from insulin-like growth factor-1. These would be weighed, one against the other, and cell fate determined. Integral to such an apopstat would also be molecules of the bcl-2 family, some of which promote survival (bcl-2, bcl-w, bcl-$x_L$), others which promote death by apoptosis (bax, bak, bad) [reviewed in 5]. Essentially, the stoichiometry of pro- and anti-apoptotic molecules, perhaps integrated with survival signals through the activity of molecules such as bad, together set the threshold of survival of a particular cell type. Since some cells would be easier to kill than others then perhaps this contributes to an understanding of why some cell types are likely to be more cancer prone than others – they sustain DNA damage without dying.

## Apoptosis in therapy: lessons from the chemosensitive tumours

Several early onset tumours such as testicular germ cell cancer (TGCT) respond well to therapy even at an advanced stage. Recent evidence suggests that this may be because they have an unusually low DNA damage threshold for drug-induced cell death [1]. The same level of drug-induced damage can result in up to 10-fold higher loss of viability in a sensitive testis tumour compared with a resistant tumour type, such as transitional cell carcinoma of the bladder (TCC). We also showed that TGCT has a relatively high expression of apoptosis promoters (bax and bak) compared with in-

hibitors (bcl-2 and bcl-XL), whereas relatively resistant bladder carcinoma cell lines showed strong expression of bcl-2 [1] and of other members of the apoptosis suppressors (unpublished). Several investigators are now attempting to modulate the expression of genes in the inherently resistant carcinomas so as to reduce survival thresholds and render them sensitive to drugs. One of the key players is the tumour suppressor gene p53.

## p53 and the responses to therapy: a controversy?

The influence of p53 on drug sensitivity depends very much on the cellular context in which p53 is activated [reviewed in 3]. In some cellular contexts the p53-dependent expression of the $G_1$/S cell cycle checkpoint protein $p21^{waf\text{-}1/cip\text{-}1}$ leads to a permanent withdrawal from the cell cycle, into a state resembling senescence. In other contexts the activity of $p21^{waf\text{-}1/cip\text{-}1}$ is transient, providing the damaged cell with time to restore sufficient genomic integrity to re-enter the cell cycle, particularly if GADD45 is also upregulated, as this contributes to repair. In yet other contexts, moderate levels of p53 expression promote a cell cycle checkpoint. High levels of p53 promote apoptosis. Thus, when the p53 status of different tumour types is compared, it is not surprising that the data on p53 and outcome *appear* to be controversial. They may not really be controversial but instead reflect the contextual differences outlined above. So, in several of the inherently resistant human carcinomas, such as the bladder, lack of functional p53 has been demonstrated to have negligible effect on sensitivity to DNA strand break-inducing agents. Loss of p53 may actually increases sensitivity to DNA damaging agents and to taxol – presumably because p53 provides a ''checkpoint'' permitting repair and survival in this context. This may explain why these agents show some activity against tumour types with a high frequency of mutations in p53 [2]. The different outcomes from the activation of p53 may also explain why, in in vitro experiments, measurement of apoptosis does not always correlate with loss of clonogenicity; the latter will also occur if cells are blocked in their cell cycle. Understanding the determinants of transient arrest versus apoptosis will be critical for rational therapies involving reactivation of p53 activity; a prolonged arrest, even without apoptosis, is of course a satisfactory outcome of therapy.

## Bcl-2 family proteins: central players of the apopstat

The idea of a cellular ''rheostat'' for the determination of a survival/death threshold set by the ratios of expression of the members of the pro- and anti-apoptotic bcl-2 family is seductive [reviewed in 5]. The nature of their interactions, which together act to set the ''apopstat'', described above, is unknown. The role of bcl-2 as a determinant of radio- and chemosensitivity has again been somewhat controversial, both in clinical and laboratory studies. In prostrate cancer a high level of bcl-2 is a marker of a poor prognosis [4]. However, the fact that bcl-2 expression alone is not always a good predictor of chemosensitivity is not surprising: bcl-2 is only one member of a rapidly expanding family of related, interacting proteins which show tissue specificity in expression and probably some redundancy in function. In addition, the activity of bcl-2 and related proteins is affected by extracellular survival signals, postranslational modification and by interaction with other proteins. This was demonstrated in the in vitro studies of Walker et al. [7] where it was shown that simple overexpression of bcl-2 merely delayed the onset of chlorambucil-induced death in Burkitts lymphoma cells. However, when the in vivo environment of the B cell (the germinal centre) was mimicked in vitro, then bcl-2 provided a significant long-term survival advantage.

## Tough tissues give rise to tough tumours

The excitement about apoptosis comes from an understanding that carcinogenesis requires that cells accumulate genomic damage without initiating an apoptotic death. Once these mechanisms for survival are in place it may be difficult to kill them by imposing further genomic damage, leastwise not without imposing considerable toxicity on normal tissues since these normal cells are still able to delete themselves after DNA damage. Finding the determinants of the threshold that sets the high survival potential of tumours is a critical quest in the search for inroads to promoting the selective death of tumour cells.

## References


1. Chresta CM, Masters JRW, Hickman JA (1996) Hypersensitivity of human testicular tumors to etoposide-induced apoptosis is associated with functional p53 and a high Bax to Bcl-2 ratio. Cancer Res 56:1834
2. Cote RJ, Esrig D, Groshen S, Jones PA, Skinner DG (1997) p53 and treatment of bladder cancer. Nature 385:123
3. Levine AJ (1997) p53, the cellular gatekeeper for growth and division. Cell 88:323
4. McDonnell TJ, Troncoso P, Brisbay SM, Logothesis C, Chung LW, Hsieh JT, Tu SM, Campbell ML (1992) Expression of the proto-oncogene bcl-2 in the prostate and its association with the emergence of androgen-independent prostate cancer. Cancer Res 52:6940
5. Reed JC (1997) Bcl-2 family proteins: strategies for overcoming chemoresistance in cancer. Adv Pharmacol 41:501
6. Salvesen GS, Dixit VM (1997) Caspases: intracellular signaling by proteolysis. Cell 91:443
7. Walker A, Taylor ST, Hickman JA, Dive C (1997) Germinal centre derived signals act with bcl-2 to decrease apoptosis and increase clonogenicity of drug-treated human B lymphoma cells. Cancer Res 57:1939