SYMPOSIUM OVERVIEW

Perturbation of the Mitosis/Apoptosis Balance: A Fundamental Mechanism in Toxicology

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Received May 27, 1997; accepted May 29, 1997


Perturbations of the balance between cell gain via mitosis and cell loss by apoptosis play a pivotal role in mediating and modifying the action of carcinogens and other toxicants in tissues such as liver, brain, the immune system, the gastrointestinal tract, and the reproductive organs. Apoptosis describes a highly conserved morphology associated with the death of many different cell types from diverse tissues. This symposium focused on induced changes in this critical balance as a key mechanism of action of a variety of diverse toxicants. In the colon, the "toxicology" of 5 fluorouracil (5FU) is entirely dependent on p53, since p53 knockouts lose the pathology of 5FU damage. Presumably, this is because DNA damage is not detected and there is no cell cycle arrest. In the testes, testicular germ cell survival is mediated by adjacent Sertoli cells via the Fas ligand (FasL)–Fas receptor (Fas) system. This system appears to mediate germ cell apoptosis after exposure to testicular toxicants such as the phthalate, mono(2-ethylhexyl) phthalate (MEHP). Interestingly, MEHP is a member of the peroxisome proliferator (PP) class of nongenotoxic carcinogens. PPs perturb both hepatocyte apoptosis and mitosis. This suppression of apoptosis occurs via activation of the peroxisome proliferator-activated receptor α (PPARα), providing a paradigm for the regulation of liver growth via activation of nuclear receptors. Similarly, the toxicological effects of dioxins are mediated via the Ah receptor (AHR), another ligand-activated nuclear receptor. This receptor upregulates a variety of genes (the Ah gene battery) associated with the toxicology of dioxins. Taken together, the data presented in this symposium illustrate to the toxicologist the need to quantitate and interpret modulations in apoptosis alongside more conventional assessments of S-phase. Although the toxicant may initiate cell damage, genes like Bcl-2, p53, Fas, PPARα, and AHR are final arbiters of the choice between death, survival, and proliferation.

Introduction

A symposium entitled Perturbation of the Mitosis/Apoptosis Balance: A Fundamental Mechanism in Toxicology was held at the 36th Annual Meeting of the Society of Toxicology (SOT) in Cincinnati, Ohio in 1997. This symposium, sponsored by the Carcinogenesis Speciality Section of the SOT, sought to consider the critical role played by perturbation of the balance between cell gain via mitosis and cell loss by apoptosis in mediating the action of toxicants (Fig. 1). Data that described the perturbation of apoptosis in various target tissues, with particular emphasis on molecular mechanisms, were presented. Although there has been recent progress in understanding apoptosis in the action of nongenotoxic hepatocarcinogens, early evidence suggests that similar insight could be gained by a consideration of apoptosis as a key mediator of the action of other types of toxicant in tissues such as brain, the immune system, and the reproductive organs. The symposium focused on induced changes in this critical balance as a key mechanism of action of a variety of diverse toxicants. The molecular mechanism of the perturbation of apoptosis was also considered since tissue-specific expression or induction of key genes such as p53, bcl2, and Fas may mediate and modulate the toxicology observed after toxic insult.

Relevance of Apoptosis to Toxicology (John A. Hickman)

Apoptosis describes a highly conserved morphology associated with the death of many different cell types from diverse species. This mode of cell death is involved in development and tissue homeostasis but may also be initiated after cellular perturbation by toxicants. Highly conserved genetic
controls of apoptosis have been described, relating to some but not necessarily all features of the morphology of cell death. Toxin-induced cell death may be genetically controlled and the ability of a cell to survive or to die is determined by the repertoire of gene products. Their differential expression is a critical determinant of cell and tissue sensitivity to toxicants.

A simple observation gave rise to the idea that apoptosis is critically important in rationalizing the toxicology of many cytotoxic anticancer drugs (Dive and Hickman, 1991; Dive et al., 1992); there are hierarchies among different cell types with respect to their inherent ability to survive. Some cells die more readily than others, reflecting the phenotypes of the different cell types. Damaged cells that undergo apoptosis are deleted and cannot produce mutant, malignant progeny, whereas those that survive genomic damage can. In humans, hematopoietic cells readily undergo deletion (whole-body radiation shows how sensitive the bone marrow is to the engagement of cell death); perhaps because of this, hematopoietic tumors are comparatively rare. In contrast, epithelial cells have a relatively high threshold for cell death in order to survive their environmental challenges (sunlight, atmospheric pollution, dietary toxicants, changing hormonal environments). Perhaps as a consequence of this higher threshold, the majority of human cancers are epithelial with colon cancer being one of the most common.

The small intestine is composed of epithelia with a staggering turnover; studies show that a cell division occurs every 5 min in each intestinal crypt of the mouse (Potten, 1992). Surprisingly, the small intestine is remarkably resistant to cancer, whereas the colon is far more susceptible. For some time it was considered that the greater incidence of tumors seen in the colon reflected significant differences in the kinetics of proliferation compared to that of the small intestine. Careful analysis of the data from the mouse does not support this idea (Potten, 1992). However, analysis of apoptotic cells in crypt epithelia after whole-body γ-radiation (Fig. 2) showed that apoptosis peaks in the small intestinal crypts at the cell positions considered to harbor the stem cells (positions 4–6), whereas, in the colon, apoptosis was spread along the length of the crypt. This suggested (Merritt et al., 1993, 1995) that the rapid deletion of damaged small intestinal stem cells after DNA damage is an effective tumor suppressor. Analysis of the expression of the tumor suppressor protein p53 after γ-irradiation showed that it was focused in the small intestinal crypt epithelia at cell positions coincident with those undergoing apoptosis (Merritt et al., 1993) (Fig. 2). In contrast, expression of p53 in the colon appeared to be attenuated and was not focused around the stem cell positions. In addition, a second key modulator of apoptosis, bcl-2, was differentially expressed between the small and large bowel since only colonic crypt epithelia expressed bcl-2. Since the bcl-2 gene product protects cells from apoptosis (reviewed by Reed, 1995), this differential expression could be expected to alter cell survival.

In addition to irradiation-induced cell death, apoptosis pathways may be initiated after cellular perturbation by toxicants. In addition, the differential expression of key genes may be a critical determinant of cell and tissue sensitivity. Administration of the cytotoxin 5-fluorouracil (5-FU) initiates apoptosis in crypt stem cells but in bcl-2−/− mice ("knockouts"), cell death of the stem cells is greatly increased. In contrast, the toxicology of 5FU in the colon is entirely dependent on p53 since p53 knockouts lose the pathology of 5FU damage. Thus, the DNA damage caused by 5FU is not detected, resulting in reduced cell cycle arrest and little inhibition of mitosis.

In summary, the quantitation and characterization of cell damage initiated by toxicants are important when considering the role of apoptosis and mitosis in toxicology. What the toxicologist defines as toxicity to a particular organ is determined pathohistologically, usually some time after drug insult (1 day or more). Analysis of p53-induced apoptosis, inhibition of DNA synthesis, and inhibition of mitosis induced by the intestinal cytotoxin 5-FU showed that although...
FIG. 2. The apoptotic response of the murine small intestine and midcolon after irradiation. The positional incidence of and morphology of apoptosis before and after whole-body irradiation of BDF1 mice in small intestine (A, C) and colon (B, D). Cell positions are numbered from the base of the crypt (Potten, 1992). Apoptotic events are arrowed.
these peaked by 24 hr, a fall in the cellularity and integrity of the crypt was not observed until 4 days. In p53-null animals there was a significant reduction in the amounts of apoptosis (Pritchard et al., 1997) and this translated to a maintenance of crypt integrity. These results show that the final arbiter of toxicity, expressed as late histopathological changes, is the expression of genes that modulate the cellular response to damage rather that the amount of damage per se. Thus, pathological outcome is not a measure of cellular damage and quantitation of cellular damage does not predict outcome. This has many implications for toxicology where predictive measures of toxicity frequently depend upon acute measurements of cell and tissue damage.

**Phthalate-Induced Alterations in Testicular Germ Cell Apoptosis (John H. Richburg)**

Apoptosis occurs in the testis as an important physiologic mechanism to limit the number of germ cells in the seminiferous epithelium (Billig et al., 1995). During the process of spermatogenesis, clonal proliferation of germ cells occurs via many rounds of mitosis, greatly expanding the germ cell population. If this expansion were left unchecked, the number of germ cells would quickly outgrow the supportive capacity of the Sertoli cells. Therefore, a delicate balance exists in testes between proliferation and apoptosis. It is estimated that up to 75% of the potential population of mature germ cells in the testis is lost by active elimination (De Rooij and Lok, 1987).

The Sertoli cell of the testicular seminiferous epithelium has been implicated in the control of germ cell apoptosis in the testis. Sertoli cells tightly regulate the proliferation, differentiation, and viability of germ cells by creating a specialized compartment into which Sertoli cells secrete hormonal and nutritive factors. The importance of this specialized microenvironment on germ cell viability is indicated by the increased incidence of germ cell apoptosis in response to growth factor or hormone withdrawal (Kyprinacou and Isaacs, 1989) as well as after toxicant-induced Sertoli cell injury (Richburg and Boekelheide, 1996). The dependence of germ cell viability on Sertoli cell factors and the intimate contact that exists between these two cell types suggests that the Sertoli cell directly regulates germ cell apoptosis in the testis through a paracrine mechanism.

Recent work has identified the (Fas)/APO-1/CD95 system as a key regulator of Sertoli cell-directed germ cell apoptosis (Lee et al., 1997). The Fas system is a receptor–ligand-mediated process in which the Fas receptor (Fas), a type I integral membrane protein, is stimulated by Fas ligand (FasL), a type II integral membrane protein, to initiate an intrinsic cell death pathway within the Fas-bearing cell. In the testis, FasL and Fas receptor have been localized to Sertoli cells and select germ cells, respectively (Lee et al., 1997). The ability of Sertoli cell-expressed FasL to trigger apoptosis in Fas-bearing germ cells has been demonstrated in a Sertoli cell–germ cell coculture model (Lee et al., 1997). In coculture, germ cells die by apoptosis at a slow, defined rate. Inhibition of Sertoli cell FasL expression by an antisense oligonucleotide directed against FasL increased the survival time of the germ cells. These observations point to a role for the Fas system in the mechanism of Sertoli cell-directed germ cell apoptosis.

One of the major consequences of exposure of rats to the Sertoli cell toxicant mono(2-ethylhexyl) phthalate (MEHP) is an early and progressive detachment of germ cells from the seminiferous epithelium. Many of these die by apoptosis (Richburg and Boekelheide, 1996). MEHP is the active metabolite of the plasticizer di(2-ethylhexyl) phthalate (DEHP) that is found widely dispersed in the environment. After 3 hr of exposure of young rats (28-day-old) to MEHP (2 g/kg, po), there is an inhibition in the normal physiologic incidence of germ cell apoptosis followed later (12 hr) by an increase (Richburg and Boekelheide, 1996). These observations suggest that the MEHP-induced disruption of the Sertoli cell–germ cell physical interaction alters the normal Sertoli cell-directed regulation of germ cell apoptosis.

An involvement of the Fas system in mediating the effects of MEHP was indicated by a robust induction in the expression of FasL and Fas mRNA transcripts (Lee et al., 1997). Maximal induction of FasL and Fas expression was at 6 and 12 hr after MEHP exposure, respectively. By immunohistochemistry, FasL was localized to the basal membrane of Sertoli cells under normal physiological conditions (Lee et al., 1997). However, the localization pattern of Sertoli cell FasL was changed 12 hr after MEHP exposure to a diffuse cytoplasmic staining pattern, particularly at sites of Sertoli cell–germ attachment (Lee et al., 1997). The incidence of germ cell Fas immunostaining also was increased 12 hr after MEHP exposure (Lee et al., 1997). The increased incidence of germ cells staining positively for Fas 12 hr after MEHP exposure closely corresponded to the observed incidence of germ cell apoptosis at that time point (Richburg and Boekelheide, 1996).

Taken together, these observations suggest that under normal physiological conditions the Sertoli cell mediates the death of Fas-bearing germ cells via the expression of FasL on its cell membrane (Fig. 3A). The initial (3-hr) MEHP-induced disruption of the Sertoli cell–germ cell physical contact may result in the uncoupling of the Fas-mediated signal transduction process between these cells leading to a decrease in germ cell apoptosis (Fig. 3B). At later stages (6 hr), there is an induction of Sertoli cell FasL expression aimed at eliminating damaged germ cells. This may be mediated by the generation of a soluble form of FasL from Sertoli cells (Fig. 3C). The production of this form by cleavage of a portion of the extracellular domain of FasL has been demonstrated to occur in various lymphoid cell lines. The
Perturbation of Apoptosis and Mitosis in Nongenotoxic Carcinogenesis (Ruth A. Roberts)

Peroxisome proliferators (PPs) are a diverse group of chemicals that include the hypolipidemic drugs nafenopin, Wy-14,643, and clofibrate as well as chemicals of industrial and environmental importance such as the plasticizer diethylhexyl adipate and the chlorinated solvents (see Moody et al., 1991, for review). It is probable that the elevated S-phase induced by PPs plays a role in their hepatocarcinogenicity (Ames and Gold, 1990; Ashby et al., 1994). However, liver homeostasis is controlled by the balance between cell gain by mitosis and cell death by apoptosis (see Schultz-Hermann, 1979; Fausto and Webber, 1993, for reviews). Hepatocyte apoptosis may act to delete DNA-damaged or excess cells from the liver, thereby removing potential targets for carcinogenic promotion. Using an in vitro model, we have demonstrated that PPs can suppress both spontaneous hepatocyte apoptosis and that induced by exogenous transforming-growth factor β1 (TGFβ1) (Bayly et al., 1994; James and Roberts, 1996); additional data suggest that rising levels of active TGFβ1 are responsible for the spontaneous apoptosis (Strange and Roberts, 1996). We have shown also that nafenopin suppresses apoptosis induced by DNA-damaging drugs in vitro (James and Roberts, 1996; Gill et al., 1997) and can reduce basal levels of apoptosis in rat liver in vivo (Roberts et al., 1995). Following these observations, three key questions arose: (i) do species differences in the suppression of apoptosis mirror species differences in liver enlargement and hepatocarcinogenesis? (ii) what is the role of the peroxisome proliferator-activated receptor-α (PPARα) in the suppression of apoptosis? and (iii) how does the suppression of apoptosis act in concert with the induction of S-phase during liver enlargement and hepatocarcinogenesis?

In rat and mouse, acute effects are seen in the liver in response to PPs such as enzyme induction, peroxisome proliferation, and elevated S-phase followed by the development of hepatocellular carcinoma (see Ashby et al., 1994, for review). However, human hepatocytes display neither peroxisome proliferation nor induction of S-phase in response to PPs in vitro and no increased incidence of hepatocarcinogenesis has been seen in patients treated with hypolipidemic drugs (Elcombe and Mitchell, 1986; Bentley et al., 1993). We have demonstrated previously that the PP nafenopin can suppress rat hepatocyte apoptosis both in vitro and in vivo. As expected, nafenopin could suppress apoptosis and induce S-phase in mouse hepatocytes but, surprisingly, we found that nafenopin could also suppress apoptosis in hamster and guinea pig hepatocytes (James and Roberts, 1996). In contrast, only rat and mouse hepatocytes showed an induction of S-phase in response to nafenopin (James and Roberts, 1996). Overall, species differences in response to the nongenotoxic hepatocarcinogens studied correlated with induction of DNA synthesis rather than with the suppression of apoptosis.

The precise molecular mechanisms through which PPs effect these pleiotropic changes remain to be elucidated fully. However, the discovery in mouse of a member of the

![Diagram of germ cell apoptosis](https://example.com/diagram.png)

**FIG. 3.** Proposed pathogenic sequence of MEHP-induced alterations in Fas-mediated germ cell apoptosis in the testis. In this model, the Sertoli cell mediates the death of Fas-expressing germ cells by expressing on its cell membrane FasL. (A). The initial MEHP-induced disruption of the Sertoli-germ cell physical contact results in the uncoupling of the Fas-mediated signal transduction process between these cells leading directly to a decrease in germ cell apoptosis (B). An increase in the production of a soluble form of FasL from Sertoli cells can then overcome the physical separation between the Sertoli and germ cells and is predicted to account for the increase in germ cell apoptosis seen after 12 hr of MEHP exposure (C).
steroid hormone receptor superfamily that can be transcriptionally activated by these compounds, the PPARα (Issemann and Green, 1990), suggests that transcriptional regulation is one important mechanism of PP action. PPARα is highly expressed in rodent liver and is activated by a diverse range of PPs (Issemann and Green, 1990). In addition, transgenic mice lacking PPARα do not develop hepatic peroxisome proliferation in response to PP administration (Lee et al., 1995). In common with other PPARs, PPARα directly regulates gene transcription by forming heterodimers with the retinoid X receptor (RXR) (Issemann et al., 1993). These heterodimers bind specifically to peroxisome proliferator response elements (PPREs) in the promoters of PP-regulated genes such as those involved in mitochondrial and peroxisomal fatty acid metabolism and cytochromes P450 (Tugwood et al., 1992; Aldridge et al., 1995).

We wished to determine whether activation of PPARα was responsible for the suppression of hepatocyte apoptosis by PPs. Parallel experiments in our laboratory led to the isolation of a human PPARα variant, hPPARα-6/29, with a number of amino acid changes from published hPPARα sequences (Tugwood et al., 1996). hPPARα-6/29 was able to bind to the rat acyl CoA oxidase PPRE in the presence of RXR but could not be transcriptionally activated by PPs (Roberts et al., 1997). These properties of DNA binding coupled with lack of transcriptional activity are reminiscent of other natural and synthetic nuclear receptors that exhibit “dominant negative” repressor activity (reviewed in Yen and Chin, 1994). The ability of hPPARα-6/29 to act as a dominant negative repressor of mPPARα was demonstrated using a PPRE-containing reporter gene transfected into Hepa 1c1c7 cells (Roberts et al., 1997).

Since hPPARα-6/29 was not transcriptionally active and acted as a dominant negative repressor of mPPARα function in a reporter gene assay, we investigated the effects of hPPARα-6/29 on rat hepatocyte apoptosis. Nafenopin suppressed both spontaneous and TGFβ1-induced hepatocyte apoptosis but the addition of increasing amounts of hPPARα-6/29 ablated the effects of nafenopin, returning the apoptosis to control levels (Fig. 4) (Roberts et al., 1997). PB, like nafenopin, was able to suppress both spontaneous and TGFβ1-induced apoptosis in rat hepatocytes. However, hPPARα-6/29 was unable to abrogate this suppression of apoptosis (Roberts et al., 1997). These data demonstrate that, as expected, the effects of this dominant negative receptor appear specific for the suppression of apoptosis by PPs. Taken together, our data demonstrate that the suppression of hepatocyte apoptosis by PPs is mediated by activation of one or several isoforms of PPAR, a member of the steroid hormone receptor superfamily of ligand activated transcription factors. PPARα is likely to play the predominant role in this regulation.

We and others have proposed previously that the suppression of apoptosis by nongenotoxic carcinogens may prevent the removal of DNA-damaged, potentially initiated cells (Bursch et al., 1984; Richardson et al., 1985; Oberhammer and Roberts, 1994). These hypotheses imply that the daughter cells newly created in the presence of hyperplastic nongenotoxic carcinogens will be those to undergo apoptosis on removal of the stimulus. Surprisingly, we found that the majority (>90%) of the hepatocytes generated during compound-induced hyperplasia were protected from apoptosis during liver regression (Roberts et al., 1995). Despite the lack of coincidence of DNA synthesis and subsequent apoptosis on a cell-by-cell basis, apoptotic bodies and DNA synthesis were found in the same (periportal) region of the liver with very little centrilobular labeling. This agrees with previous data where the induction of mitosis by nafenopin (Eacho et al., 1991; Barrass et al., 1993; Grasl-Kraupp et al., 1993) was mainly periportal. Our data show that both
cell-gain and cell-loss perturbations in response to nongenotoxic carcinogens take place around the portal vein, although it appears that the newly created cells may be largely protected from cell death. These data imply that nongenotoxic hepatocarcinogens may have two distinct effects: stimulation of mitosis and suppression of apoptosis. One could be the natural consequence of the other so that inhibition of apoptosis results inevitably from upregulating cell replication. Overall, these data contribute to our understanding of clonal selection and promotion during nongenotoxic carcinogenesis and may assist in a more accurate assessment of the risk such compounds may pose to man.

In summary, species differences in response to PPs correlate with induction of DNA synthesis rather than with suppression of apoptosis. These data suggest that perturbation of both sides of the growth equation is required for hepatocarcinogenesis; neither induction of S-phase nor suppression of apoptosis alone is sufficient (Fig. 5). Data on the coincidence of S-phase and apoptosis suggest that only a small percentage of those cells protected from apoptosis are recruited into S-phase by PPs; perhaps these cells are the key to the early stages of hepatocarcinogenesis. Experiments using a dominant negative repressor of PPARα activity, hPPARα-6/29, demonstrate that activation of PPARα is the causative step in the suppression of apoptosis by PPs. This demonstration of the modulation of apoptosis by PPARα may represent a paradigm for the regulation of cell growth by nongenotoxic carcinogens via nuclear receptor activation.

Possible Role of the Dioxin-Inducible (Ah) Gene Battery in Apoptosis (Daniel W. Nebert)

On the basis of our current knowledge about the evolution of drug-metabolizing enzymes, it appears to be extremely likely that these enzymes play a critical role in maintaining steady-state levels of the ligands involved in ligand-modulated transcription of genes effecting growth, differentiation, and apoptosis (Fig. 6). Among environmental pollutants, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; dioxin) is one of the most potent rodent tumor promoters known (Puga et al., 1992). In murine hepatoma cells, the first observable effects of TCDD are a rapid, transient increase in Ca^{2+} influx and a minor but significant elevation of activated, membrane-bound protein kinase C (Puga et al., 1992). These changes are then followed by induction of the immediate early proto-oncogenes c-fos, jun-B, c-jun, and jun-D, and by large increases in AP-1 transcription factor activity. Induction of these changes by TCDD is delayed compared with that by phorbol esters, although the magnitude of the effects caused by both treatments is similar, and both induction processes can be blocked by staurosporine, a protein kinase C inhibitor. In cultured cells, proto-oncogene induction by TCDD appears to be independent of the presence of a functional Ah receptor or nuclear translocation protein. These results reveal that TCDD can stimulate genes associated with cell replication, contributing to TCDD-induced tumor promotion (Puga et al., 1992).

Many genes are induced by TCDD, and many others are induced by electrophilic metabolites such as quinones and H_2O_2; using several mouse experimental systems, we have defined a subset of six of these genes as constituting the...
(Ah) battery by the sole criterion that a functional CYP1A1 or CYP1A2 enzyme is able to repress the expression of genes that are members of this gene battery (Nebert et al., 1993). The six genes in the mouse dioxin-inducible (Ah) gene battery are Cyp1a1/Cyp1a2 together with four phase II, Nmo1, NAD(P)H: menadione oxidoreductase, Ahd4, an aldehyde dehydrogenase, Ugt1a6, a UDP glucuronosyltransferase, and Gsta1, glutathione transferase Ya. All six genes are upregulated when the dioxin-bound Ah receptor (AHR) and the Ah receptor nuclear translocator (ARNT) bind as heterodimers to the aromatic hydrocarbon response elements. All four phase II genes participate in regulation of intracellular redox status, whereas ARNT and possibly the AHR are involved in regulating responses to hypoxia. Hypoxia-inducible factors HIF-1α and HIF-1β bind to hypoxia response elements during AP1-dependent induction of Nmo1.

In addition to inducing the expression of genes associated with mitosis such as AP-1, perturbation of redox equilibrium and hypoxia are known to stimulate MEKK, Src, and Bcl2 via the induction of reactive oxygen metabolites (Puga et al., 1992; Nebert et al., 1993). The net effect of this altered gene expression is likely to be an induction of S phase and the suppression of apoptosis via Bcl2. Bcl2 is homologous to the Caenorhabditis elegans gene Ced9. The upstream open-reading frame of Ced9 is similar to succinate dehydrogenases, which are members of the Nmo1 gene superfamily. Pleiotropic effects of bcl2-related proteins include rises in mitochondrial membrane potential and mediation if reactive oxygen-gated metabolite levels. In summary, it is probable that the dioxin-inducible Ah gene battery plays a central role in mediating the perturbation of apoptosis and mitosis by dioxins.

Conclusions

Much interest and effort have been focused on cell growth as an important mediator in a number of physiological processes (Goldsworthy et al., 1996a). Death, mitosis, and differentiation are all critical aspects of the cell’s lifecycle and homeostatic control is maintained through a three-way dynamic balance. A number of diseases and pathological processes have been shown to result from perturbation of this cell growth/cell survival balance. The ability of a number of extrinsic toxicants to interact with intrinsic factors and influence the decision of a cell to undergo apoptosis or mitosis has led toxicologists to consider this process in the action of toxicants.

Taken together, the data presented in this symposium illustrate to the toxicologist the need to quantitate and interpret modulations in apoptosis alongside more conventional assessments of S-phase (Goldsworthy et al., 1996b; Roberts, 1996). The observed modulations may be toxicant-dependent but can also be dependent on the particular molecular arbiters in the target tissue and species. For example, MEHP/DEHP can induce testicular germ cell apoptosis but can suppress hepatocyte apoptosis; the outcome may depend as much on the molecular regulation within the individual tissue as on the administered toxicant and dose.

REFERENCES


