Chemotherapy: induction of stress responses

E Tiligada

Department of Experimental Pharmacology, Medical School, University of Athens, M. Asias 75, GR-11527 Athens, Greece

(Requests for offprints should be addressed to E Tiligada; Email: aityliga@med.uoa.gr)

Abstract

Eukaryotic cells, from yeast to mammals, respond and adapt to environmental and microenvironmental stressors by evolutionary conserved multicompartment endogenous systems that utilise a network of signal transduction pathways to regulate the adaptive and protective phenotype. The balance between cell survival and cell death is decisive for sensitivity or resistance to DNA-damaging chemotherapeutic agents. Anticancer drugs may themselves act as stressors to induce adaptive signals that could limit their clinical value. Related research has been focused on the modulation of the expression and function of the heat shock proteins, the unfolded protein response, the mechanisms of subcellular translocation of signalling components, the genomic and non-genomic actions of drugs and endogenous functional components like hormonal pathways, the input of inflammation and alterations in the microenvironmental milieu and on the control of the cell cycle and proliferation. The outcome seems to be driven by the first-line responses that support cellular integrity and by specific mechanisms that depend on the type of cell and the nature, and duration and severity of the noxious stimulus. Data obtained from experimental organisms like the yeast have added valuable information on the basic conservation in cellular stress-related processes in eukaryotes and on the consequences that may accompany the adaptive and protective phenotype during the stress response to anticancer agents. Understanding the complex molecular pathways mediating these processes has started to contribute to the reevaluation of the current therapeutic regiments and to revolutionise the approaches for improved anticancer therapy.

Endocrine-Related Cancer (2006) 13 S115–S124

Introduction

The rich and complex body of knowledge in the field of cancer research has provided limited beneficial information on the induction of resistance during chemotherapy. Yet, this unresolved obstacle may be attributed, at least in part, to the complexity of the broad spectrum of distinct types and subtypes of tumours, the simplified evaluation and interpretation of the variable cellular and molecular circuits and to the technical rather than conceptual approach to cancer pathogenesis and treatment (Hanahan & Weinberg 2000).

No single therapeutic regimen benefits all patients while the dynamic multistep defence machinery of tumour cells against the harmful effects of chemotherapy adds further complexity to the treatment (Kohno et al. 2005). It becomes progressively clear that additional stress responses may couple the genotoxic stress response induced by anticancer agents (Sanchez-Prieto et al. 2000, Benhar et al. 2001). These may emerge and operate in complementary, conflicting or even autonomous ways. By identifying anticancer agents as a threat to their existence, neoplasms may activate adaptive and protective mechanisms against endogenous or exogenous stressful stimuli (Tiligada et al. 2002). The latest evidence generates the concept that concerted genomic and non-genomic alterations drive the resistant phenotype and incorporate formerly unrelated processes to the typical cellular stress response. Amongst them, classic inflammation components like the nuclear factor kappa B (NFkB), now appear to control the stress response, cell...
proliferation and death, as well as resistance to anticancer drugs (Luo et al. 2005). Although limited direct correlations between the type of stress and selective endogenous communication signals can be established at present, anticancer drug development is driven away from the classical DNA interacting approach in the direction of signalling cascade modulation (Workman & Maloney 2002, Nicholson et al. 2004, Luo et al. 2005). These strategies introduce a new perspective to cancer chemotherapy research.

The cellular stress response

At the cellular level, stress could be regarded as a disturbance to normal development, which may affect structure, function, stability, growth and survival. The environmental and microenvironmental stimuli that act as potential stressors are numerous. Typically, they include hyper- or hypothermia, hypoxia, reactive oxygen species (ROS), radiation, starvation, hypo- or hyperosmotic conditions, mutations, factors underlying metabolic deficiencies and other pathologic conditions, heavy metals, toxic agents and drugs (Tiligada et al. 2002). In an attempt to reestablish their homeostasis, cells react to these chemical and physical changes through the highly conserved cellular stress response (Kultz 2005). Many aspects of the response to macromolecular damage are not stressorspecific, whereas under particular conditions, the stress stimulus may induce different responses depending on its nature, duration and severity (Kultz 2005). Thus, preconditioning – exposure to mild adverse conditions – prepares the cells, from unicellular to multicellular organisms, to survive under and recover from the subsequent severe, otherwise lethal circum-
stances (Jaattela 1999, Nadin et al. 2003). In the absence of this adaptive response or when tolerance limits are exceeded, a more potent stressor induces signals leading to apoptosis and an even stronger one to necrosis (Jaattela 1999).

In some cases, the stress response may be circumvented (Tiligada et al. 2006) or it may be modulated by co-existing disorders (Pantos et al. 2004). The available data point to a vital highly conserved, nevertheless complex procedure. Continuing efforts are required to organise the rather chaotic information and to assess the significance of the response at the level of the entire organism. Currently, it is not possible to evaluate the optimal means of pharmacological intervention; it is neither likely to predict any complementary nor conflicting systemic effects of such modification. Especially in the case of cancer, it is not known whether interfering with components of the response would potentiate physiological defence mechanisms against the malignant phenotype or whether it would enable tumour cells to further adapt to chemotherapy or apoptosis (Tomida & Tsuruo 1999). Thus, circumvention and modification of the cellular stress response provide new scopes for the ongoing research in systems biology.

Cellular and molecular elements participating in the stress response

Sensing membrane lipid, protein and DNA damage, as well as alterations in the redox status, energy metabolism, cell cycle and proliferation potential are key functional aspects of the cellular stress response (Kultz 2005). Research in this field was initially focused on the universally conserved minimal stress proteome: the heat shock proteins (HSPs), the glucose-regulated proteins (GRPs) and ubiquitin (Feder & Hofmann 1999). Subsequently, additional components were added to the palette of stress response effectors. GRPs are mainly involved in the unfolded protein response (UPR), a stress reaction initiated by the accumulation of unfolded proteins within the endoplasmic reticulum (ER stress), triggered by disturbances in cellular redox or Ca$^{2+}$ regulation and glucose deprivation and involving, amongst others, mitogen-activated protein kinase (MAPK) signalling pathways (Herr & Debatin 2001).

In parallel to their normal housekeeping character in folding proteins into their tertiary structure and in facilitating binding of steroid hormones to their receptors, the frequently protective induction of HSPs in response to stress and their role in the regulation of death signals are well recognised (Ciocca & Calderwood 2005, Calderwood et al. 2006). Commonly, the expression of genes encoding these proteins is regulated by the activation and nuclear translocation of heat shock transcription factors (HSFs) and by their interaction with signal transducers and activators of transcription (STATs) (Stephanou & Latchman 1999, Santoro 2000). HSP-associated subcellular trafficking is also in focus because of its regulatory role in the cellular stress response (Tiligada 2006). Under stress, HSF separates from its intrinsic repressor HSP90 and following phosphorylation and translocation to the nucleus, it binds to heat shock elements, thus regulating HSP gene transcription and cytoplasmic reassembling of HSP90 via autoregulatory and feedback processes (Goetz et al. 2003).

At the biochemical level, the modifications that support cells to reprogramme their physiology and to circumvent the deleterious stimuli include
post-translational phosphorylation and dephosphorylation, acetylation, methylation, glycosylation, farnesylation, ubiquitination and adjustment of the cellular energy status (Bensaude et al. 1996, Tiligada et al. 1999a, Keyse 2000, Sanchez-Prieto et al. 2000). The integration of upstream activators and downstream effectors couples the noxious extracellular stimuli to the nuclear events mostly via a network of constitutive and inducible kinases and phosphatases that orchestrate intracellular cascades, DNA binding and subcellular translocation of various components (Keyse 2000, Tiligada 2006). Duration and magnitude of signalling through c-Jun N-terminal kinases (JNKs) and p38 MAPK isoforms is thought to be an important determinant of the cellular stress response in terms of either cell survival or death (Sanchez-Prieto et al. 2000). MAPK activity is balanced by nuclear translocation of various signalling molecules like STATs and by dual specificity MAPK kinases (MEK or MKK) and specific protein phosphatases (Keyse 2000).

The cellular stress response and cancer chemotherapy

The stress response connection to cancer

Contrary to normal tissues, tumours are characterised by hypoxia, low pH and low levels of glucose, causing the glucose-regulated stress response of cancer cells (Tomida & Tsuru 1999). The events of cell stress and cell death are linked, partly via the function of stress chaperones, kinases, caspases, hormone receptors and other proteins that could serve as targets for diagnostic and therapeutic interventions in cancer chemotherapy (Shain et al. 2000, Tiligada et al. 2002, Nicholson et al. 2004, Ciocca & Calderwood 2005, Calderwood et al. 2006).

HSPs, like HSP70 and HSP27, balance tumour cell death and growth (Hanahan & Weinberg 2000, Calderwood et al. 2006) and are implicated in the prognosis of specific cancers (Ciocca & Calderwood 2005). Interestingly, tumour-derived HSPs elicit specific immunity to tumours (Vanaja et al. 2000). The endoplasmic reticulum contributes to cellular stress through the UPR and the stress-inducible apparatus uses molecules such as p53, JNK, NFkB, MAPKs and sphingomyelins (Herr & Debatin 2001). The tumour suppressor p53 is associated with over 45% of cancers and is involved in the transcription of HSP genes. The optimal location of wild-type p53 for promoting cell arrest and apoptosis is the nucleus (Shain et al. 2000), while persistent binding to HSP90 locks p53 mutants in the cytoplasm under stress conditions and in transformed cells, p53 mutations lead to enhanced HSP70 transcription (Calderwood et al. 2006).

Oncoproteomic and pharmacogenomic technologies offer an optimistic insight into the classification of cancers and drug resistance and guide the way to personalised cancer therapy. In the oxidative stress response, proteomic approaches have uncovered differentially expressed stress proteins in non-malignant and malignant breast epithelial cells (Yan et al. 2005). Therefore, since tumour cells manage to survive and proliferate in ever changing harmful microenvironments, the hypothesis that cancer may be an adaptive response to cellular stress must not be disregarded.

Crosstalk between chemotherapy and the stress response

Amongst stress response parameters, the HSPs are implicated in both the effectiveness and the tolerance to chemotherapy, although they are not of diagnostic value as yet (Ciocca & Calderwood 2005). The stress response in solid tumours leads to the induction of resistance to drugs that act primarily on rapidly dividing cells and this resistance is reversible or decays upon removal of the stress conditions (Tomida & Tsuru 1999). The phenomenon of multidrug resistance (MDR) is associated most frequently with anthracyclines (doxorubicin, daunorubicin and epirubicin), antimetabolites (methotrexate, fluorouracil, 5-azacytosine, 6-mercaptopurine and gemcitabine), epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel), vinca alkaloids (vinorelbine, vincristine and vinblastine), camptothecin-11 (irinotecan), dactinomycin and mitomycin C. Expression of the MDR1 gene, encoding P-glycoprotein that creates ionic gradients to reduce drug accumulation in cancer cells, was shown to be regulated by HSFI (Vilaboa et al. 2000) and to be induced by stressful stimuli, including low pH, heat, anticancer drugs, transfection with oncogenes and radiation (Szabo et al. 2000).

Depending on the time and severity of exposure, thermal stress has been coupled to the effects of anticancer agents in several, often controversial ways. As reviewed recently (Tiligada et al. 2002), hyperthermia induced the anti-inflammatory stress response in combination with chemotherapy, modulated the action of doxorubicin, cisplatin, bleomycin, mitomycin C and teniposide, and thermotolerant cells acquired resistance to daunorubicin and etoposide, whereas other reports argued for failure of thermal stress to induce resistance to doxorubicin, colchicine, 5-fluorouracil, cisplatin, actinomycin D, methotrexate and even sensitised cancer cells to doxorubicin and amsacrine,
Chemotherapy-induced stress response

Experimental evidence supports the dual capability of anticancer drugs to act as lethal agents for tumour cells as well as to induce the adaptive stress response in the neoplastic environment. Anticancer drugs activate cell death programmes (Herr & Debatin 2001) and modulate signal transduction pathways and expression of genes that are essential for drug resistance (Kohno et al. 2005). Research and development of classic antineoplastic agents have been based on their cytotoxic effects on tumour cells. However, their potential to induce survival signals in malignancy, by acting as microenvironmental pharmacological insults, deserves careful thought and the identification of their relevant genomic and/or non-genomic actions is a matter of active research.

To date, data concerning the induction of the stress response by chemotherapeutic agents have not been successful in providing conclusions on clinical value, mainly because of the reports derived from inconsistent experimental protocols. Besides, the effects of anticancer agents largely rely on the plasticity of cancer cells and on the course of the disease, but laboratory studies ignore the advanced stages of tumours frequently. However, it is accepted that anticancer drugs may elicit their wanted or side effects through interference with the stress response cascades, in addition to their conventional direct DNA interactions (Hanahan & Weinberg 2000, Tiligada et al. 2002, Ciocca & Calderwood 2005).

Even though care must be taken in extrapolating evidence from alternative experimental organisms to mammalian cells, related data derived from yeast have provided indications connecting anticancer agents to the stress response. The yeast has been extensively characterised both biochemically and genetically and provides a unicellular eukaryotic organism suitable for studying chemotherapeutic drug actions (Delitheos et al. 1995) as well as the physiological parameters that affect a cell’s ability to survive under stress conditions (Tiligada et al. 1999a, Miligos et al. 2000, Vovou et al. 2004, Papamichael et al. 2006). Thermotolerance describes the acquisition of protection from death due to extreme heat treatment following a shift in the incubation temperature. In this case, thermotolerant cells showed a variable proliferation phenotype attributed to the stress-induced ‘optimal tuning’ of the cell cycle, while without prior exposure to mild adverse conditions, cells surviving the lethal heat shock exhibited limited proliferation potential (Vovou et al. 2004). The information obtained from this experimental organism may be useful in understanding basic chemotherapy-mediated actions in tumour cells, and, being a normal cell system itself, in examining the possible contribution of the non-transformed tissues in interventions against malignancy, an approach having been overlooked considerably in cancer research.

Exposure of yeast to various drugs led to disturbances in cellular morphology, which were characteristic for the DNA-interacting agents but not for the chromatin function inhibitors or other pharmacologically active substances (Tiligada et al. 1999b, Stavrinidis et al. 2002). Following exposure of non-synchronised yeast cultures to sub-lethal doses of a number of chemotherapeutic agents, the induction of the adaptive heat shock response showed the capability of these agents to confer cross-resistance to a potentially lethal thermal shock (Fig. 1A), largely via de novo protein synthesis-dependent processes (Miligos et al. 2000, Tiligada et al. 2006). These
observations made the yeast cell a candidate system for studying the adaptive and protective mechanisms underlying the cellular stress response during exposure to agents used in chemotherapy and for elucidating evolutionary conserved stressor-related processes.

**Contribution of stress protein cascades in chemotherapy-induced stress response**

Anticancer agents elicit preconditioning-type effects in various tissues, while HSPs can be induced by several cytotoxic drugs (Vargas-Roig et al. 1998, Nadin et al.)
E Tiligada: Chemotherapy induced stress responses

2003). Besides genotoxic (Benhar et al. 2001) and ER stress induction by cisplatin (Linder & Shoshan 2005), the ribosomal protein RPL36 and HSP10 were found to be directly responsible for resistance to this drug (Shen et al. 2006). In biopsy specimens from breast cancer patients receiving chemotherapy, nuclear HSP27 and HSP70 expressions were increased and the high nuclear proportion of HSP70 correlated significantly with drug resistance (Vargas-Roig et al. 1998). In addition to the increases in HSP70 and small HSPs following treatment with chemotherapeutic agents, many drugs of this category have been reported to act as oxidative stressors (see Tiligada et al. 2002). However, each cell type may show a distinct response and drug-specific gene expression pattern, as it was reported for basal-like and luminal epithelium breast cell lines after treatment with doxorubicin or 5-fluorouracil (Troester et al. 2004).

HSP expression and nuclear translocation of HSP27, HSP70 and HSP90 in particular have been reported to accompany doxorubicin administration in a number of studies (see Tiligada et al. 2002, Nadin et al. 2003). Several co-chaperones of HSP90 elicit a marked redistribution to the nucleus in response to stress. HSP90 has been investigated mostly because of its interaction with hormone receptors, its role in ending nuclear receptor effects during transcription and in assembling signalling molecules involved in anticancer drug action and in cell proliferation (Marx 2002, Workman & Maloney 2002, Goetz et al. 2003). The antiproliferative and anti-inflammatory properties of the benzoquinone ansamycin antibiotic, geldanamycin, have been attributed to its binding to HSP90 and its endoplasmic reticulum homologue GRP94, while the less toxic derivative, 17-allylamino-17-demethoxygeldanamycin (17AAG), is one of the first chaperone-targeting agents that have already found their way to the clinical trials (Workman & Maloney 2002, Goetz et al. 2003). Interestingly, these agents were shown to act as preconditioning agents (Fig. 1A), conferring de novo protein synthesis-dependent resistance to a subsequent potentially lethal shock in yeast (Papamichael et al. 2006). However, upon long-term treatment, only 17AAG induced the stress response, while on the contrary, the parent compound geldanamycin appeared to interfere with the cell cycle and with the potential of yeast cells to proliferate (Fig. 1A) after exposure to a lethal thermal stimulus (Papamichael et al. 2006). The differential actions of these new closely related molecules in yeast may reflect yet unknown differences in target selectivity.

Contribution of phosphorylation/dephosphorylation in the adaptive response

In yeast, the protective effect of preconditioning against a subsequent potentially lethal heat shock was not a property restricted to anticancer agents in contrast to the induction of morphological alterations (Tiligada et al. 1999a, Vovou et al. 2004). The non-selective phosphatase inhibitor, sodium molybdate, induced de novo protein synthesis-independent thermotolerance and under protein biosynthesis-limiting conditions, it is likely that concerted modifications of constitutive cellular components (Fig. 1A) were capable of partially overcoming the severe thermal insult (Tiligada et al. 1999a). This is supported by a comparable action elicited by suramin and by the circumvention of camptothecin-11-induced resistance by the protein phosphatase 1/2A inhibitor okadaic acid (Tiligada et al. 2006).

Interestingly, camptothecin-11 and suramin, two agents that independently induced the cellular stress response, exhibited an antagonistic effect when applied in combination not only in yeast (Tiligada et al. 2006), but also in prostate cancer cell lines (Yamazaki et al. 1993). This pharmacological evidence argued for potential complementary actions of topoisomerase I and II in the adaptive stress response and pointed to the reevaluation of the functional inhibition of these enzymes in chemotherapy. Furthermore, it suggested that the extent of selective phosphorylation of nuclear components may balance chemotherapy-induced preconditioning.

First-line mechanisms involved in the control of the protective response

Outlining the above data, it is evident that upon exposure to non-lethal stress insults, including anticancer agents, cells from yeast to mammals activate adaptive mechanisms to defend themselves against a subsequent severe shock at least by de novo synthesizing potentially protective proteins (Vargas-Roig et al. 1998, Miligkos et al. 2000, Nadin et al. 2003). On the other hand, rapid protective processes appear to couple sudden unfavourable environmental alterations. Pharmacological evidence has pointed to a membrane-mediated ionic influence on the action of antineoplastic agents (Tiligada & Delitheos 1993, Tiligada et al. 1996). By using agents interfering with membrane components (Fig. 1B) like tetraethyl-ammonium ions, amiodarone and omeprazole, it was shown that at least ionic balancing, alone or in an energy- or intracellular signalling-related way, can play a decisive role in protecting unconditioned cells from an acute severe shock (Vovou et al. 2003, 2004).
Given that components of the plasma membrane are in direct communication with the extracellular microenvironment, the protective machinery may be triggered by the activation of first-line mechanisms. The reported alterations in small HSPs and proton-pumping ATPase levels in response to stress in the plasma membrane (Panaretou & Piper 1992) and the dose-dependent preconditioning phenotype following blockade of the proton-pump by omeprazole (Vovou et al. 2004) raised the possibility of complementary systems implicated in adaptive and protective responses (Fig. 1A and B). Based on this evidence, drugs may elicit a differential effect on the stress response depending on their genomic or non-genomic functional characteristics, which need to be considered in their application in clinical practice. This suggestion is supported by the complementary interplay of the non-genomic oestrogen receptor activity and its nuclear effects that have been linked to the effectiveness and resistance to endocrine therapy (Gururaj et al. 2006).

Adjustment of the stress response by hormonal machinery

In addition to the stress protein-mediated actions of hormones, recent evidence indicates that hormones may modulate the expression and the phosphorylation-dependent function of some HSPs (Pantos et al. 2004). In chemotherapy research, studies on hormonal processes have been focused on endocrine-related cancers, while data on a possible endocrine implication in the outcome of chemotherapy in other forms of cancer are inadequate. Being evolutionarily distant from higher eukaryotes, the yeast lacks known homologues of nuclear receptors, but it maintains sufficient homology with mammalian basal signalling and transcription machineries to be useful in modelling hormonal paths (Hall et al. 1993). Moreover, it is now recognised that hormones exert their physiological activities through extranuclear molecular mechanisms in addition to the well-established genomic ligand–nuclear receptor interactions (Pantos et al. 2004, Nicholson & Johnston 2005, Gururaj et al. 2006).

In yeast cultures, tamoxifen has been reported to exert a cytotoxic action depending on the dose of the drug and the phase of growth (Tiligada et al. 1997). Its action was manifested in logarithmically grown cell populations and attributed to membrane-mediated mechanisms rather than to direct genomic interactions with oestrogen-binding proteins. Regarding coupling of the hormonal machinery to the stress response, preconditioning with prednisolone displayed alterations in cell cycle and conferred thermotolerance to post-logarithmically grown cells during subsequent exposure to otherwise lethal conditions (Papamichael et al. 2006). Preliminary unpublished data of our group indicated that long-term thyroxine administration can confer protection to transcriptionally active yeast cells against lethal thermal insults unlike 17-β-oestradiol and that the hormone is capable of modifying the action of some anticancer agents either by increasing cell survival under stress conditions or by modifying the proliferation potential (Fig. 1A).

Considering the physiological importance of hormones in governing cellular homeostasis and development in many organisms, these data revealed a basic conservation in the hormonal processes in the eukaryotes with no known physiological consequences. Available literature rather excludes direct hormone–nuclear receptor interactions in yeast. However, the observed selectivity in the action of hormones or hormone-related agents in this simple organism favours the implication in the stress response of evolutionary conserved pathways that might have been generated by targeting membrane components and/or the cellular signalling and transcription machinery, thus adjusting cell survival, growth and proliferation potential in a phase of growth-dependent way.

The microenvironmental contribution to the stress response

As stated by Hanahan & Weinberg (2000), research has been focused on cancer cells and the genes within them, whereas tumours must be regarded as complex tissues in which mutant cancer cells have conscripted and subverted their normal counterparts to serve as their active collaborators. These facts along with the complexity of the stress response raise a number of questions and certainly justify several reservations. A main concern is the differential modification of the protective versus the adaptive stress response depending upon the characteristics of the noxious stimulus, microenviromental parameters, or the state of the cell. Thus, the hypothesis that interactions between non-transformed and transformed cells may provoke and/or sustain the chemotherapy-induced stress response deserves investigation. Supporting evidence comes from various reports. HSP expression could be induced by microenvironmental stress imposed by the tumour milieu (Calderwood et al. 2006) and the bone marrow microenvironment provided chemotherapy resistance via the ER stress response and possibly through protective soluble factor(s) (Yanamandra et al. 2006).

In an analogous situation, the microenvironment played a critical role in providing yeast cells with
survival signals (Vovou et al. 2004). In this model system, the cell-free supernatant of preconditioned cells conferred thermotolerance to a heat-sensitive cell precipitate (Fig. 1B). However, the data were derived from asynchronous yeast cultures and the components of the mixed transcriptionally active and inactive cells that balanced the signal(s) supplied to the culture milieu could not be determined. Further complexity was added by data that argued for the stressor-related character of this phenotype. The protective cell-free supernatant was derived from cultures exposed either to a mild heat stress or to agents targeting post-translational processes like phosphorylation. In contrast, anticancer agents appeared to activate the adaptive machinery of the cells but were incapable of generating protective signals in the extracellular microenvironment (Fig. 1A). Consequently, this challenging differential response and the nature and source of the protective signal(s) are subjects of present investigation.

Conclusion
The effectiveness of mechanism-based approaches in chemotherapy is limited by the incomplete understanding and the complexity of the signalling pathways that integrate to produce the malignant phenotype. The latest era of extensive analysis, unparalleled by the simultaneous synthesis of the in vitro and in vivo data, has overlooked the orchestration of activities dealing with the entity of the organism. Consequently, this ample information has produced only limited beneficial end points, and while available data seem encouraging, they do not substantiate a universal cellular stress response determinant that governs the response to chemotherapy.

The mechanisms underlying cytoprotective reprogramming following microenvironmental stress remain enigmatic with numerous contributors but modest clarity about effectors that balance tumour cell survival, death and resistance. While new targets have started to emerge in chemotherapy, a motivating yet unexploited line of research concerns the reevaluation of the pharmacological properties of antineoplastic agents on the basis of their crosstalk with signalling cascades and the cellular environment in both the non-transformed and/or transformed cells.

In an effort to integrate different levels of information regarding the interplay between the cellular stress response and cancer chemotherapy, the use of yeast as a simplified in vivo experimental model has provided basic evidence for the capability of anticancer agents to act as preconditioning agents and for the contribution of membrane components, signalling cascades, physiological hormone-mediated pathways and microenvironmental modifications in adjusting cell survival, death and proliferation during the chemotherapy-induced stress responses (Fig. 1A). With the hope of eventually being able to reassemble and evaluate all available information into a whole system, the relative impact that these findings have in normal and malignant mammalian systems remains to be elucidated.

Acknowledgements
The author would like to thank the PhD students, who have contributed to the field of anticancer drug research in yeast in our department.

Funding
Research on yeast was supported by the University of Athens, Greece. The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

References

Hall BL, Smit-McBride Z & Privalsky ML 1993 Reconstitution of retinoid X receptor function and combinatorial regulation of other nuclear hormone receptors in the yeast Saccharomyces cerevisiae. PNAS 90 6929–6933.


E Tiligada: Chemotherapy induced stress responses


