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Transcription factors and drug resistance

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Abstract

Intrinsic or acquired resistance to anticancer agents is a major obstacle to the success of chemotherapy. Anticancer agents are known to modulate signal transduction pathways and alter expression of genes that play an important role in drug resistance. Emerging evidence suggests that the complexity of genomic response against anticancer agents arise from elaborate gene expression by multiple transcription factors. Here, we briefly describe the development of solid tumours and the appearance of drug-resistant cells. We also review what is known of the transcription factors that are involved in resistance to drugs, particularly cisplatin.

Keywords: Transcription; DNA damage; Drug resistance; DNA repair; Cisplatin

1. Introduction

The transcriptional regulation of gene expression requires the participation of a large and diverse collection of nuclear factors, such as sequence-specific DNA-binding proteins, transcriptional cofactors, chromatin-remodelling factors, modifying enzymes and basal transcription factors [1–3]. These factors interact in a complex fashion.

Cancer is a genomic disease that is thought to arise from the accumulation of mutations leading to immortal cell proliferation. Either the activation of protooncogenes or the inactivation of tumour suppressor genes is responsible for this activity. Many protooncogenes and tumour-suppressor genes encode transcription-related factors and modulate cellular sensitivity to anticancer agents. However, little is known about those that affect responses to anticancer agents. Both intrinsic and acquired drug-resistance hinder the treatment of solid tumours. Anticancer agents activate a variety of signal transduction pathways and trigger genome-wide responses. Transcription factors contribute to drug-induced responses and can induce either transient or acquired drug resistance. Molecular dissection of the functions of transcription factors allows the complexities of solid tumour development and drug resistance to be elucidated.

Our research has focused on factors affecting the sensitivity of solid tumours to anticancer agents. The post-genomic approach has enabled us to analyse the complexity of genetic responses to anticancer agents. This is likely to reflect the activity of transcriptional networks that control the expression of many different genes and depend on the combinatorial action of numerous transcription-related factors. Investigation of the interactions between factors that are activated in response to anticancer agents is therefore essential for understanding the complexity of the genomic response. Moreover, these factors and molecular interactions constitute potential targets for chemotherapy. It is well-known

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that drug resistance is influenced by many factors, which affect intracellular drug accumulation, levels of cellular thiols and DNA-repair activity. The importance of a particular mechanism varies with the tissue origin of a tumour and the anticancer agents that are used. In this review, we focus mainly on selected transcription factors that are involved in the development of solid tumours and cisplatin resistance.

2. Solid tumour development and transcription factors

Alterations affecting transcription factors that are encoded by protooncogenes and tumour-suppressor genes are crucially involved in the malignant transformation of epithelial cells [4,5]. The common biochemical phenotype of rapidly growing cells is their ability to utilise glucose at high rates [6]. Tumour cells grow under hypoxic conditions and produce acid metabolites, such as lactate; hence, they activate transcription factors, such as hypoxia-inducible factor-1 (HIF-1), nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), in order to avoid apoptosis in response to acidosis [7–13]. These transcription factors are involved in crucial aspects of cancer biology, including pH regulation, angiogenesis, invasion, glycolysis, methylation and cell survival. Cellular acidosis reduces DNA-repair activity and causes genomic instability, leading to malignant progression. Such sequential aspects of tumour development and progression are critical for maintaining the proliferation of a solid tumour (Fig. 1).

The formation of vessels is decisive for the clinical manifestation of a solid tumour. Various endothelial cell growth factors are produced by tumours and function through either autocrine or paracrine pathways. Rapid tumour growth accompanied by angiogenesis produces many acidic metabolites and finally induces extracellular acidosis, which in turn leads to the activation of metalloproteinases. In this way, solid tumours acquire the ability to invade tissues and metastasis.

Sp1 was the first transcription factor to be cloned and is a ubiquitously expressed member of the Cys2–His2 zinc-finger family. It is frequently overexpressed in human tumours and this activity is closely correlated with the up-regulation of target genes, such as vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR) and growth-related genes. Tumour cells might operate anti-apoptotic mechanisms to avoid the induction of apoptosis by cellular acidosis. A major cellular pH regulator is the proton pump and the expression of its subunits is thought to be regulated by Sp1 [14,15]. Interestingly, there is evidence that the DNA-binding activity of Sp1 and its interaction with TATA-binding protein (TBP) are increased under low pH conditions [16]. This indicates that Sp1 should function well in solid tumours and help them to grow rapidly. Recently, p300 has been shown to act together with Sp1. This transcriptional co-activator can acetylate transcription factors and histones to regulate the cell cycle and control differentiation, and is often inactivated in tumour cells. Moreover, it has been reported that p300 expression might be involved in cellular sensitivity to anticancer agents [17].

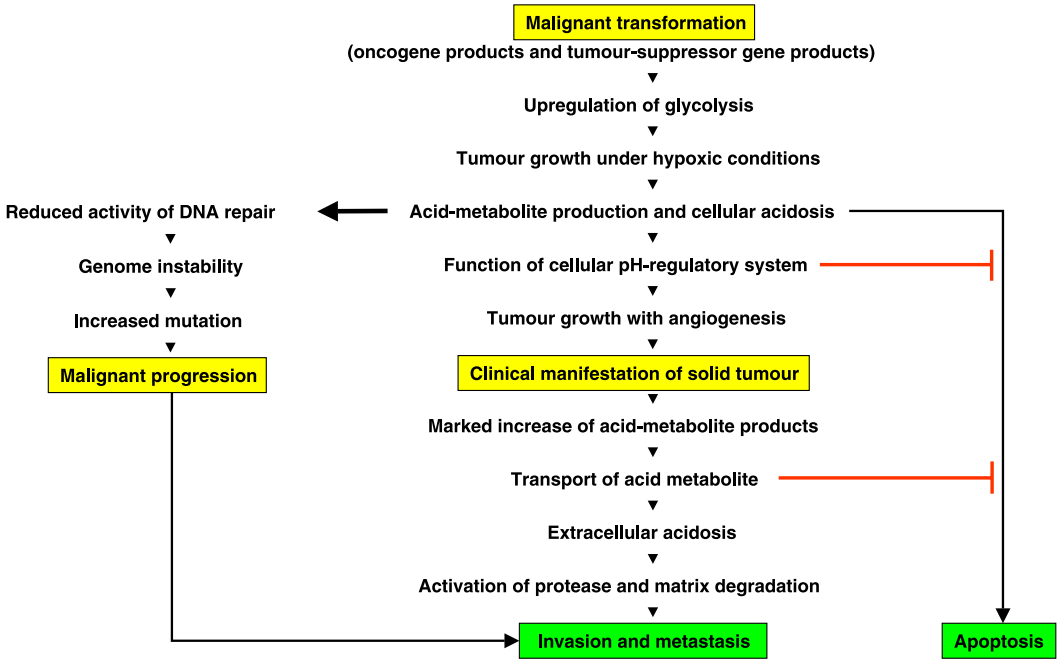

Fig. 1. Successive steps in the development and progression of a solid tumour.

3. Intrinsic and acquired resistance

The development of drug resistance by tumour cells is a major obstacle to cancer chemotherapy [18]. There are two mechanisms for the appearance of drug-resistant cells during cancer chemotherapy (Fig. 2). The first is selection, which implies that drug-insensitive cells exist in cancer cell populations and can survive selectively

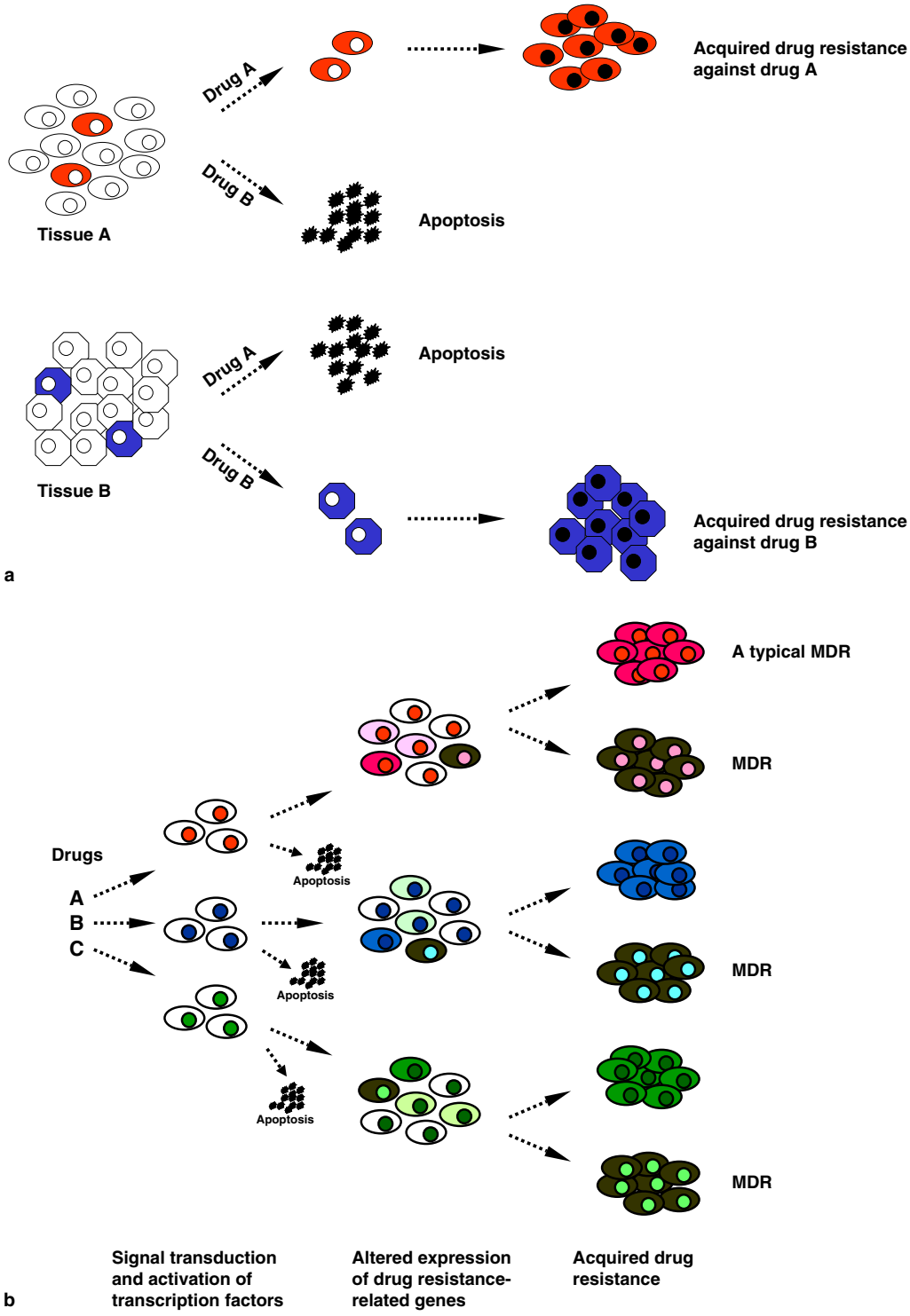

Fig. 2. Two plausible mechanisms for emergence of drug resistance during chemotherapy: (a) selection: tissue-specific expression of drug-resistance-related genes and tumour cell heterogeneity are involved. Cellular levels of drug-resistance-related gene products might be altered by genome instability leading to cellular heterogeneity in solid tumours; (b) induction: anticancer agents can activate signal transduction pathways and associated transcription factors, prompting transient expression of drug resistance- or apoptosis-related genes.

during chemotherapy. Such drug-resistant cells might be generated as a result of genetic instability. The tissue-specific expression of drug-resistance-related genes is also involved in intrinsic resistance (Fig. 2(a)). The second source of drug-resistant cells involves an induction mechanism. The treatment of cancer cells with anticancer agents might trigger signal transduction pathways and activate various transcription factors [19,20]. These can then modulate the expression of genes that are involved either in anti-apoptotic functions or in apoptosis. The nature of the signal transduction pathways that are activated by particular anticancer agents is unclear. Anticancer agents can cause genotoxic stress to cancer cells and several transcription factors might be activated, but their identity might depend on the specific drug that is used. It is also possible that different agents activate the same factors. Many target genes are transcriptionally induced by anticancer agents as part of the genomic response and specific phenotypes might be selected (Fig. 2(b)). The contribution of cancer stem cells have been recently reviewed [21]. Cancer stem cells are naturally resistant to chemotherapy through their quiescence and the expression of drug-resistant-related genes.

The establishment of drug-resistant cell lines is a well-established strategy for analysing the biochemical changes underlying drug resistance. Such analyses have revealed several mechanisms that are thought to increase drug resistance, such as increased drug efflux [22,23], the production of cellular thiols [24,25] and augmented DNA-repair activity [26,27]. These findings have potentially important implications for our understanding of intrinsic resistance. The tissue-specific expression of genes that are related to drug resistance is one of the critical determinants of the intrinsic resistance of solid tumours. To understand these molecular mechanisms more fully, it is necessary to identify and characterise all of the transcription factors that are activated in drug-resistant cells or are induced by drug treatment. Indeed, it is possible that both mechanisms might contribute to the origins of drug resistance.

The discovery of the MDR1/P-glycoprotein opened a new avenue to understanding the origins of drug resistance. The ABC transporter family is the best-studied group of membrane proteins in the field of multidrug resistance [28]. Its members are the most important determinants of both intrinsic and acquired resistance, and their tissue-specific expression is clearly involved in intrinsic tumour resistance. One member of the ABC transporter family, P-glycoprotein, is frequently present in recurrent cancers and appears after chemotherapy for various human malignancies. This indicates that the *MDR1* gene (encoding P-glycoprotein) is a suitable model for analysing the transcription factors that regulate the expression of resistance genes in response to anticancer agents. Y-box-binding protein-1 (YB-1) has been identified as a transcription factor that binds to the inverted CCAAT box of the MDR1 promoter [29], and a plausible association between YB-1 and drug resistance has been observed in cultured cancer cell lines and clinical samples. YB-1 is mainly located in the cytoplasm; however, when cells are challenged with anticancer agents, heat shock or ultraviolet (UV) irradiation, YB-1 is immediately translocated to the nucleus [30]. Moreover, the promoter activity of the *MDR1* gene increases in response to various environmental stresses in a Y-box-dependent manner [31–33]. When the expression of YB-1 was lowered by antisense constructs in human cancer cells, their sensitivity to DNA-damaging agents increased; the same was true when one *YB-1* allele was disrupted in mouse embryonic stem cells [29,34,35]. YB-1 expression induced a strong cellular resistance to malignant transformation through the phosphatidyle inositol 3-kinase pathway [36,37]. Contrary to this findings, it has been shown that novel transgeneic mouse model with human hemagglutinin-tagged YB-1 controlled by the β-lactoglobulin promoter provokes diverse breast carcinomas through the induction of genetic instability [38]. It remains unclear whether YB-1 possesses oncogenic function. YB-1 is often overexpressed in cisplatin-resistant cell lines and can recognise cisplatin-modified DNA [29,39,40]. Furthermore, it interacts with molecules that are involved in DNA repair, such as proliferating cell nuclear antigen (PCNA), Ku80 and mutS homologue-2 (MSH2) [41]. YB-1 has pleiotropic functions and modulates cell growth, apoptosis, drug resistance, DNA repair, transcription and translation [42–44].

These observations indicate that YB-1 is upregulated by the activation of transcription factors and acts at the end of one or more drug-induced stress-response pathways. These findings support the induction mechanism postulated in Fig. 2(b).

It is very important to analyse the expression of YB-1 using clinical specimens, because human tumours models such as cell lines only partially reflect the complexity of human cancer. Many reports on YB-1 expression is solid tumours have been published previously (Table 1). Nuclear expression of YB-1 was reported to be involved in P-glycoprotein expression, malignant progression, poor prognosis and drug resistance. Therefore, YB-1 could be a useful indicator of malignancy as well as a promising target for cancer therapy.

4. Drug resistance and transcription factors

Drug and apoptosis resistance are two sides of the same coin. Oncogenic transcription factors, such as Myc, NF-κB, AP-1 and tumour suppressor gene products such as p53 and p73 have been connected to several aspects of carcinogenesis, including the cell cycle, differentiation, apoptosis and drug resistance [4,45]. c-Myc

Table 1
The association of YB-1expression with malignant characteristics

Tumor type	Malignant characteristics	References
Ovarian cancer	P-glycoprotein expression and poor prognosis[a]	[70]
	P-glycoprotein expression and poor prognosis[a]	[71]
	Cisplatin resistance	[72]
Breast cancer	P-glycoprotein expression	[73]
	P-glycoprotein expression and poor prognosis[a]	[74]
	Drug resistance	[75]
	Tumor aggressiveness	[76]
Osteosarcoma	P-glycoprotein expression	[77]
Synovial sarcoma	P-glycoprotein expression and poor prognosis[a]	[78]
Prostate cancer	P-glycoprotein expression and poor prognosis[a]	[79]
Lung cancer	Poor prognosis	[80]
	Disease progression and poor prognosis[a]	[81]
	Proliferation-associated maker	[82]
Thyroid carcinoma	Anaplastic transformation	[83]
Colon cancer	Proliferation-associated maker	[84]

[a] Disease progression or prognosis is significantly correlated with nuclear YB-1 expression.

binds to E-box and transactivates various genes including YB-1 [46]. Low expression of c-Myc results in increased susceptibility to cisplatin [47,48]. NF-κB is well-known as key transcriptional mediator of a variety of cellular responses. NF-κB has been shown to induce drug resistance through MDR1 expression [49]. It has been reported that NF-κB inhibition increases resistance to cisplatin [50]. The activation protein-1 (AP-1) is involved in crucial aspects of cancer biology and its activity is induced by various environmental stimuli [51]. AP-1 was found to involve in various drug-resistant related genes, including, P-glycoprotein [52,53], GST-π [54] and ERCC1 [55]. The two tumour-suppressor genes, p53 and p73, are central to the genomic response to DNA damage [56,57]. Cancer cells carrying mutant p53 are generally less sensitive to anticancer agents [58]. p73 possesses structural and functional similarities to p53. It has recently been reported that p73α overexpression is associated with resistance to DNA-damaging agents [59]. Hypoxia-inducible factor 1 (HIF-1) is expressed in many human cancers and transactivates the genes that are involved in solid tumour development including glucose metabolism, angiogenesis and invasion [7]. It has been shown that hypoxia activates signal transduction pathway and increases the expression of P-glycoprotein. This activity is mediated through the HIF-1 [60]. Several excellent reviews have been published on the apoptosis-related genes that are regulated by these transcription factors [61–64], and the transcriptional and epigenetic regulation of MDR1 has been studied extensively [22,42,44,65].

One of the major obstacles to the successful treatment of cancers is the complex biology of solid tumour development (Fig. 1). Cisplatin is one of the most potent anticancer agents and is used in the treatment of various solid tumours. The nature of the cellular determinants of platinum compound sensitivity is therefore important for defining clinical strategies. Cisplatin treatment induces DNA-damage signalling as well as oxidative and endoplasmic reticulum (ER) stresses [66]. This suggests that cellular sensitivity to cisplatin is highly complex. DNA is the primary target of cisplatin and one of its major cytotoxic effects is the formation of cisplatin-DNA adducts. As it is likely that the transcription factors for genes involved in cisplatin resistance can be activated by DNA damage, the identification and study of cisplatin-induced transcription factors might provide a shortcut for assessing cisplatin sensitivity in a clinical setting.

Two transcription factors, activating-transcription factor-2 (ATF2) and ATF4, are involved in cisplatin resistance [67,68]. These are both members of the ATF/cyclic AMP-response element-binding (CREB) family of transcription factors, which are widely expressed in tumours and function as homo- or heterodimers. ATF2-dependent resistance is due to increased DNA-repair activity [67], whereas ATF4-dependent resistance might be due to increased glutathione (GSH) levels [68]. This difference in mode of action is probably due to variation in the partners with which these two factors interact. A significant finding is that the cellular expression of ATF4 correlates with cisplatin sensitivity in human lung cancer cell lines, suggesting that ATF4 is the first transcription factor known to affect intrinsic drug resistance. Little is known about the target genes of ATF2 and ATF4.

The zinc-finger transcription factor ZNF143 is the human homologue of selenocysteine tRNA gene transcription-activating factor (Staf). Expression of the *ZNF143* gene is upregulated by cisplatin treatment and, as its promoter region contains a cAMP-responsive element (CRE), it might be a target of either ATF2 or ATF4. Furthermore, ZNF143, like YB-1, binds preferentially to cisplatin-modified DNA, suggesting that it might participate in the surveillance of DNA damage [69]. A schematic summary of the pathways of cisplatin

resistance is shown in Fig. 3 and the transcription factors considered in this review are listed in Table 2.

Alterations of nuclear architecture and genetic instability are hallmarks of cancer. Cisplatin actually targets DNA as part of chromatin, and might cause structural alterations that disturb the functional cooperation of tumour suppressors, non-histone chromosomal proteins, histone, chromatin-remodelling factors, DNA-repair

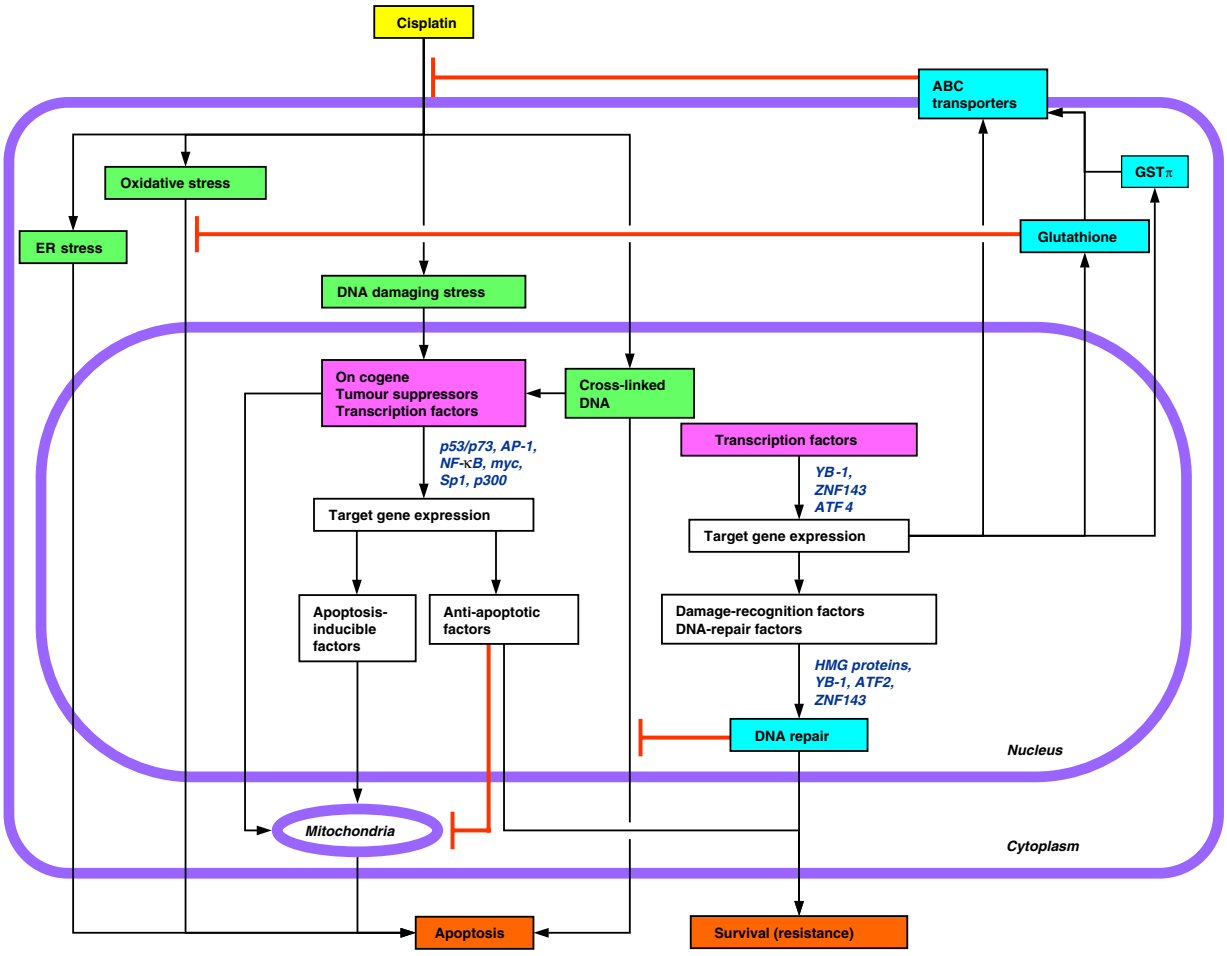

Fig. 3. Schema for cisplatin-induced cytotoxic signalling and cisplatin resistance. The associated transcription factors discussed in this review are shown.

Table 2
Selected transcription factors associated with drug resistance

Transcription factor	Selected target genes	Selected interacting factors	Drug resistance	Other functions	References
c-Myc	*Bax, p53, YB-1*	Sp1, Max	CDDP	Cell proliferation	[47,48,85]
NF-κB	*Fas/Fas ligand, MDR1*	I-κB, c-Jun	CDDP, Paclitaxel, DOX, 5-FU	Angiogenesis	[49,50]
AP-1 (c-Jun)	*GSTπ, MDR1, ERCC1*	NF-κB		Angiogenesis and sensitivity to CDDP	[52–55,86]
p53/p73	*Bax, MDR1*	HMG1, YB-1, p300	CDDP	Cell-cycle arrest and DNA repair	[56–59,87]
HIF-1α	*MDR1*	DNA-PK		Tumor hypoxia	[7,60,88–90]
Sp1	*MDR1, Topoisomerase IIα*	p300	TAS-103, DOX	Cell proliferation	[17,91]
ATF4	*ZNF143*		CDDP	Glutathione biosynthesis	[68]
YB-1	*MDR1, Topoisomerase IIα*	p53, PCNA	CDDP, MMC	Damage recognition	[39,87]
ZNF143	*mtTFA*		CDDP	Damage recognition	[69]

5-FU, 5-fluorouracil; AP-1, activator protein-1; ATF4, activating transcription factor-4; CDDP, cisplatin; DNA-PK, DNA-dependent protein kinase; DOX, doxorubicin; GST, glutathion-*S*-transferase; HIF-1α, hypoxia-inducible factor-1α; HMG, high mobility group; I-κB, inhibitor-kappa B; MDR, multi-drug resistance; MMC, mitomycin C; mtTFA, mitochondria transcription factor A; NF-κB, nuclear factor-kappa B; PCNA, proliferating cell nuclear antigen; Sp1, specificity protein-1; YB-1, Y-box binding protein-1; ZNF143, zinc finger 143.

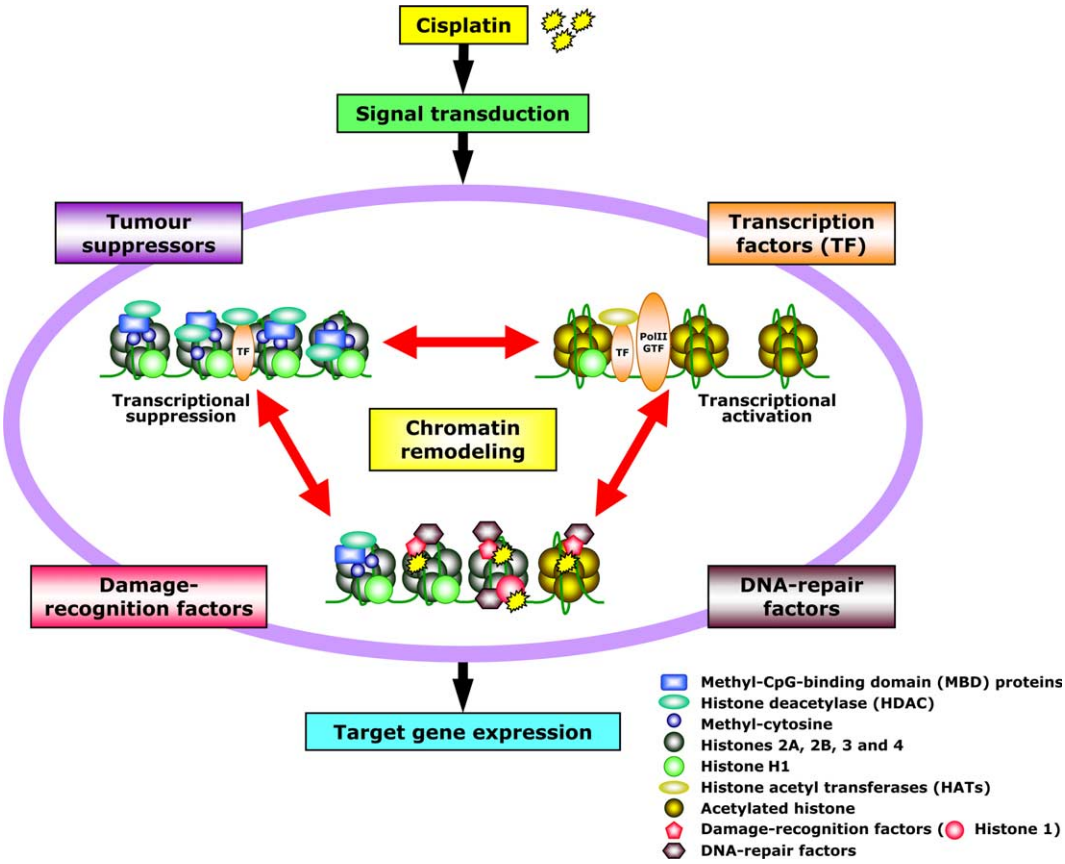

Fig. 4. Molecular interactions involved in DNA surveillance and gene expression systems. Cisplatin treatment activates *inter alia* transcription factors, DNA-repair factors, damage-recognition factors, tumour suppressors and chromatin-remodelling factors, which interact to form complexes that function in the nucleus. Drugs might alter interaction profiles.

factors and transcription factors [2,3] (Fig. 4). Among these chromatin constituent, histone H1, TATA binding protein and high mobility group (HMG) proteins are known to recognise the cisplatin-modified DNA (64). These observations indicate that chromatin components make an important contribution to the architectural regulations required to genetic instability, gene expression and drug resistance.

5. Conclusions

Knowledge of the molecular links between transcription factors and drug resistance promises to provide the foundation for novel molecularly targeted cancer chemotherapies. Microarray studies of drug-treated cells or drug-resistant cell lines have mainly identified easily detected and highly expressed genes. These studies might fail to reveal the transcriptional network that governs the genomic response to anticancer agents, because transcription factors might function mainly by interacting with other components. Both the quality and quantity of transcription factors is tightly regulated in cells. It is therefore crucial to identify the relevant transcription factors by analysing the promoters of genes that are either induced by drug treatment or overexpressed in drug-resistant cells.

Furthermore, we should pay attention to subtle changes in transcription factors, such as single nucleotide polymorphisms. The ability to detect small changes in transcription factors is important for interpreting expression profiles. Finally, although analysis of the transcriptional regulation of drug-resistance genes is fundamentally important, analysis of the interactions of transcription factors as they are modified by anticancer agents, either post-transcriptionally or by interactions with other proteins, will also be essential in order to understand the total genomic response. Such studies should enhance our understanding of drug sensitivity and permit the development of novel molecularly targeted drugs [10].

Conflict of interest statement

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