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Biochemical Pharmacology 64 (2002) 943–948

Biochemical Pharmacology

Transcriptional regulators of the human multidrug resistance 1 gene: recent views

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Received 5 March 2002; accepted 8 April 2002

Abstract

The multidrug resistance (MDR) phenotype is the major cause of failure of cancer chemotherapy. This phenotype is mainly due to the overexpression of the human *MDR*1 (h*MDR*1) gene. Several studies have shown that transcriptional regulation of this gene is unexpectedly complex and is far from being completely understood. Current work is aimed mainly at defining unclear and new control regions in the h*MDR*1 gene promoter as well as clarifying corresponding signaling pathways. Such studies provide new insights into the mechanisms by which xenobiotic molecules might modify the physiological h*MDR*1 expression as well as the possible role of oncogenes in the pathological dysregulation of the gene. Here we report recent findings on the regulation of h*MDR*1 which may help define specific targets aimed at modulating its transcription.

Keywords: h*MDR*1 gene; Multidrug resistance; P-glycoprotein; Transcriptional regulation

1. Introduction

It is generally admitted that cancer cells that develop resistance to several drugs and express the multidrug resistance (MDR) phenotype, are the most deleterious. This phenotype is characterized by a pleiotropic resistance to various lipophilic drugs, most of which are natural compounds, such as antibiotics and plant or fungal alkaloids. This phenomenon is related to a decrease in the intracellular accumulation of drugs [1] that results, at least partially, from an energy-dependent increase of efflux [2]. It is now clear that one of the major mechanisms of drug resistance in MDR mammalian cancer cells involves an increased expression of a 170 kDa membrane protein called P-glycoprotein (Pgp) [3], the structure of which is under study [4–6]. Pgp, which is a member of the ATP binding cassette (ABC) transporter family [7,8], is encoded by the *MDR*1 class of genes [9] also called *ABCB1*. Each case of Pgp-related MDR has been related to an increased human *MDR*1 (h*MDR*1) mRNA level that can be linked either to gene amplification and/or increased gene transcription [10,11]. Amplification of the *MDR*1 gene involves four to five neighboring genes that are not related to MDR and which are organized in amplicon [12].

In certain MDR cell lines and tumors, h*MDR*1 transcripts are initiated upstream of the common +1 start site suggesting either the existence of an upstream promoter [13] or of a heterologous promoter that has been translocated to the 5′ end of the h*MDR*1 gene [14]. Like many TATA-less promoters, the promoter of *MDR*1 genes contains multiple start sites [15].

Work is in progress to elucidate both new and poorly understood regions in the h*MDR*1 gene promoter and corresponding regulators. Data obtained so far reveal a complex regulatory pattern. Here we describe current

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Abbreviations: ABC, ATP binding cassette; *APC*, *adenomatous polyposis coli*; EMSA, electrophoretic mobility shift assay; HSE, heat shock element; IL-1, interleukin-1; IL-6, interleukin-6; INR, initiator region; invMED1, inverted MED-1 element; MDR, multidrug resistance; *MDR*1, multidrug resistance 1 gene; h*MDR*1, human *MDR*1 gene; mRNA, messenger RNA; Py, pyrimidine; SXR, steroid xenobiotic receptor; TNF, tumor necrosis factor; TPA, 12-*O*-tetradecanoylphorbol-13-acetate.

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PII: S0006-2952(02)01156-5

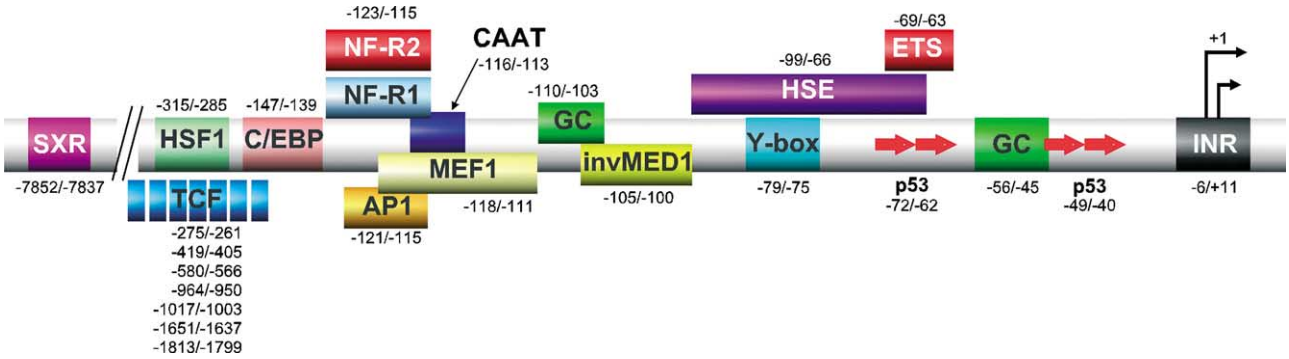

Fig. 1. Untranslated 5′ regulatory region of the human *MDR*1 gene showing promoter elements. All elements represented in the figure are discussed in the text. Numbers indicate their position relative to the major +1 start site. Two arrows over the initiator window indicate the major and secondary start sites reported in the literature.

knowledge in this area which may lead to new concepts on the way to therapeutic downregulation.

2. Initiator region

Regulation of the transcriptional activity of the h*MDR*1 gene depends on several *trans*-acting proteins that bind consensus *cis*-elements (Fig. 1). This gene differs greatly from its murine homologues in that its promoter lacks a TATA-box [13] and contains an initiator element (INR) [16]. The INR is defined by the consensus formula Py-Py-A(+1)-N-(T/A)-Py-Py [17] and is necessary to direct basal transcription at the major initiation start point [18]. Positions of bases cited below refer to the major +1 start site as defined in the above formula.

Transient transfection studies have indicated that sequences between −6 and +11 were sufficient for proper initiation of transcription [16].

3. h*MDR*1 gene promoter elements

3.1. GC-box

Several experiments have revealed a GC-rich region in the h*MDR*1 promoter located −56 to −45 bases upstream of the major +1 start site, to which Sp1 was found to bind [19]. Sp1 is a 105 kDa constitutive and ubiquitous nuclear transcription factor that binds mostly TATA-less promoters [20]. This factor plays an important facilitating role but it is not itself implicated in changing transcription rates of genes. For this reason, Sp1 is mostly involved in house-keeping genes.

Mutation of the GC-box in the h*MDR1* gene reduced promoter activity 5-fold, indicating a transcriptional stimulatory role for Sp1 [19]. The same authors showed that this region contains overlapping sites allowing the specific binding of both Sp1 and EGR1, a zinc finger 80 kDa protein also implicated in the activation of the h*MDR*1 gene.

Interestingly, during aberrant Pgp overexpression in hematopoietic cancers, it has been reported that 12-*O*-tetradecanoylphorbol-13-acetate (TPA) increases transcription of the h*MDR*1 gene and activates the h*MDR*1 promoter through binding of EGR1 [21]. In the same study, WT1, the Wilms' tumor suppressor, another member of the EGR family, downregulates h*MDR*1 gene transcription through direct binding of WT1 to the same GC element [22]. These results suggest that the h*MDR*1 gene is regulated by both EGR1 and WT1 in an antagonistic manner through competition for the same binding region during normal and tumoral hematopoiesis. Moreover, competition between EGR1 or Sp1 and WT1 has also been reported in other gene promoters, thereby reinforcing the previous hypothesis [23,24].

3.2. Inverted CCAAT element (Y-Box)

One-third of all promoters studied appear to contain a CCAAT element that is found in the sense orientation or in the inverse complement ATTGG, also called the Y-Box. Most studies of TATA-less promoters report the presence of a Y-box. In the case of the h*MDR*1 gene, the Y-box is located at the −79 to −75 sequence position. It has been shown that induction of the h*MDR*1 gene by UV radiation or by various anticancer molecules involves the Y-box [25]. Several recent studies seem to point to NF-Y as the most likely protein to bind to this element in order to activate h*MDR*1 in MDR tumor cell lines [26,27].

Other studies challenge the role of YB-1 and its binding to the Y-box [25,26,28]. This disagreement may relate to its possible role other than solely as a DNA-binding protein, such as RNA binding [29–31].

Transcriptional regulation at this Y-box seems, however, to be more complex since mutational analyses have provided evidence that the Y-box and the closely located GC-box may cooperate in regulating h*MDR*1 gene expression [26]. Both Y-box and GC elements have recently been reported to be essential for activation of h*MDR*1 after UV irradiation [28]. These results, which suggest a cooperative interaction between the GC- and Y-boxes, have recently been reinforced by the demonstration of the physical interaction between Sp1 and NF-Y in the absence of DNA and in a context unrelated to MDR [32].

Moreover, mutation of the proximal Y-box in other promoters has led to the disruption of binding to the adjacent GC-box [33]. These results open the way to new emerging ideas in which NF-Y could play an essential role in both the architectural and functional organization of TATA-less promoters, perhaps by connecting upstream regulators to the general transcriptional machinery [34].

3.3. p53 element

Several tumors that have never been in contact with any anticancer drug express the Pgp-dependent MDR phenotype. Since cellular oncogenes and tumor suppressor genes are often reported to be altered in the cancer progression process, it is likely that the resulting altered proteins may influence Pgp expression. A considerable amount of data has been focused on the effects of the p53 tumor suppressor gene and protein on the MDR phenotype. These report an inhibitor role for wild type p53 on the h*MDR*1 gene promoter whereas mutant versions of p53 act as activators [35], probably by the loss of their inhibitor effect [36,37]. Another possibility may reside in the interaction between mutated p53 and the proto-oncogenic ETS-1 factor, which binds its element located from −69 to −63 bases [38].

In some cases wild type p53 has been reported as an activator of the h*MDR*1 gene [39], an apparent contradiction probably due to the wide spectrum of action of p53 and to major differences in experimental conditions. In all cases, p53-mediated regulation of the h*MDR*1 gene involves the minimal promoter region from −39 to +53 even though no p53 consensus binding sequence has been discovered. The consensus p53 binding site consists of two half-sites, each comprising two repeats of five nucleotides arranged head to head [40]; under this configuration, p53 *trans*-activates several genes. Recently, a new model has been suggested to explain the action of p53 on h*MDR*1. In this model, a binding region has been proposed in the h*MDR*1 gene in which the two half-sites are arranged in a head to tail configuration leading to p53 repression [37]. Apart from several debates concerning the direct binding of p53 to the h*MDR*1 promoter, it is possible to imagine a modulating effect resulting from its interaction with such factors as Sp1, NF-Y, C/EBPβ, or AP-1, all of which bind the h*MDR*1 gene promoter.

3.4. AP-1 element

Many studies propose that AP-1 mediated signals may be important regulators of h*MDR*1. To date, only indirect data implicate c-*fos* and c-*jun* in the formation of regulating complexes on the h*MDR*1 gene. One argument lies in the fact that MDR cells often contain a higher level of c-*fos* and c-*jun* proteins than their sensitive parental cells. Moreover, several putative AP-1 sites may be found on the h*MDR*1 gene promoter. To strengthen this idea, a recent report points to the possible activating role of a c-*jun* dimer on an AP-1 site located between bases −121 and −115 [41].

3.5. CAAT element

A CAAT element (bases −116 to −113) has been found to bind a complex of NFκB/p65 and c-*fos* proteins and which exerts a negative regulatory effect on sensitive tumor cells but not on their resistant counterparts [42]. This interestingly draws to our attention a new regulatory mechanism in which two unrelated factors interact to exert a negative transcriptional regulation.

3.6. C/EBP element

The C/EBP family of proteins is involved in the basal and tissue-specific expression of a number of genes. C/EBPβ, also called NF-IL-6, has been shown to induce a positive regulation of the h*MDR*1 gene [43]. Its putative binding sequence is located between positions −147 to −139. C/EBPβ is usually expressed at low levels in most tissues; however, it may be rapidly induced in response to lipopolysaccharides, inflammation cytokines (IL-1, IL-6, TNF) and retinoic acid.

3.7. Heat shock element (HSE)

It has been shown that heat shock increases both h*MDR*1 mRNA levels [44] and h*MDR*1 gene transcription in reporter vectors [45]. Several putative HSE sequences have been identified in the h*MDR*1 promoter, suggesting that this gene may be considered as a stress gene. An HSE region spanning bases −99 to −66 has been proposed as a requirement for the heat shock response. However, no direct interaction with HSF proteins has been mentioned [46]. Recently, another HSE region (bases −315 to −285) has been reported to directly regulate the expression of h*MDR*1 through HSF1 since a dominant negative mutated HSF1 fails completely to respond to heat induction [47].

3.8. TCF elements

Members of the TCF family of factors have been reported as tumor inducers [48] and are involved in the proliferation and progression of cancer [49]. These factors are transcriptionally inactive but become activated after interaction with β-catenin and then overactivate their target genes as a result of elevated β-catenin levels in many cancer types. The increased level of β-catenin results from a mutation in the *adenomatous polyposis coli* (*APC*) gene, a tumor suppressor, or from a mutation in the β-catenin gene, therefore stabilizing the protein. These mutations have been linked to colorectal adenomas (for *APC*) and to skin and liver tumors (for β-catenin). More specifically, a TCF4/β-catenin complex, which binds seven elements spanning the −1813 to −261 sequence, has been reported as an h*MDR*1 transcriptional activator that may promote early abnormal expression of this gene in colorectal carcinogenesis [50].

3.9. Steroid xenobiotic receptor (SXR) element

A recently discovered upstream enhancer containing a motif related to broad specificity xenobiotic sensitivity has been attributed to the −7852 to −7837 sequence in the h*MDR*1 promoter. This sequence binds a pregnane xenobiotic receptor/retinoid xenoboitic receptor α (PXR/RXRα) heterodimer that activates *MDR*1 transcription in response to several xenobiotic inducers such as nifedipine, RU486, dexamethazone, and rifampin [51]. The SXR family of nuclear receptors is involved in the regulation of drug clearance pathways and may coordinate drug metabolism *via* cytochrome P450 genes (*CYP3A4* and *CYP2C8*) and drug efflux *via* h*MDR*1. In addition, SXR may also regulate MDR in SXR-expressing tumors [52].

4. A new −123/−100 cluster of interest

The h*MDR*1 gene promoter contains an interesting region spanning 23 bases from positions −123 to −100. This cluster has been shown to bind AP-1 and NFκB/p65/c-*fos* in overlapping sequences. In addition, it may also bind new regulators hitherto undescribed.

- The sequence −123 to −115 has previously been shown to bind two different proteins NF-R1 and NF-R2 in an MDR-independent manner, resulting in antagonistic effects on transcription [53,54]. However, the role of these proteins still remains unclear as no further data have been reported.
- A GC-rich region (bases −110 to −103) has been shown to bind an unknown but specific nuclear factor that acts as an h*MDR*1 repressor which has not been reported previously [19].
- A 130 kDa protein called MDR1 promoter-enhancing factor 1 (MEF1) has recently been shown to upregulate the h*MDR*1 gene upon binding to the sequence −118 to −111 [55]. This protein has been detected after EMSA experiments in HL60/vcr resistant cells but not in MCF-7/adr resistant cells suggesting that its expression and/or binding may be tissue or cell-line dependent.
- Interestingly, overlapping the −110/−103 GC-rich element is an inverted MED-1 element (invMED1) which has been recently described in the human resistant lymphoblastic leukemia cell lines (CEM) and which plays an important role in the control of h*MDR*1 gene transcription [56]. This element spans 6 bases from −105 to −100. A transcriptional decoy, which reproduces this sequence in order to sequester invMED1-binding proteins, has allowed us to functionally down-regulate h*MDR*1, therefore sensitizing chemoresistant CEM cell lines. Deletion of this element induced a 60% inhibition in h*MDR*1 transcriptional activity in transient transfection experiments of moderately and highly resistant CEM/VLB0.45 and CEM/VLB5 cells, respectively. This result suggests that invMED1 acts as a *cis*-activator for this gene [57]. We also showed that this sequence specifically binds to a nuclear protein, the characterization of which is in progress.

5. Regulation at a higher level of complexity

All data collected from the study of the h*MDR*1 gene promoter suggest a complex regulation pattern, probably extending beyond the simple house-keeping TATA-less gene concept. In addition, the recently discovered binding sites in the h*MDR*1 gene promoter suggest the idea that transcription factors may act through competitive or cooperative interactions.

It is now clear that overlapping binding elements do play functional roles in the regulation of gene transcription through competition between several factors for DNA binding [58]. However, one should keep in mind that such competition depends both on tissue and cell co-expression of transcription factors and on variations in their relative quantities according to physiological and environmental conditions. Under these circumstances, the previously mentioned −123/−100 cluster would represent an important region for the regulation of the h*MDR*1 gene. This reinforces the necessity to intensify the study of this region and its related factors.

Another way to modulate gene expression comes from the study of interactions between gene regulation-related proteins. Depending on the cellular context, a DNA-binding factor may bind different co-factors. In addition, interactions between different DNA-binding factors in the same gene may promote the building of complex regulatory structures such as constitutive and regulated transcription factors that participate together in making up enhanceosomes [59,60]. This may be the case, for example, of Sp1 and NF-Y as previously discussed; the −123/−100 cluster may also be a good candidate for such organization.

Following on from this protein interplay, the accessibility of promoter elements to their binding factors is regulated at the level of chromatin assembly. Levels of both histone acetylation and DNA methylation are known to regulate gene expression. The h*MDR*1 gene is no exception to this rule [61,62] and the accessibility of certain elements or clusters of elements in the gene promoter may participate in its fine regulation or in its abnormal overexpression.

6. Conclusion

Knowledge of the transcriptional regulation of the h*MDR*1 gene is far from being complete. However, the previously mentioned studies bring new insights into the links, on the one hand, between xenobiotics and the

physiological modulation of h*MDR*1 and, on the other, between oncogenes and the pathological expression of h*MDR*1 in tumors.

In the light of the emerging novel organization of DNA-binding elements in the h*MDR*1 promoter, the combination of such regions, which is unique to a given promoter, clearly represents an important element of the specific expression of this gene.

Even though a few new chemosensitizers are undergoing clinical trials, the difficulties encountered with several generations of these products in modulating the MDR phenotype may be counter-balanced by the search for an adequately specific target in the regulatory structures of the h*MDR*1 promoter. This reinforces the necessity to increase understanding of the transcriptional regulation of this gene.

Acknowledgments

This work was supported by grants from the ''Ligue contre le Cancer Comité du Rhône'', and the ''Association Retina France''. Stéphane Labialle, Landry Gayet and Eric Marthinet are recipients of grants from the Fondation Mérieux, the ''Ligue contre le Cancer Comité de la Loire'', and the ''Fondation pour la Recherche Médicale'', respectively.

References

[1] Kessel D, Botterill V, Wodinsky I. Uptake and retention of daunomycin by mouse leukemic cells as factors in drug response. Cancer Res 1968;28:938–41.
[2] Danø K. Active outward transport of daunomycin in resistant ehrlich ascites tumor cells. Biochim Biophys Acta 1973;323:466–83.
[3] Juliano RL, Ling VA. Surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochim Biophys Acta 1976;455:152–62.
[4] Rosenberg MF, Callaghan R, Ford RC, Higgins CF. Structure of the multidrug resistant P-glycoprotein to 2.5 nm resolution determined by electron microscopy and image analysis. J Biol Chem 1997; 272: 10685–94.
[5] Dong M, Ladavière L, Deleage G, Penin F, Baggetto LG. Secondary structure of P-glycoprotein from circular dichroism and prediction from its sequence. Biochim Biophys Acta 1998;1371:317–34.
[6] Rosenberg MF, Velarde G, Ford RC, Martin C, Berridge G, Kerr ID, Callaghan R, Schmidlin A, Wooding C, Linton KJ, Higgins CF. Repacking of the transmembrane domains of P-glycoprotein during the transport ATPase cycle. EMBO J 2001;20:5615–25.
[7] Walker JE, Saraste M, Runswick MJ, Gay NJ. Distantly related sequences in the α- and β-subunits of ATPsynthase, myosin, kinases and other ATP-requiring enzymes and a common nucleotide binding fold. EMBO J 1982;1:945–51.
[8] Higgins CF, Hyde SC, Mimmack MM, Gileadi U, Gill DR, Gallagher MP. Binding protein-dependent transport systems. J Bioenerg Biomembr 1990;22:571–93.
[9] Gros P, Ben Neriah YB, Croop JM, Housman DE. Isolation and expression of a complementary DNA that confers multidrug resistance. Nature 1986;323:728–31.
[10] Shen DW, Fojo A, Chin JE, Roninson IB, Richert N, Pastan I, Gottesman MM. Human multidrug-resistant cell lines: increased mdr1 expression can precede gene amplification. Science 1986; 232:643–5.
[11] Fojo AT, Whang-Peng J, Gottesman MM, Pastan I. Amplification of DNA sequences in human multidrug-resistant KB carcinoma cells. Proc Natl Acad Sci USA 1985;82:7661–5.
[12] de Bruijn MHL, Van der Bliek AM, Biedler JL, Borst P. Differential amplification and disproportionate expression of five genes in three multidrug-resistant Chinese hamster lung cell lines. Mol Cell Biol 1986;6:4717–22.
[13] Ueda K, Pastan I, Gottesman MM. Isolation and sequence of the promoter region of the human multidrug resistance (P-glycoprotein) gene. J Biol Chem 1987;262:17432–6.
[14] Mickley LA, Spengler BA, Knutsen TA, Biedler JL, Fojo T. Gene rearrangement: a novel mechanism for MDR-1 gene activation. J Clin Invest 1997;99:1947–57.
[15] Ince TA, Scotto KW. Transcriptional regulation of multidrug-resistant genes. Encyclopedia of cancer 1997;III:1751–64.
[16] Van Groenigen M, Valentijn LJ, Baas F. Identification of a functional initiator sequence in the human *MDR*1 promoter. Biochim Biophys Acta 1993;1172:138–46.
[17] Javahery R, Khachi A, Lo K, Zenzie-Gregory B, Smale ST. DNA sequence requirements for transcriptional initiator activity in mammalian cells. Mol Cell Biol 1994;14:116–27.
[18] Smale ST, Baltimore D. The ''initiator'' as a transcription control element. Cell 1989;57:103–13.
[19] Cornwell MM, Smith DE. Sp1 activates the *MDR*1 promoter through one of the two distinct G-rich regions that modulate promoter activity. J Biol Chem 1993;268:19505–11.
[20] Lania L, Majello B, De Luca P. Transcriptional regulation by the Sp family proteins. Int J Biochem Cell Biol 1997;29:1313–23.
[21] McCoy C, Smith DE, Cornwell MM. TPA activation of the *MDR*1 promoter is mediated by EGR-1. Mol Cell Biol 1995;15:6100–8.
[22] McCoy C, McGee SB, Cornwell MM. The Wilms' tumor suppressor WT1 inhibits 12-O-tetradecanoylphorbol-13-acetate activation of the multidrug resistance-1 promoter. Cell Growth Differ 1999;10:377–86.
[23] Harrington MA, Konicek B, Song A, Xia XL, Fredericks WJ, Rauscher III FJ. Inhibition of colony-stimulating factor-1 promoter activity by the product of the Wilms' tumor locus. J Biol Chem 1993; 268:21271–5.
[24] Moshier JA, Skunca M, Wu W, Boppana SM, Rauscher III FJ, Dosescu J. Regulation of ornithine decarboxylase gene expression by the Wilms' tumor suppressor WT1. Nucleic Acids Res 1996;24:1149–57.
[25] Ohga T, Koike K, Ono M, Makino Y, Itagaki Y, Tanimoto M, Kuwano M, Kohno K. Role of the human Y box-binding protein YB-1 in cellular sensitivity to the DNA-damaging agents cisplatin, mitomycin C, and ultraviolet light. Cancer Res 1996;56:4224–8.
[26] Sundseth R, MacDonald G, King AC. DNA elements recognizing NF-Y and Sp1 regulate the human multidrug-resistance gene promoter. Mol Pharmacol 1997;51:963–71.
[27] Jin S, Scotto KW. Transcriptional regulation of the *MDR*1 gene by histone acetyltransferase/deacetylase is mediated by NF-Y. Mol Cell Biol 1998;18:4377–84.
[28] Hu Z, Jin S, Scotto KW. Transcriptional activation of the MDR1 gene by UV irradiation. Role of NF-Y and Sp1. J Biol Chem 2000; 275:2979–85.
[29] Wolffe AP. Structural and functional properties of the evolutionarily ancient Y-box family of nucleic acid binding proteins. Bioessays 1994; 16:245–51.
[30] Skabkin MA, Evdokimova V, Thomas AA, Ovchinnikov LP. The major messenger ribonucleoprotein particle protein p50 (YB-1) promotes nucleic acid strand annealing. J Biol Chem 2001;276:44841–7.
[31] Evdokimova V, Ruzanov P, Imataka H, Raught B, Svitkin Y, Ovchinnikov LP, Sonenberg N. The major mRNA-associated protein YB-1 is a potent 5′ cap-dependent mRNA stabilizer. EMBO J 2001;20:5491–502.
[32] Roder K, Wolf SS, Larkin KJ, Schweizer M. Interaction between the two ubiquitously expressed transcription factors NF-Y and Sp1. Gene 1999;234:61–9.

[33] Linhoff MW, Wright KL, Ting JP. CCAAT-binding factor NF-Y and RFX are required for in vivo assembly of a nucleoprotein complex that spans 250 base pairs: the invariant chain promoter as a model. Mol Cell Biol 1997;17:4589–96.
[34] Mantovani R. A survey of 178 NF-Y binding CCAAT boxes. Nucleic Acids Res 1998;26:1135–43.
[35] Nguyen KT, Liu B, Ueda K, Gottesman MM, Pastan I, Chin KV. Transactivation of the human multidrug resistance (MDR1) gene promoter by p53 mutants. Oncol Res 1994;6:71–7.
[36] Chin KV, Ueda K, Pastan I, Gottesman MM. Modulation of the activity of the promoter of the human *MDR*1 gene by Ras and p53. Science 1992;255:459–62.
[37] Johnson RA, Ince TA, Scotto KW. Transcriptional repression by p53 through direct binding to a novel DNA element. J Biol Chem 2001; 276:27716–20.
[38] Sampath J, Sun D, Kidd VJ, Grenet J, Gandhi A, Shapiro LH, Wang Q, Zambetti GP, Schuetz JD. Mutant p53 cooperates with ETS and selectively up-regulates human MDR1 not MRP1. J Biol Chem 2001;276:39359–67.
[39] Goldsmith ME, Gudas JM, Schneider E, Cowan KH. Wild type p53 stimulates expression from the human multidrug resistance promoter in a p53-negative cell line. J Biol Chem 1995;270:1894–8.
[40] May P, May E. Twenty years of p53 research: structural and functional aspects of the p53 protein. Oncogene 1999;18:7621–36.
[41] Daschner PJ, Ciolino HP, Plouzek CA, Yeh GC. Increased AP-1 activity in drug resistant human breast cancer MCF-7 cells. Breast Cancer Res Treat 1999;53:229–40.
[42] Ogretmen B, Safa AR. Negative regulation of MDR1 promoter activity in MCF-7 but not in multidrug resistant MCF-7/Adr cells by cross-coupled NF-kappa B/p65 and c-Fos transcription factors and their interaction with the CAAT region. Biochemistry 1999;38: 2189–99.
[43] Combates NJ, Rzepka RW, Chen YN, Cohen D. NF-IL6 a member of the C/EBP family of transcription factors binds and trans-activates the human *MDR*1 gene promoter. J Biol Chem 1994;269:29715–9.
[44] Chin KV, Tanaka S, Darlington G, Pastan I, Gottesman MM. Heat shock and arsenite increase expression of the multidrug resistance (*MDR*1) gene in human renal carcinoma cells. J Biol Chem 1990; 265:221–6.
[45] Kioka N, Yamano Y, Komano T, Ueda K. Heat-shock responsive elements in the induction of the multidrug resistance gene (*MDR*1). FEBS Lett 1992;301:37–40.
[46] Miyazaki M, Kohno K, Uchiumi T, Tanimura H, Matsuo K, Nasu M, Kuwano M. Activation of human multidrug resistance-1 gene promoter in response to heat shock stress. Biochem Biophys Res Commun 1992;187:677–84.
[47] Vilaboa NE, Galan A, Troyano A, de Blas E, Aller P. Regulation of multidrug resistance 1 (MDR1)/P-glycoprotein gene expression and activity by heat-shock transcription factor 1 (HSF1). J Biol Chem 2000;275:24970–6.
[48] Roose J, Clevers H. TCF transcription factors: molecular switches in carcinogenesis. Biochim Biophys Acta 1999;1424:M23–37.
[49] Soler C, Grangeasse C, Baggetto LG, Damour O. Dermal fibroblast proliferation is improved by beta-catenin overexpression and inhibited by E-cadherin expression. FEBS Lett 1999;442:178–82.
[50] Yamada T, Takaoka AS, Naishiro Y, Hayashi R, Maruyama K, Maesawa C, Ochiai A, Hirohashi S. Transactivation of the multidrug resistance 1 gene by T-cell factor 4/beta-catenin complex in early colorectal carcinogenesis. Cancer Res 2000;60:4761–6.
[51] Geick A, Eichelbaum M, Burk O. Nuclear receptor response elements mediate induction of intestinal MDR1 by rifampin. J Biol Chem 2001;276:14581–7.
[52] Synold TW, Dussault I, Forman BM. The orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux. Nat Med 2001;7:584–90.
[53] Ogura M, Takatori T, Tsuruo T. Purification and characterization of NF-R1 that regulates the expression of the human multidrug resistance (MDR1) gene. Nucleic Acids Res 1992;20:5811–7.
[54] Takatori T, Ogura M, Tsuruo T. Purification and characterization of NF-R2 that regulates the expression of the human multidrug resistance (MDR1) gene. Jpn J Cancer Res 1993;84:298–303.
[55] Ogretmen B, Safa AR. Identification and characterization of the *MDR*1 promoter-enhancing factor 1 (MEF1) in the multidrug resistant HL60/VCR human acute myeloid leukemia cell line. Biochemistry 2000;39:194–204.
[56] Marthinet E, Divita G, Bernaud J, Rigal D, Baggetto LG. Modulation of the typical multidrug resistance phenotype by targeting the MED-1 region of human MDR1 promoter. Gene Ther 2000;7:1224–33.
[57] Labialle S, Marthinet E, Gayet L, Rigal D, Baggetto LG. Characterization of a new activating transcriptional element on the human *MDR*1 gene promoter in multidrug resistant cancer cells. In: Cell signaling, transcription and translation as therapeutic targets. Proceedings of the Third Congress on Signal Transduction, Luxembourg 2002; 262.
[58] Ackerman SL, Minden AG, Williams GT, Bobonis C, Yeung CY. Functional significance of an overlapping consensus binding motif for Sp1 and Zif268 in the murine adenosine deaminase gene promoter. Proc Natl Acad Sci USA 1991;88:7523–7.
[59] Merika M, Thanos D. Enhanceosomes. Curr Opin Genet Dev 2001; 11:205–8.
[60] Brivanlou AH, Darnell Jr JE. Signal transduction and the control of gene expression. Science 2002;295:813–8.
[61] Kusaba H, Nakayama M, Harada T, Nomoto M, Kohno K, Kuwano M, Wada M. Association of 5′ CpG demethylation and altered chromatin structure in the promoter region with transcriptional activation of the multidrug resistance 1 gene in human cancer cells. Eur J Biochem 1999;262:924–32.
[62] El-Osta A, Kantharidis P, Zalcberg JR, Wolffe AP. Precipitous release of methyl-CpG binding protein 2 and histone deacetylase 1 from the methylated human multidrug resistance gene (MDR1) on activation. Mol Cell Biol 2002;22:1844–57.