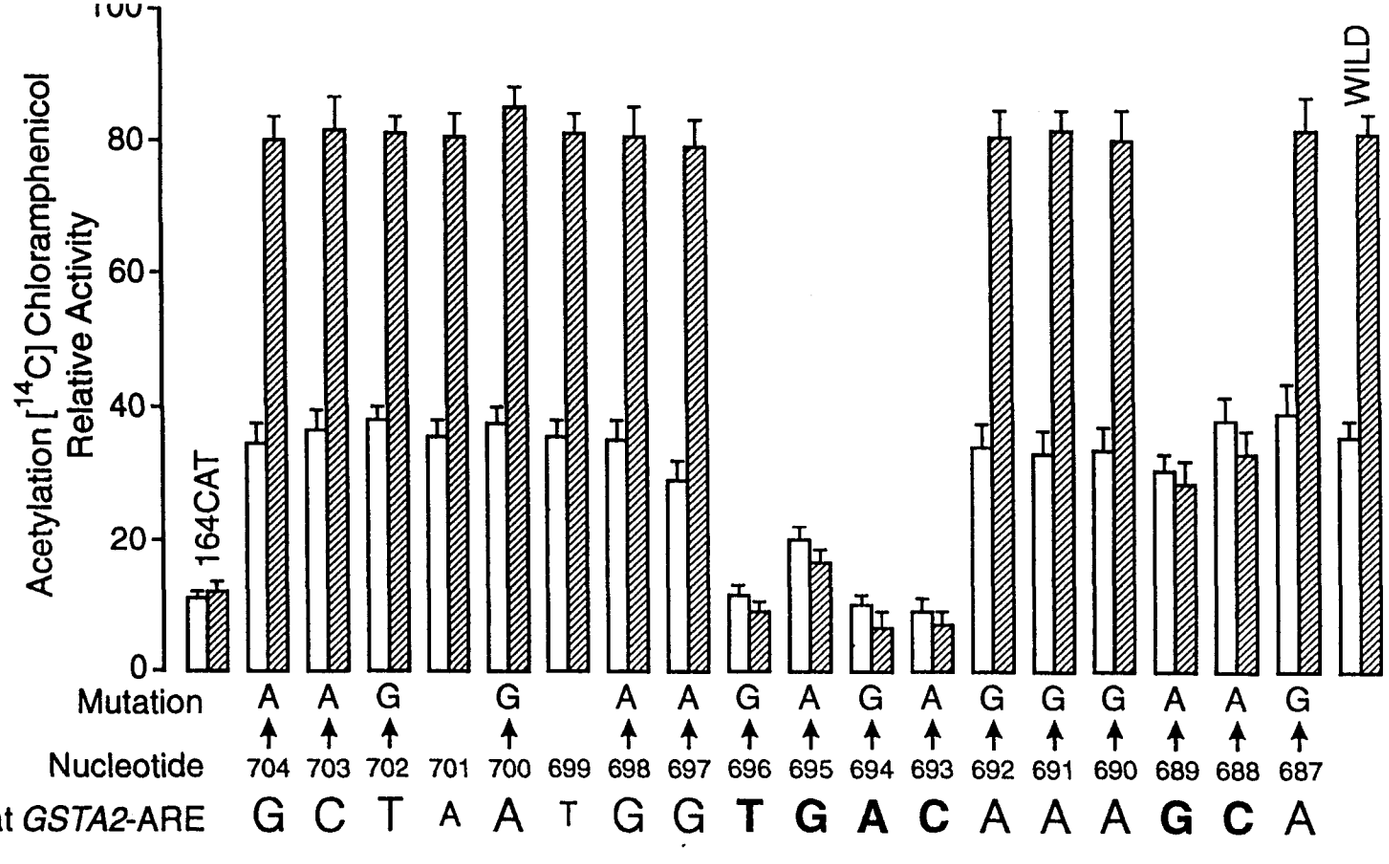
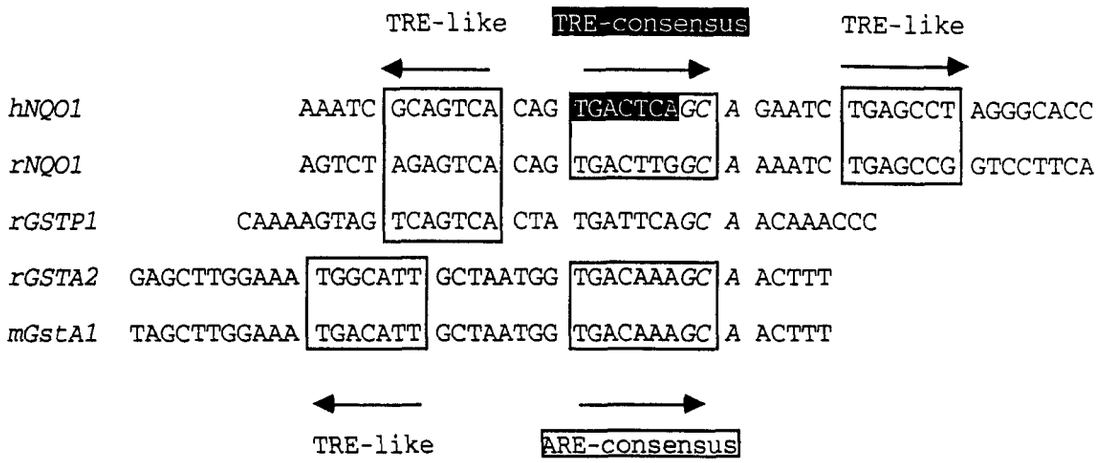


FIGURE 20. Identification of the ARE. The rat ARE ligated to the CAT reporter gene (i.e., 164CAT, the GSTA2 minimal promoter fused to CAT) was transfected into HepG2 cells. Following recovery from transfection, the HepG2 cells were either exposed to 50 μ*M* β-NF for 24 h (shaded histogram bars) or were left untreated for 24 h (open histogram bars). Mutant ARE sequences ligated to the CAT reporter gene were also transfected separately into HepG2 cells and similarly treated with β-NF. The cells were harvested, lysed and CAT activity measured; a β-galactosidase expression plasmid, which was cotransfected with the ARE-CAT constructs, was used as an internal control for transfection efficiency. The CAT activity obtained from the normal wild-type ARE is shown by two bars on the right designated "WILD." Each mutant ARE contained a single point mutation, the nature of which is indicated. The influence of each point mutation on the basal transcriptional activity of the ARE can be seen by comparing the relative heights of the open histogram bars. The influence of mutations on inducible transcriptional activity can be seen by comparing the relative heights of the shaded histogram bars. This figure is based on the data of Rushmore et al.[565]

A. Alignment of enhancers in the 5'-flanking regions of five genes that are responsive to antioxidants.



B. Comparison between the C1 promoter region of rat and human class pi GST genes.

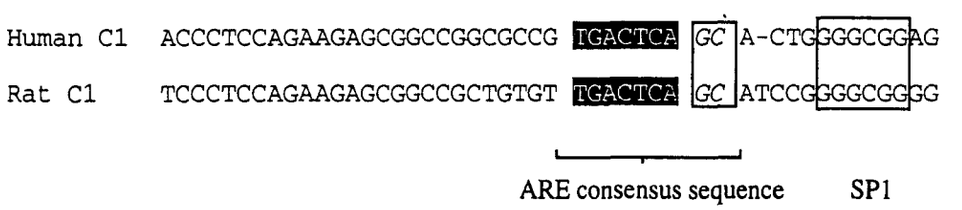
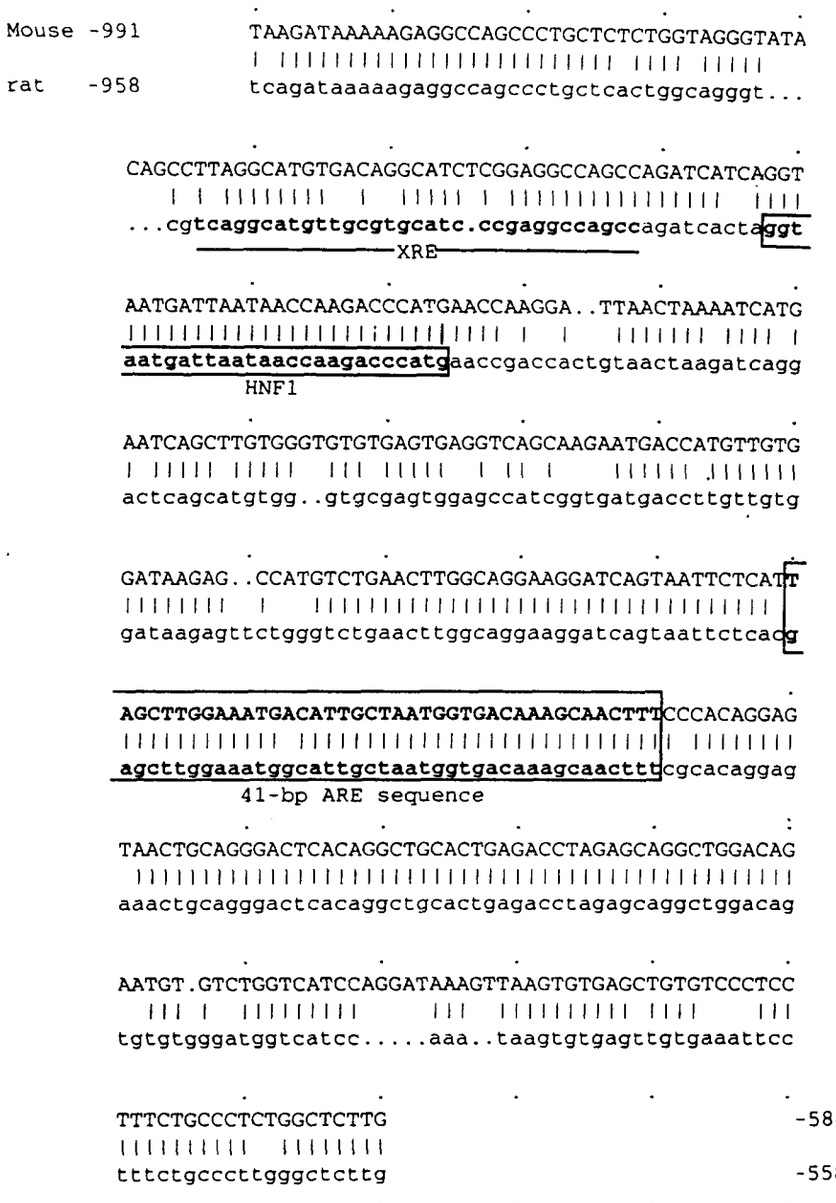


FIGURE 21. Comparison between the ARE and TRE-like sequences in GST and NQO genes. (A) Alignment of enhancers in the 5′-flanking regions of five genes that are responsive to antioxidants. (B) Comparison between the C1 promoter region of rat and human class pi genes. (A) Alignment of enhancers in the 5′-flanking regions of five genes that are responsive to antioxidants. The TRE and TRE-like sites and their orientation are indicated by the boxed sequences and arrows. The middle TRE site in the human *NQO1* gene represents a perfect consensus sequence and is indicated by the shaded box. Both ARE consensus sequences and imperfect TRE consensus sequences are indicated by the open boxes. The conserved GCA sequence flanking the central ARE motif is indicated by italics. Abbreviations: *hNQO1*, human *NQO1* gene; *rNQO1*, rat *NQO1* gene; *rGSTP1*, GPE1 enhancer element from the rat *GSTP1* gene; *rGSTA2*, ARE enhancer element from the rat *GSTA2* subunit gene; *mGstA1*, part of the EpRE enhancer element from the mouse *GSTA1* subunit gene. This figure is adapted from the review of Jaiswal.[598] (B) Comparison between the C1 region of the human and rat class pi GST promoter. The ARE consensus sequence, including the conserved core and the GC (indicated in italic type) box, is shown. The core sequence comprises a consensus AP-1 site that binds a Fos-Jun complex. This region is represented by boxed nucleotides. Although the C1 promoter regions contain the consensus ARE nucleotide sequence, the flanking sequences around the ARE are unlike those seen in other proposed ARE (compare panel A with panel B).

A comparison between the nucleotide sequences of the 41-bp ARE-containing region in the rat *GSTA2* gene with the 41-bp 5′-flanking region of the mouse *GstA1* gene shows the existence of only two nucleotide differences (Figure 22).



Sequence alignment between the promoter regions of the mouse *GstA1* and rat *GSTA2* genes. The 41-bp ARE sequence (boxed region) and 5' and 3' flanking nucleotides are shown. The rat *GSTA2* promoter also contains the enhancer element, HNF1 and a putative XRE. As can be seen from the figure, these regions, and in particular the HNF1 enhancer element, are also highly conserved between the two gene promoters. In addition, other regions within the immediate flanking sequences are also highly conserved.

FIGURE 22. Sequence alignment between the 5′-flanking region of mouse *GstA1* and rat *GSTA2* genes.

The flanking region of the murine *GstA1* gene contains the identical 5′-TGACAAAGC-3′ sequence described for the ARE in rat *GSTA2* (located between –696 and –688 bp). However, whereas the rat 41-bp element contains a single consensus ARE, inspection of the mouse

enhancer reveals that an additional ARE consensus, 5′-TGACATTGC-3′, is present 6 bp upstream from the 5′-TGACAAAGC-3′ element common to both rat and mouse genes (Figure 21). In the rat *GSTA2* gene, this enhancer is replaced by the sequence 5′-TGGCATTGC-3′ (located between –711 and –703 bp), which does not serve as a functional ARE. Thus, although the rat and mouse enhancers appear to function in a similar manner, the presence of an additional ARE consensus in the EpRE may influence the mechanism of *trans*-activation.

The possibility that the rat ARE and mouse EpRE are functionally distinct is worthy of consideration. Table 14 shows the responsiveness in HepG2 cells of the rat ARE and the mouse EpRE to various inducers. Similar doses of H_2O_2, hydroquinone, and tBHQ are required to stimulate transcription directed by the ARE and EpRE. However, the EpRE appears to be 8- and 500-fold more responsive to catechol and β-NF than the ARE. These data, therefore, suggest that the tandem arrangement of two enhancers within the EpRE may render it more responsive than the ARE to certain inducing agents. Prestera et al.[595] have proposed that in the mouse *GstA1* gene a putative Ets binding site which is adjacent to the distal ARE, within the EpRE, may augment its activity; rat *GSTA2* also contains an Ets binding site but this is adjacent to the nonfunctional ARE-like motif situated between –711 and –703 bp. The hypothesis that the Ets binding site can influence the activity of the ARE merits further investigation.

Other sequences that are immediately adjacent to the core ARE and EpRE enhancers may also be required for maximal basal and inducible expression of the mouse *GstA1* and rat *GSTA2* genes. As Figure 22 shows, sequences that flank both the 41-bp ARE and EpRE are highly conserved, suggesting that additional functional requirements constrain sequence divergence.

4. Relationship between the ARE and AP-1-Binding Sites

In the literature, the relationship between the ARE and the AP-1-binding motif is somewhat confused because, although the consensus sequence required for AP-1 binding is distinct from that of the ARE, the two consensus sequences are not mutually exclusive and allow the coexistence of both enhancers within a stretch of 9 bp of DNA. Indeed, to emphasize this point, it is worth noting that the TPA-inducible human *MTIIA* gene, which was used by Angel et al.[596] to define the TRE consensus, contains both an AP-1-binding site and an ARE.

AP-1 was originally identified as a factor (i.e., the Fos/Jun containing complex) that stimulated basal levels of transcription *in vitro*, and its binding site was also identified with TPA inducibility in certain enhancer elements.[596,597] Through alignment of putative AP-1-binding sequences, the 7-bp motif 5′-TGA(G/C)T(C/A)A-3′ was identified in the control regions of TPA-inducible genes such as human collagenase, human metallothionein, human interleukin 2, rat stromelysin, and SV40. The AP-1 DNA-binding site, or TRE, contains the sequence 5′-**TGAC**TCA-3′ that shares some homology with the core consensus ARE sequence (5′-**TGAC**NNNGC-3′), suggesting that *trans*-acting factors that bind to the TRE may interact with the ARE.

Jaiswal[598] has compared the ARE and ARE-related enhancers flanking the *GST* and *NQO* genes (Figure 21). He suggested that the various *cis*-acting elements contain two or three copies of either the TRE or a TRE-like element in a stretch of 40 to 45 nucleotides of DNA. However, with the exception of the human *NQO1* gene, which contains a perfect TRE, the remaining genes all have imperfect TRE consensus sequences. The rat *GSTP1* gene contains two

TABLE 14
Comparison between the Chemical-Mediated Transactivation of Rat *GSTA2* and Mouse *GstA1* Subunit Genes in HepG2 Cells

Construct	Concentration of chemical required to double reporter protein levels (i.e., CAT or GH) in HepG2 cells (μmol/l)		Concentration of chemical required to double quinone reductase activity in Hepa 1c1c7 cells (μmol/l)
	Rat pGTB1.6CAT	Mouse p284YaGH	
Compound			
1,2-Benzanthracene	25	—	—
2,3-Benzanthracene	25	—	—
p-Benzoquinone	15	—	—
Benzyl isothiocyanate	—	0.7	3.7
3,5-Di-*tert*-Butylcatechol	15	—	—
Cadmium chloride	—	7.3	11
Catechol	80	8.5	4.5
1-Cyclohexen-2-one	—	15	9
1-Cyclopenten-2-one	—	80	32
CuOOH	—	21	210
1,2-Dithiole-3-thione	—	15	1
Fisetin	250	—	—
2-(5*H*)-Furanone	—	240	36
Hydroquinone	40	12	5.3
Hydrogen peroxide	250	210	560
Menadione	10	—	—
Mercuric chloride	—	1.9	0.5
2-Methylene-4-butyrolactone	—	2.4	4.5
3-Methylene-2-norbornanone	—	3.1	1.5
α-Naphthoflavone	25	—	—
β-NF	25	0.05	0.03
1-Nitro-1-cyclohexene	—	1.0	0.46
Phenylarsine oxide	—	0.05	—
Tert-Butylhydroquinone	15	11	6
1,2,3-Trihydroxybenzene	35	—	—
Trans-4-Phenylbut-3-en-2-one	—	16	15
Quercetin	50	—	—
TCDD	5 (only with XRE)	—	—

Note: Data derived using rat pGTB1.6CAT in HepG2 cells are from references 565 and 594. Data derived using mouse p284YaGH in HepG2 cells and quinone reductase enzyme assays of Hepa 1c1c7 cell extracts are from Prestera et al.[595] CuOOH, cumene hydroperoxide; β-NF, β-naphthoflavone; TCDD, tetrachlorodibenzo-*p*-dioxin.

adjacent imperfect TRE consensus sequences within GPE1, and although it is responsive to TPA[570,599] and can bind AP-1 *in vitro*,[600] it does not contain an ARE consensus sequence nor is it thought to respond to monofunctional inducers. Furthermore, the GPE1 element is active in undifferentiated F9 embryonic stem cells, suggesting that it may not be regulated in a classic AP-1-dependent fashion because this cell line possesses very low levels of AP-1 activity.[599] Evidence suggests that the two imperfect TRE elements within GPE1 can bind Jun, but that they act synergistically to enhance transcriptional activity.[600]

Although both human and rat *NQO* genes contain a central TRE-like consensus element that is flanked by similar elements either side of the core, the rat *GSTA2* and mouse *GstA1* genes contain only two TRE-like elements that can be arranged in either orientation with respect to each other, and are spaced between 3 and 8 bp apart. As described by Rushmore et al.,[565] the minimum ARE sequence required for expression and induction of rat *GSTA2* is 5′-

TGACNNNGC-3′, thus suggesting that only one TRE-like element is required for responsiveness to monofunctional inducers. By contrast, reports on the EpRE in mouse *GstA1* indicate that both of the TRE-like elements[569] are required for transcriptional activation by tBHQ or β-NF. In addition, Li and Jaiswal[601] observed that mutations of a perfect TRE in the human *NQO1* gene result in loss of basal and β-NF-induced expression. These results indicate the importance of TRE-like sequences in the function of the ARE but, although some genes require at least two TRE-like sequences for responsiveness to monofunctional inducers, this is not a universal requirement.

A striking feature of the ARE sequences described in Figure 21 is the presence of a conserved 3 bp sequence, GCA, immediately 3′ of the TRE-like sequence. As already indicated, the GC nucleotides are required for induction of transcription of rat *GSTA2*,[565,592] as well as mouse *GstA1*,[602] and its presence in other ARE-containing sequences suggests an essential function. The fact that the GCA sequence is situated outwith the region in the ARE that shares homology with the TRE, suggests that *trans*-acting factors other than the AP-1 complex are involved in ARE-mediated regulation of gene expression.

5. Role of Barbie Box Sequences in Induction of GST by Barbiturates

The levels of many GST subunits are increased in rodent organs following treatment with PB. The molecular basis for this increase in GST is not clear. However, Fulco and his co-workers[567] have identified a *cis*-acting barbiturate-responsive element in *Bacillus megaterium* that mediates induction of $CYP_{BM\text{-}1}$ and $_{BM\text{-}3}$ by barbiturates. This element, called the Barbie box, is 15 bp in length and is located in the 5′-regulatory regions of the *B. megaterium* CYP genes. Through searching for similar sequences in the genes of other barbiturate-inducible proteins, Liang et al.[567] identified Barbie boxes in the regulatory region of many eukaryotic genes. This analysis allowed the following 5′-ATCAAAAGCTGGAGG-3′ consensus to be proposed as the element responsible for barbiturate inducibility. The core 4 bp sequence AAAG (position 5 to 8) was present in all the barbiturate-regulated genes, but the other adjacent 5′- and 3′-flanking nucleotides within the Barbie box are not conserved and may not be essential. Within the Barbie boxes, most barbiturate-inducible rat and murine genes contain between 8 and 12 of the 15 consensus nucleotides, but all of these enhancers contain the AAAG core.

Several potential Barbie box elements can be identified in rat and mouse GST genes. The core AAAG Barbie box motif is contained within the 5′-TGACAAAGC-3′ ARE, which is common to the regulatory regions of both rat *GSTA2* and mouse *GstA1*. Although it is possible that the ARE is involved in GST induction by PB, as suggested by Pinkus et al.,[603] this seems unlikely as outwith the core AAAG motif, the homology between the ARE and the Barbie box is not high: in both rat *GSTA2* and mouse *GstA1*, the ARE-containing sequence, 5′-tgacAAAGCaactt-3′, contains 5 of the 15 consensus nucleotides. Other potential Barbie box candidates exist in the rodent GST genes. For example, the sequence 5′-ATaAAAAGagGccaG-3′, located between –950 and –936 bp from the transcriptional start site, in rat *GSTA2* represents a candidate Barbie box element, as does the sequence 5′-AgggAAAGgTGGtGG-3′ located between –179 and –165 bp from the transcriptional start site in mouse *GstA1*. It will clearly be important to establish whether these potential Barbie box elements are functional.

6. Cis-Acting Elements for Nuclear Factor (NF)-κB

Putative NF-κB-binding sites have been identified in the flanking region of a number of genes encoding enzymes involved in GSH homeostasis (γ-glutamylcysteine synthetase)[604,605] and drug metabolism (dihydrodiol dehydrogenase and GST).[606,607] The best characterized example of the involvement of NF-κB in GST regulation involves the human class pi gene where an NF-κB-like element (5′-GGGACCCTCC-3′), located between –98 and –89 bp from the transcriptional start site, appears to be responsible for suppression of *GSTP1* expression in MCF7 cells;[607] the consensus DNA sequence for recognition by NF-κB is the following 10-base motif 5′-GGGR(C/A/T)TYYCC-3′. Nuclear proteins that bind to this silencer element prevent transcription mediated by the C1 region of the *GSTP1* promotor which contains an overlapping ARE/TRE motif (5′-TGACTCAGC-3′), located between –69 and –61 bp. Overexpression of *GSTP1* in vincristine-resistant human mammary carcinoma VCREMS cells is achieved by displacement of the inhibitor complex from the NF-κB-like element, presumably by another transcription factor. As the NF-κB and the ARE/TRE motifs are situated approximately 20 bp apart, factors that are bound to these sites are aligned on the same side of the DNA double helix, thus facilitating a protein-protein interaction between the two complexes.

NF-κB is a member of the Rel family of transcriptional activator proteins.[608] It responds to oxidative stress in a cell-specific fashion and is responsible for increased transcription of inflammatory response genes. The NF-κB signal transduction pathway is regulated by both redox and phosphorylation.[609,610] NF-κB comprises two related subunits that are retained in the cytoplasm as an inactive complex. Substantial heterogeneity exists among the NF-κB complexes and this accounts for the variety of signal transduction pathways that can utilize this family of factors. Presumably heterogeneity in NF-κB also accounts for the specificity of interaction with different enhancers within the genes that they can activate. Several different types of Rel dimers exist; the first type comprises homodimers or heterodimers of mature p50 and p65 protein, whereas the second type comprises heterodimers of mature p65 protein and unprocessed Rel protein precursor (e.g., p105). Within the cytosol the p50 and p65 dimers form inactive complexes with any one of a family of inhibitory subunits including IκB-α, IκB-β, IκB-γ, and Bcl-3. The cytosolic complexes formed between the p65 and the p105 subunits are also inactive.[608,611] The DNA-binding activity of NF-κB is revealed by either dissociation of the IκB subunit or processing of the p105 protein, events that result in translocation of the p50:p65 heterodimer to the nucleus. It should be noted that IκB-α and IκB-β dissociate from NF-κB in response to different subsets of inducers and may influence the duration of induction. Activation of NF-κB is triggered by tyrosine kinase activity and occurs in response to a diverse number of agents including H_2O_2, phorbol esters, UV light, γ-rays, and inflammatory cytokines; activation of NF-κB is diminished by the tyrosine kinase inhibitors herbimycin A and erbstatin, antioxidants, and protease inhibitors.[612] Many of the agents that activate NF-κB produce ROS, suggesting that either the signal transduction pathway or dissociation of IκB from NF-κB is redox sensitive.[613] The activity of NF-κB itself is also redox sensitive but surprisingly, in this case, oxidation of a labile cysteine at amino acid position 62 in p50 results in reduced binding to its DNA-enhancer motifs. *In vitro* experiments show that the DNA-binding activity of NF-κB requires cysteine 62 of p50 to be reduced,

whereas other experiments suggest that NF-κB is activated *in vivo* by oxidative stress, paradoxical facts that appear incompatible. However, it seems likely that the triggering of NF-κB activation by oxidative stress is linked to phosphorylation events and is separate from the requirement for NF-κB to be reduced to bind to DNA-enhancer motifs. It has been suggested that, following oxidant-triggered dissociation of NF-κB from IκB, the p50 subunit may be reduced *in vivo* by thioredoxin as this cellular reducing catalyst is induced following transient oxidative stress.[614,615]

In the context of the overexpression of *GSTP1* in the VCREMS cell line,[616] NF-κB is capable of interacting synergistically with various transcription factors, including c-Jun, Ets, and Sp1. As Rel family members bind their recognition sequences with an unusually high affinity compared with most eukaryotic activators, it is distinctly possible that, in the VCREMS cells, a member of the Rel family is responsible for displacing an inhibitory complex from the NF-κB-like site within *GSTP1* and that this allows a synergistic interaction between the NF-κB protein and c-Jun (or other bZIP proteins) bound at the adjacent ARE/TRE site.

7. Glucocorticoid Regulation of GST

Hepatic GST activity in rat and mouse can be modulated by treatment with the synthetic glucocorticoid dexamethasone (Table 11). The levels of the rGSTA2 subunit in liver are increased about five-fold following administration of dexamethasone,[500] and examination of the 5′-flanking region of the rat *GSTA2* gene showed the existence of a putative GRE, 5′-AGAACAAGCTGTACC-3′, between nucleotides −1609 and −1595.[566] It appears likely that induction of rGSTA2 by dexamethasone is mediated by this region of the gene. The structure of the GRE can vary significantly, but it is frequently found to contain two canonical hexamers, TGTTCT, that are separated by three nucleotides.[617,618] It is probable that this enhancer will mediate induction of GST by pregnenolone-16α-carbonitrile, a model inducer of the CYP3A family, but this possibility has not been explored.

The cDNA of a glucocorticoid-inducible class mu GST from Syrian hamster, which shares closest homology with rGSTM2, has been isolated by Fan et al.[189] Cloning and sequence analysis of the regulatory region of this gene failed to identify a GRE that might be responsible for induction by triamcinolone acetonide. Cyclohexamide blocks induction of this GST, suggesting that increased expression requires ongoing protein synthesis. It has therefore been proposed that induction of class mu GST represents a secondary effect of glucocorticoids. The induction has been attributed, in part, to a region between −353 and −239 bp that contains four helix-loop-helix consensus-binding domains.

8. Increased Expression of GST by Insulin

The expression of human *GSTP1* is enhanced by insulin.[619] This activity is attributed to an 8-bp sequence, 5′-CCCGCGTC-3′, located at +48 to +55 bp from the transcriptional start site in intron 1, demonstrating the existence of enhancer sequences 3′ of the transcriptional initiation site. Like human *GSTP1*, the orthologous gene in the rat, is also induced in response to insulin treatment.[620]

VIII. TRANSCRIPTION FACTORS INVOLVED IN INDUCTION OF GST BY ANTIOXIDANTS, PRO-OXIDANTS AND MICHAEL REACTION ACCEPTORS

A. Interaction of the ARE with Transcription Factors

Over recent years, evidence has accumulated suggesting that transcriptional regulatory proteins such as Jun and Fos are involved in coupling extracellular signals to gene expression in the nucleus by interacting with AP-1-binding sites (TRE motifs) in target genes. Thus, recognition that the ARE in the regulatory region of various GST genes is similar to the TRE has suggested that Fos and Jun might be involved in GST induction. The observation by Choi and Moore[621] that c-*fos* and c-*jun* gene expression is also increased by BHA, butylated hydroxytoluene, catechol, and, to a smaller extent, by hydroquinone, has also added credibility to the thesis that induction of GST by phenolic antioxidants might involve Jun and Fos. More recent data from Yoshioka et al.[622] have shown that the major ARE-binding and activating protein is not a Jun-Fos heterodimer, but this does not exclude the possibility that heterodimers containing either Jun or Fos can bind this element.

Photochemical cross-linking experiments have demonstrated that a heterodimer comprising subunits of approximately 28 and 45 kDa can bind specifically to the ARE.[623] The presence of a subunit of about 45 kDa is consistent with a member of the AP-1 family of transcription factors being involved in binding. However, *in vitro* translated c-Jun and c-Fos do not bind to the ARE flanking rat *GSTA2*. Furthermore, combinations of *in vitro* translated c-Fos with Jun-B or c-Fos with Jun-D are also unable to interact with the ARE during electrophoretic mobility shift assays.[592] These results suggest that although the enhancer element contains an imperfect TRE, neither c-Jun, Jun-B, Jun-D, nor c-Fos forms part of a complex that interacts with the ARE. The AP-1 protein family is extensive and the ability of a number of Fos-related factors such as Fos-B, Fra1, and Fra2 to interact with the ARE has not been tested to date.

Evidence suggests that members of the Maf family of transcription activator proteins are able to interact with the ARE *in vitro*. Maf is a member of a family of bZIP proteins that includes the *c-maf* protooncogene[624] and the human retina-specific gene *nrl*.[625] Using truncated polypeptides that encompassed the leucine zipper and basic region of these proteins, Kerppola and Curran[626] investigated the dimerization and DNA-binding activities of the Maf and Nrl proteins. The purified Maf and Nrl homodimers bound the palindromic sequence TGC$(N)_{6-7}$ GCA . However, Maf and Nrl dimerized with Fos and Jun, and the resulting heterodimers exhibited unique DNA-binding specificity.[627] These workers demonstrated that Fos-Nrl, Jun-Nrl, and Fos-Maf heterodimers bind to nonpalindromic sequences containing the consensus 5′-TGAC$(N)_{3-4}$GCA-3′. Most significantly, this sequence closely resembles the 5′-TGACNNNGC-3′ ARE consensus,[565] thus implicating these complexes in the induction of *GST* and *NQO1* gene expression. It can be speculated that among Fos-Nrl, Jun-Nrl, and Fos-Maf heterodimers, Fos and Jun are responsible for binding to the 5′ region of the ARE (TGAC), whereas Maf and Nrl bind to the 3′ region (GCA). Therefore, although homodimers and heterodimers formed between Jun and Fos do not appear to effect transactivation of genes via the ARE, they may, nonetheless, be involved in

ARE-mediated transcriptional activation of GST through their ability to dimerize with Maf and Nrl. A large number of Maf homologs exist,[628,629] most notably small Maf proteins[630] that appear to lack a transactivation domain, but the ability of these proteins to bind the ARE has not been studied.

B. Interaction of AP-1 with *cis*-Acting Elements in *GST* Genes

In contrast to the ARE in rat *GSTA2*, Friling et al.[569] suggested that *trans*-activation of the mouse *GstA1* gene through the EpRE requires the Fos-Jun heterodimeric complex. Exposure of NIH3T3 cells to antioxidants such as tBHQ, and to other inducers of cellular stress, results in an increase in Fos and Jun expression.[593] Although treatment of NIH3T3 cells with cycloheximide does not prevent the tBHQ-induced increase in fos or jun mRNA, it does inhibit the binding activity of AP-1 to the EpRE, suggesting that ongoing protein synthesis is required for the interaction of AP-1 with this element. Daniel et al.[593] have reported that treatment of either HepG2 or H4II cells with tBHQ, H_2O_2, and other xenobiotics increases the TRE-binding activity within nuclear extracts. The most compelling evidence to suggest that an AP-1 complex can interact with the mouse EpRE comes from experiments showing that *in vitro* synthesized Fos and Jun proteins can interact cooperatively with the enhancer element. Furthermore, when F9 embryonic cells were cotransfected with an EpRE *GstA1*-CAT reporter construct, along with increasing amounts of both c-fos and c-jun expression vectors, CAT activity augmented with the increase in the amount of Fos and Jun. In the absence of Fos and Jun, no inducible activity was observed.[593] These experiments suggest that the EpRE in the regulatory region of the mouse *GstA1* gene is able to interact with Jun and Fos, and that these proteins are synthesized *de novo* following exposure to xenobiotic chemicals. It remains to be established whether Jun and Fos interact with the EpRE as heterodimers with Maf and Nrl.

The work of Daniel's laboratory on the EpRE in *GstA1* has been extended by Wasserman and Fahl[602] who have shown that at least seven different proteins, or protein complexes, can interact with the enhancer element. Although these results confirm the proposal that a 160-kDa protein complex is required for antioxidant responsiveness,[631] the involvement of an 80-kDa protein in transcriptional activation was also demonstrated. In addition, a 40-kDa protein with binding activity for the EpRE that interacted specifically with a consensus TRE and comigrated with a Jun homodimer-DNA complex in electrophoretic mobility shift assays was described. Thus, the earlier results of Daniel et al.[593] suggesting that an AP-1 complex can interact with the murine EpRE were corroborated. However, although the 40-kDa protein could bind to an EpRE that supported transcriptional induction, it also interacted with noninducible mutants of the EpRE, suggesting that it has a broad binding specificity and may not be required specifically for induction of transcription.[602]

The results discussed above suggest that a number of different *trans*-acting factors can interact with the ARE and the EpRE sequences. These factors may function either separately or in combination, and a certain amount of protein "cross-talk" may lead to changes in the expression of the genes containing these enhancers. AP-1 complexes may be able to interact with some sequences that contain an ARE, but this may depend on subtle nucleotide differences

between different enhancers. However, although AP-1 may be involved in basal level expression of some GST genes, the weight of evidence suggests that it is not involved directly in transcriptional activation of GST genes by monofunctional inducers; Fos-Nrl, Jun-Nrl, and Fos-Maf heterodimers may be responsible for induction of GST by monofunctional inducers.

Studies on the human *GSTP1* gene have identified the essential element 5′-GTGACTCAGCA-3′, situated between nucleotides –70 and –60 from the transcriptional start site, that is known as the C1 region[616] and is absolutely required for *GSTP1* transcription. Significantly, this sequence contains both the consensus ARE and TRE motifs. The C1 region was found to bind a nuclear complex that comprises a Fos-Jun heterodimer in drug-resistant VCREMS cells but not in the parental MCF7 cell line.[616] The C1 region is also present and is highly conserved in the regulatory region of the rat *GSTP1* gene (Figure 21). Although the human C1 promoter region in *GSTP1* binds a Fos-Jun complex in VCREMS cells, it does not do so in all cell types. Indeed, in the human mammary carcinoma cell line, MCF7, other *trans*-acting factors such as NF-κB may interact with the promoter.[607] The ability of multiple *trans*-acting factors, similar to those that bind the ARE, to interact with this enhancer element remains a distinct possibility. However, it should be recognized that the sequences that flank the TRE site in the C1 region of both human and rat *GSTP1* genes are entirely distinct from the flanking sequence of the 41-bp ARE and EpRE in rat *GSTA2* and mouse *GstA1* genes (Figure 21).

C. Signal Transduction Pathways Involved in GST Induction

Unlike the receptor-mediated mechanism for induction of genes that contain either the XRE or the GRE, no receptor for synthetic antioxidants has been identified that can regulate ARE-dependent transcription. As proposed by Talalay and his coworkers,[33] GST induction by monofunctional inducers does not involve any steric property of the inducing agent or a receptor but, rather, the production of Michael reaction acceptors.[33] The mechanism whereby this chemical signal (or chemical stress) is relayed to the transcriptional machinery remains to be determined, but it appears reasonable to suppose that the presence of Michael acceptors is recognized within the cell by a redox and electrophile-sensitive protein (or proteins). The location of the putative sensor is unknown; it may be either membrane bound, cytosolic, or nuclear. The role of sensor of chemical stress could be performed by a protein containing reactive cysteine residues or, possibly, by a redox-sensitive metal-chelated protein. Presumably this protein may be either a component of the transcriptional machinery or may be part of a stress-inducible protein kinase pathway. Should the sensor be part of a protein kinase pathway that responds to electrophile and oxidative stress, then it is envisaged that the signaling mechanism could involve either activation or induction of transcription factors involved in expression of xenobiotic-regulated genes. Whether monofunctional inducers, the active metabolites of bifunctional inducers, and ROS are all capable of interacting with a common sensor, or trigger distinct signal transduction pathways that converge (Figure 23), is an issue that requires further research.

As described above, Fos-Nrl, Jun-Nrl, and Fos-Maf heterodimers can bind to the ARE and related sequences *in vitro*.[627] It is possible that the transcriptional activation of GST genes by electrophile and oxidative stress requires either induction of ARE-binding bZIP proteins or activation of ARE-binding bZIP proteins by a mechanism in-

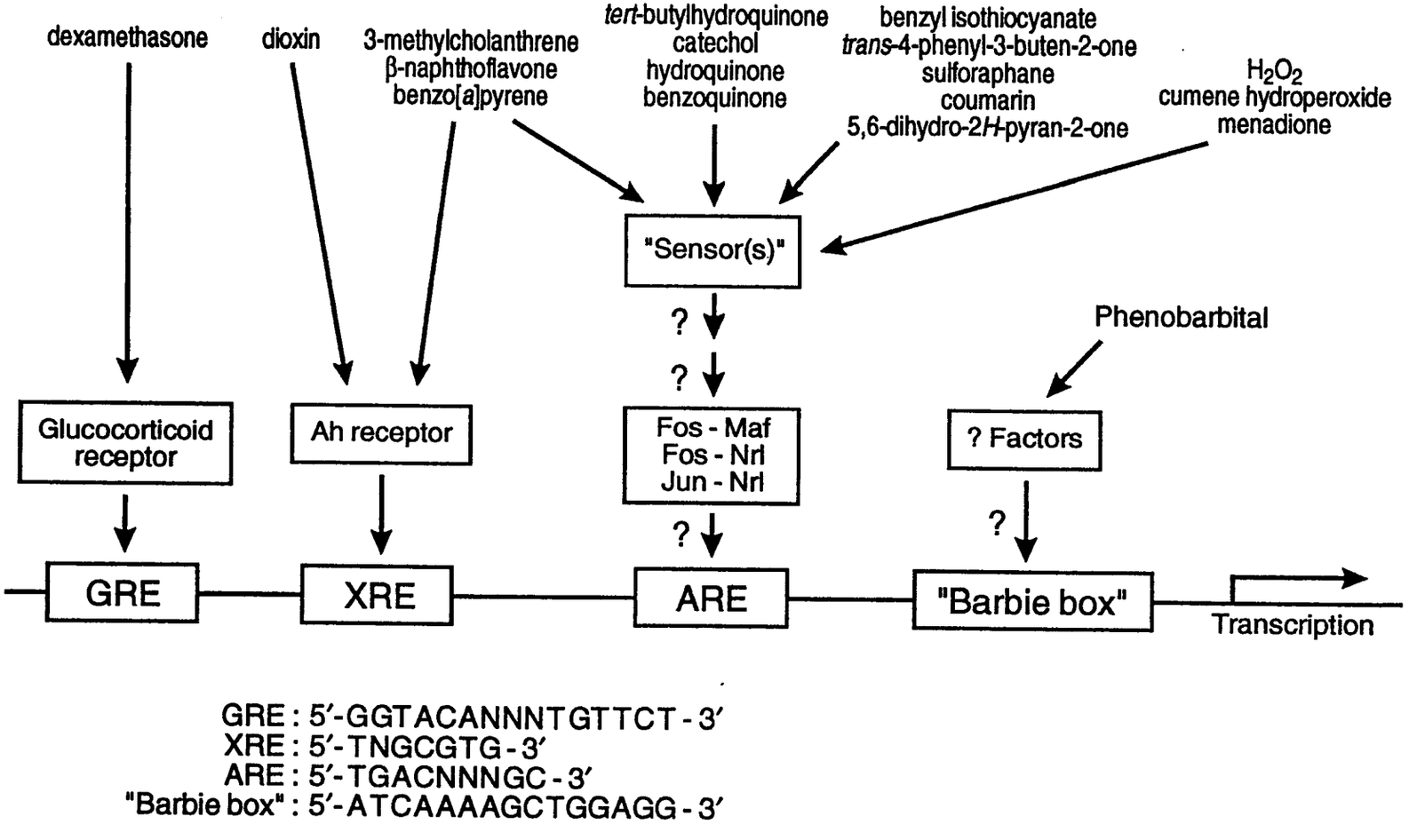


FIGURE 23. Interaction between different chemicals and various *cis*-acting elements in GST genes.

volving phosphorylation or modification of their redox status. Both induction and post-translational modification of bZIP proteins may be involved in GST induction. However, the molecular processes involved in GST induction by Michael reaction acceptors may differ from those involved in GST induction by prooxidants.

The induction of Maf and Nrl by drugs has not been described, but evidence has been provided that Jun and Fos are induced by BHA and butylated hydroxytoluene.[621] Surprisingly, tBHQ does not induce Fos in HepG2 cells. Yoshioka et al.[622] have pointed out that the preferential induction of certain bZIP proteins can have a major impact on the transcriptional activity of certain genes. These workers also showed that, although tBHQ induced expression of c-*jun*, *junB*, *fra-1*, and *fra-2*, it did not induce c-*fos*. tBHQ inhibited the ability of TPA to induce TRE-dependent transcription; it was proposed that this inhibition is due to the formation of Jun-Fra heterodimers that have low transactivation potential. It therefore seems likely that the levels of Maf and Nrl within a cell will influence inducibility of GST genes. It is possible that the small Maf proteins, which lack the transactivation domain, are able to compete with Maf and Nrl for dimerization with Fos and Jun, and thereby prevent induction of GST genes by xenobiotics.

It has been established that antioxidants may bring about changes in the expression of genes regulated by the Fos-Jun complex.[632] Abate et al.[633–635] have shown that the redox state of the cell regulates the DNA binding activity of Fos and Jun, and demonstrated that the oxidation of the sulfhydryl group of a conserved cysteine residue in the DNA-binding domain of Fos (C154) and Jun (C272) decreases DNA-binding of the complex to the AP-1 site. However, chemical reduction of Fos and Jun to the sulfhydryl increases DNA binding.[635] Further characterization of this protein-DNA binding activity revealed that a 37 kDa nuclear protein, known as Ref-1,[636] maintains Fos-Jun in a reduced state under pro-oxidant conditions in the cell. Treatment of cells with oxidizing agents results in increased synthesis by the cell of antioxidants such as thioredoxin and GSH. Ref-1 is sensitive to the redox state of the cell and is stimulated by thioredoxin to maintain the reduced sulfhydryl state of the conserved cysteine residues in the DNA-binding domain of Fos-Jun, thereby allowing the AP-1 complex to act as the *trans*-acting factor in increasing expression of specific genes during oxidative stress. The Maf and Nrl family of proteins all share a common cysteine residue, namely, C292 in chick v-Maf, C242 in chick Maf-B, C68 in chick Maf-K, C68 in chick Maf-F, C68 in mouse Maf-K, and C176 in human Nrl. This cysteine is situated on the *N*-terminal side of the leucine zipper, 11 residues from the first leucine (Figure 24). It will be interesting to determine whether the oxidation state of this cysteine can modulate the binding activity of Maf and Nrl for the ARE, because this enhancer mediates response to pro-oxidant insult. It will also be of great interest to determine whether Ref-1 can attenuate the binding of Fos-Nrl, Jun-Nrl, and Fos-Maf heterodimers to the ARE.

In addition to redox regulation of AP-1 activity, phosphorylation of Fos or Jun has been implicated in the transcriptional activation of some genes. The mitogen-activated protein (MAP) kinase, JNK1, can phosphorylate the *N*-terminal transactivation domain of c-Jun at serine 63 and 73 in response to UV light:[637] JNK1 is itself activated by phosphorylation at threonine and tyrosine residues.[638] Phosphorylation of c-Jun by JNK1 leads to enhanced induction of AP-1 target genes. A number of potential proline-directed protein kinase sites can be identified in Maf and Nrl (Figure 24), sug-

A

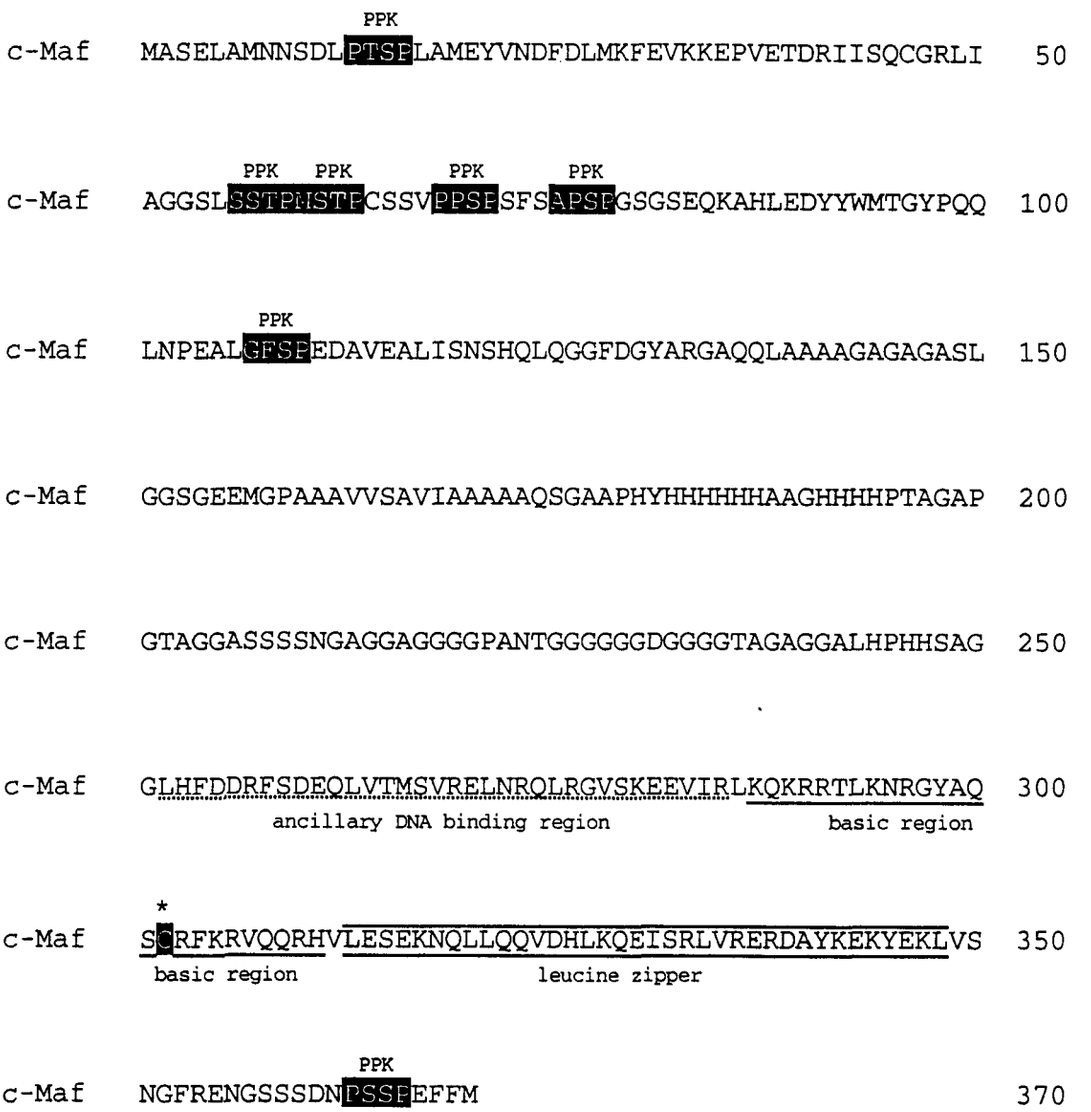


FIGURE 24. Structure of the murine c-Maf protooncogene and human Nrl polypeptides. (A) The primary structure of c-Maf has been deduced from sequencing of the cDNA clone Φ2-1.[628] The putative transactivation domain is contained within residues 1 to 256, the ancillary DNA-binding domain is composed of residues 252 to 285 (dotted underline) the basic region comprises residues 287 to 311 (solid underline), and the leucine zipper is found between residues 313 to 348 (both overline and underline). Potential sites of phosphorylation by proline-directed protein kinases (PPK) are indicated. Cysteine-302 in the basic region, which may be redox sensitive, is indicated by an asterisk. (B) The primary structure of Nrl has been deduced from sequencing of the cDNA clone AS321.[625] The putative transactivation domain is contained within residues 1 to 120, the ancillary DNA-binding domain is composed of residues 126 to 159 (dotted underline), the basic region comprises residues 161 to 185 (solid underline), and the leucine zipper is found between residues 187 to 222 (overline and underline). Potential sites of phosphorylation by proline-directed protein kinases (PPK) and mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP K2) are shown. Cysteine-176 in the basic region, which may be redox sensitive, is indicated by an asterisk.

B

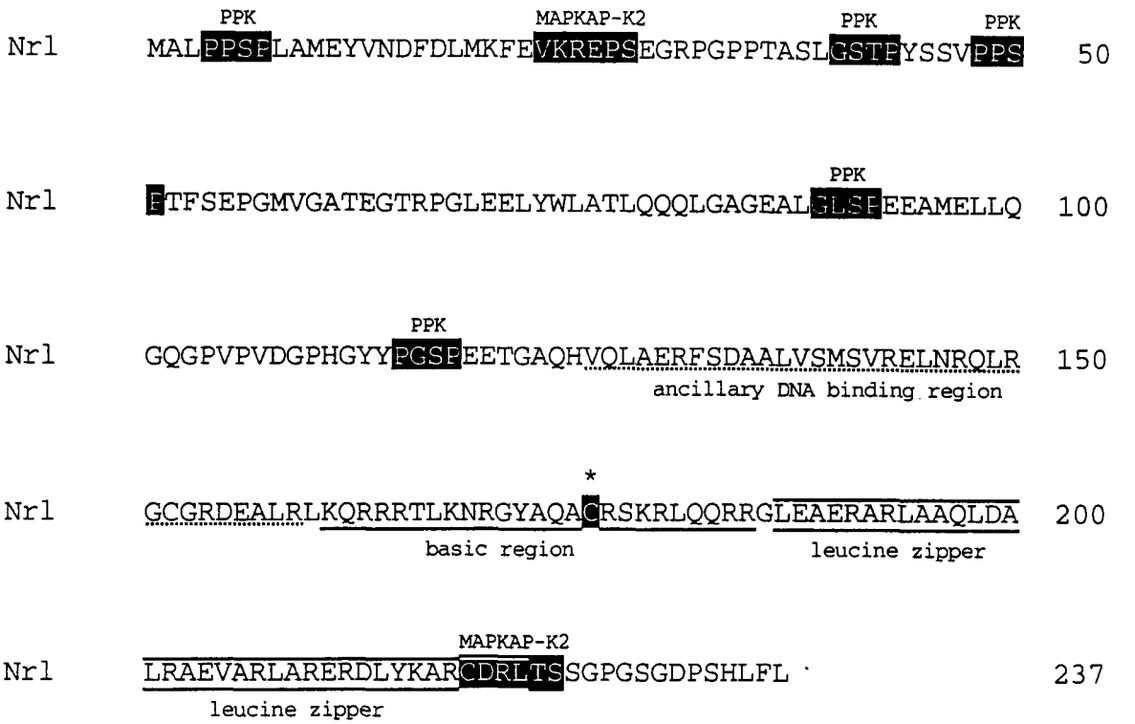


FIGURE 24 (continued)

gesting that these proteins may be phosphorylated by MAP kinases. As MAP kinases can be activated by a variety of stresses, such as H_2O_2, hemin, UV irradiation, phorbol esters, heat and osmotic shock, interleukin 1, and arsenite,[639,640] it is possible that many GST inducers can activate MAP kinase signaling pathways. Although oxidative stress can activate MAP kinases,[640] it is not known if Michael reaction acceptors (electrophile stress) can also activate these enzymes. Another reason for thinking that MAP kinases may be involved in signaling GST induction is that certain phenolic antioxidants increase the mitotic activity of liver cells in rats.[641-643] For these reasons, it will be interesting to establish whether MAP kinases can modulate the binding of Fos-Nrl, Jun-Nrl and Fos-Maf to the ARE.

Studies of GST regulation by adrenocorticotropic hormone (ACTH) in adrenocortical cells have shown that responsiveness to this hormone depends on a cyclic AMP-dependent protein kinase.[644] The cells used for these experiments were the Y1 line, which is responsive to ACTH, and the Hin 8 line (derived from Y1), which harbors a defect in the cyclic AMP-dependent protein kinase. The levels of mouse GSTM1 protein and mRNA were down-regulated by ACTH in the Y1 cells, whereas GSTM1 was not affected by hormonal treatment in the Kin 8 cells. Also, mGSTP1 expression was not affected by ACTH in either cell line. Because of the negative regulation of mGSTM1 by ACTH, this enzyme may have a physiological function in the adrenal gland

during periods of low pituitary ACTH production.

D. Posttranscriptional Control of GST

In this article, much emphasis has been placed on the transcriptional mechanisms responsible for the regulation of GST. Although transcriptional regulation of GST is of great significance, it is becoming apparent that the levels of GST can be controlled by modulation of the stability of mRNA and protein. Increases in the half-life of GST protein and mRNA have been responsible for overexpression of the class pi enzyme in human cell lines (Table 15). It is not known whether other classes of GST can also be regulated by similar mechanisms. Posttranslational modification of protein can also attenuate the activity of GST and may therefore represent another mechanism of control. For example, the activity of the microsomal GST can be increased dramatically by modification of the protein by thiol-active agents, pesticides, or proteolysis. The activity of class mu GST can be increased by treatment with ROS. The activity of rGSTM6*-6* can be modulated *in vitro* by methylation, whereas the activity of rGSTA1-2 can be modulated by phosphorylation *in vitro*. Human GSTP1-1 is glycosylated *in vivo*,[317] but it is unclear whether this modification alters its activity.

IX. PATHOPHYSIOLOGICAL REGULATION OF GST

A. Overexpression of GST during Chronic Hepatitis

Chronic hepatocellular damage is a feature of many liver diseases including hepatocellular carcinoma, viral infection, hemochromatosis, glycogen storage disease and α_1-antitrypsin deficiency. Despite the different causes of chronic liver injury, the necroinflammatory processes associated with the disease can produce marked oxidative stress. A transgenic mouse model exists for chronic hepatitis in which the hepatitis B virus large envelope protein has been placed under the control of the albumin promoter. In this model, Prochaska and coworkers[658] have found that a marked increase in the hepatic expression of mGSTA1 and mGSTM1 is associated with ongoing hepatocellular damage. They noted that the pattern of increase of phase II enzymes in the transgenic mouse during chronic hepatitis is similar to that observed in mice treated with chemoprotectors. It is likely that induction of GST and NQO during chronic active hepatitis is an adaptive response to ROS, although it is uncertain whether the mechanism of induction is direct or indirect.

B. Overexpression of GST during Carcinogenesis

1. Regulation of GST during Hepatocarcinogenesis in the Rat

Over the past ten years, class pi GST have attracted substantial attention as markers of preneoplastic lesions. This class of GST is ubiquitously distributed, but is found only in relatively small amounts in normal rat liver.[659] The earliest stages of hepatocarcinogenesis are characterized by a dramatic increase in the expression of the rat *GSTP1* gene. Administration of a single dose of a genotoxic hepatocarcinogen leading to the development of hepatic preneoplastic nodules produces a rapid and large increase in the levels of rGSTP1-1 in liver that persists until hepatocellular carcinoma development.[287–290,660] A remarkable increase

TABLE 15
Mechanisms Responsible for Increased GST Expression and/or Activity

Mechanism	Tissue	Gene/protein	Ref.
Transcriptional activation	Rat liver	Rat *GSTA2* gene by phenobarbital and 3-methylcholanthrene	571
	Rat liver	Rat *GSTA2* gene by oltipraz	645
	Rat liver	Rat *GSTP1* gene by lead nitrate	646
	Rat liver	Rat *GSTP1* gene during chemical carcinogenesis	647
	Mouse liver	Mouse *GstA2* gene by butylated hydroxyanisole	324
	Mouse liver	Mouse *GstM1* gene by butylated hydroxyanisole	324
Increased stability of mRNA	ER-negative human breast MCF7 cells	hGSTP1	648
Increased stability of protein	Human colon carcinoma HT6-8 cells	hGSTP1-1	649
Gene amplification	Chinese hamster ovary CHO-Chl^r cells	GST Yc	650
Enhanced specific activity	*In vitro* assay of rat enzyme	Microsomal GST activity increased by *N*-ethylmalaimide	205
	In vitro assay of human enzyme	Microsomal GST activity increased by *N*-ethylmalaimide	382
	In vitro assay of mouse enzyme	Microsomal GST activity increased by pesticides	651
	In vitro assay of rat enzyme	Microsomal GST activity increased by limited proteolysis	321
	In vitro assay of rat enzyme	Microsomal GST activity increased by radiation	652
	In vitro assay of rat enzyme	Activity of rGSTM1-1 and rGSTM2-2 increased by active oxygen species	318
	In vitro assay of rat enzyme	Activity of rGSTA3-3 and rGSTM2-2 increased by chenodeoxycholate	130
	In vitro assay of rat enzyme	Activity of rGSTA3-3 increased by 2,4-dichlorophenoxyacetate	653
	In vitro assay of rat enzyme	Activity of rGSTA3-3 increased by 2,4,5-trichlorophenoxyacetate	653
Reduced specific activity	*In vitro* assay of human enzyme	Oxidative inactivation of hGSTP1-1 through formation of intrasubunit disulfide bond	254, 654
	In vitro assay of rat enzyme	Oxidative inactivation of rGSTP1-1 through disulfide bond formation	655, 656
	In vitro assay of mouse enzyme	Thiol modification of mGSTP1-1 (and mGSTP2-2) at cysteine 47	657

in expression of rGSTP1 is observed in early preneoplastic foci of cells, a fact that makes this protein one of the most sensitive immunohistochemical markers for hepatocarcinogenesis in rat liver. Rat *GSTP1* is overexpressed in tumors produced by genotoxic chemical carcinogens (Figure 25), but is not expressed in tumors produced by nongenotoxic chemical carcinogens. Thus, increased levels of rGSTP1-1 are not observed in hepatomas produced by peroxisomal proliferators such as clofibrate,[661] whereas rGSTP1 expression is suppressed in primary hepatocytes by clofibrate and dexamethasone.[662] Both the peroxisome proliferator-activated receptor and the glucocorticoid receptor attenuate transcriptional activation by Fos-Jun of rat *GSTP1* via GPE1.

Studies in the rat have established that GSTP1 transcription is regulated via a TPA-responsive pathway that may involve $p21^{ras}$, Fos-Jun, and the palindromic TRE-like (GPE1) element.[570,599] Transformation of rat liver epithelial cells with v-H-*ras* or v-*raf* results in overexpression of rGSTP1-1, consistent with this proposed mechanism of regulation.[663] However, cotransfection of cells with *c-jun* and *c-fos* results in minimal activation of GPE1-mediated transcription,[664] suggesting that factors other than AP-1 are influencing GPE1. Also, anti-sense c-jun and c-fos cotransfected into F9 cells do not modulate GPE1-mediated *trans*-activation. The GPE1 enhancer comprises two palindromically oriented elements, each 8 bp, that are separated by 3 bp. The upstream half-site (5′-GTCAGTCA-3′) binds factors that are electrophoretically distinct from AP-1, whereas the downstream half-site (5′-TGATTCAG-3′) can bind AP-1. The upstream half-site has no transcriptional activity on its own, whereas the downstream half-site, which can function independently of the upstream half-site, is activated by AP-1.[664] However, both of the half-sites of GPE1 are required for AP-1-independent transcriptional activation. Indeed, the two half-sites function synergistically as GPE1 mediates a greater degree of *trans*-activation than either a single TRE or a direct TRE repeat. The protein complex that binds to the GPE1 would appear to be large as the two GPE1 half-sites can still retain activity when separated by 13 bp. It will be of great interest to establish the identity of the transcription factors responsible for the increased expression of GSTP1 during hepatocarcinogenesis.

Additional work in Muramatsu's laboratory has identified multiple *cis*-acting elements that bind silencer-binding proteins and oblate expression in normal rat liver. Sakai et al.[570] identified a stretch of sequence 400 bp upstream of the mRNA cap site that functioned as a *cis*-acting negative element in an orientation and position-independent manner in both rat and human hepatoma cell lines. Imagawa et al.[665] showed that at least two *trans*-acting factors interacted with the silencer element and partially purifed one of these factors, silencer factor A (SF-A).

In addition to transcriptional activation, Koo et al.[646] provided evidence that the increased rGSTP1-1 activity observed in liver following lead nitrate administration also involves posttranslational and posttranscriptional control. These workers suggested that rGSTP1-1 expression is regulated at multiple levels because, following lead nitrate administration, increases in hepatic GSTP1 mRNA, GSTP1 protein, and GSTP1-1 enzyme activity do not coincide.

2. Regulation of GST during Carcinogenesis in Humans

In human liver, hGSTP1-1 is essentially absent from normal hepatocytes but is expressed in high amounts in biliary epithelium.[666] Human hepatocellular carcinomas

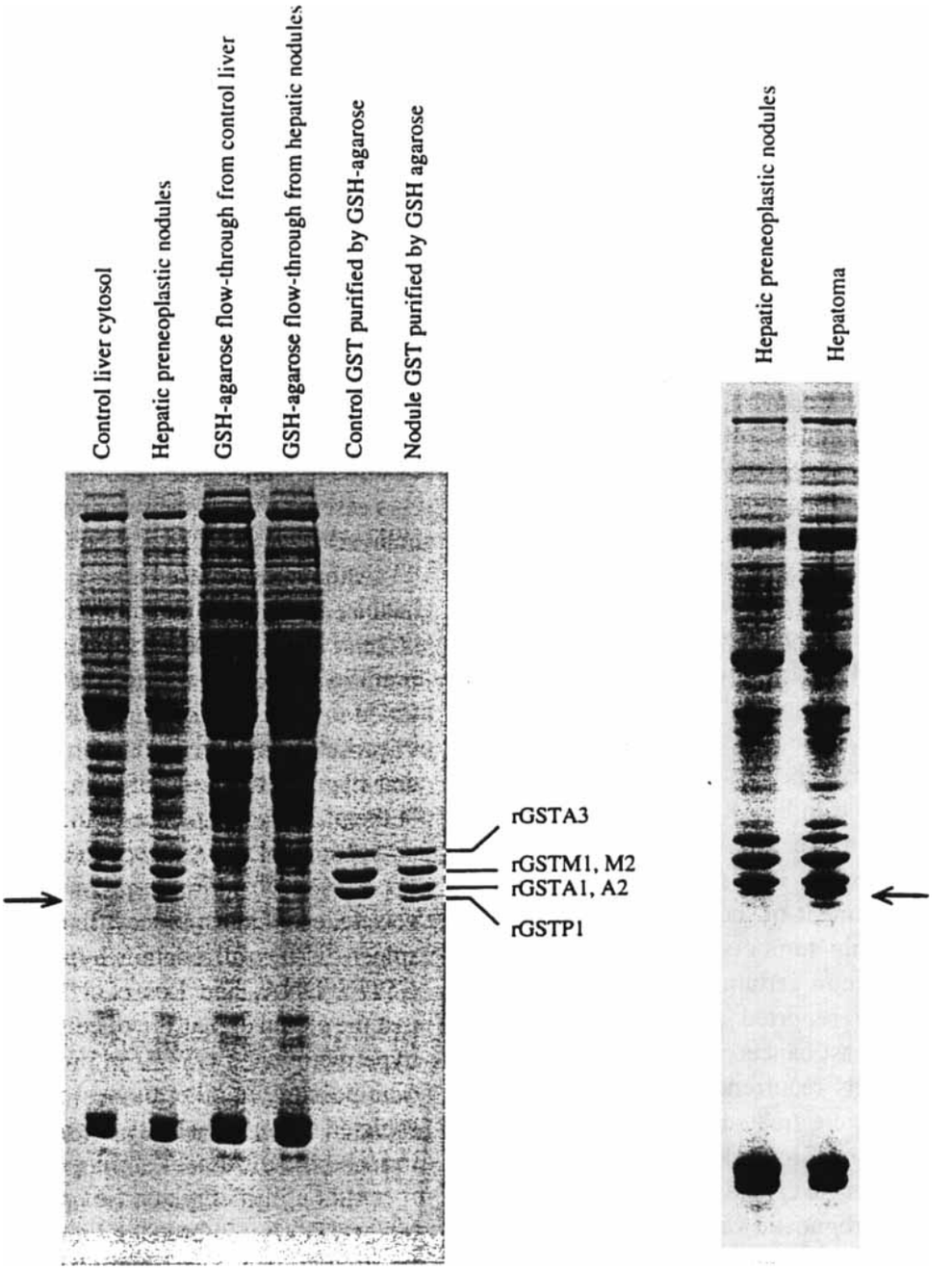


FIGURE 25. Overexpression of rGSTP1 in preneoplastic nodules. SDS/PAGE was carried out on cytosols from control rat liver, nodule-bearing rat liver, and rat hepatoma. The GST from control and nodule-bearing rat liver were purified by affinity chromatography on GSH-agarose as described in Reference 260. The arrows indicate the position of migration of the rGSTP1 polypeptide.

do not consistently overexpress hGSTP1-1, but it is found in cholangiocarcinoma, presumably reflecting the tissue of origin.[667] Hepatocytes in severe alcoholic liver disease express hGSTP1-1.[668] A high percentage of liver specimens examined from pa-

tients with alcoholic hepatitis with fibrosis, as well as those from patients with cirrhosis, express class pi GST. Also, in patients with steatosis, a high proportion were found to express hGSTP1-1 in sinusoidal lining cells (probably Kupffer cells) that do not normally express this isoenzyme. It is thought that the expression of the class pi transferase in hepatocytes during alcoholic liver disease is due to acquisition of a bile duct phenotype, as can be demonstrated by the pattern of expression of cytokeratin and tissue polypeptide antigen.[669] The class pi enzyme is not consistently overexpressed in human hepatoma, and is expressed in hepatocytes of patients with alcoholic liver disease, which has prevented its use as a histochemical marker for liver cancer. Human GSTP1-1 has been reported to be overexpressed in a variety of malignancies including carcinoma of the colon, lung, kidney, ovary, pancreas, esophagus, and stomach.[669-676] The class pi enzyme is also overexpressed in breast cancer, where levels of this enzyme are inversely related to estrogen-receptor levels in the tumor.[677,678]

Measurement of the levels of hGSTP1 protein within tumor samples may be of clinical value in certain malignancies. Gilbert et al.[679] reported that high hGSTP1 levels in breast cancer is a significant predictor of early recurrence of disease in patients who were treated surgically without chemotherapy. Similarly, Grignon et al.[680] proposed that the expression of class pi GST may be of prognostic value in patients with renal cell carcinoma, and Mulder et al.[681] suggested high hGSTP1 levels represent a poor prognostic index in patients with colorectal cancer. In ovarian tumors and acute nonlymphoblastic leukemia, low hGSTP1 expression has been reported to be associated with responsiveness to chemotherapy.[682-684] In contrast, other investigations have failed to find a correlation between GST levels and response to chemotherapy,[685,686] and it is clear that further clinical studies are required to establish the prognostic value of GST measurements.

Measurement of plasma hGSTP1-1 levels has shown that this protein is dramatically increased in lung cancer,[238] but the extent of overexpression of this protein in many tumors is frequently insufficient to allow the enzyme to serve as a general tumor marker. As a note of warning, it should be recognized that substantial amounts of GSTP1 are present in human platelets and, as the clotting process results in the release of large amounts of the protein into serum, it is essential that fresh plasma be used for analysis.[238]

Although increased class pi GST levels have been found in many human cancers, it is clearly not involved in all carcinomas. An immunohistochemical study of hGSTP1-1 failed to detect the class pi subunit in 88 of 91 prostatic cancers, and it was demonstrated that hypermethylation of cytidine residues in the promoter sequence of the gene might be responsible for the decreased *GSTP1* expression.[687] Normal prostate, seminal vesicle, esophagus, kidney, liver, lung, and spleen tissues all contain hypomethylated *GSTP1* DNA, and Lee et al.[687] suggested that the clonal expansion of cells containing hypermethylated *GSTP1* in prostatic tissue (and possibly in other tissues) might be associated with the inability of groups of cells to metabolize certain carcinogens.

Although methylation of promoter sequence DNA represents a mechanism for the regulation of human *GSTP1* expression, evidence also exists for the involvement of specific *cis*-acting regulatory elements within the structural gene. Both insulin and retinoic acid (RA) modulate expression of human *GSTP1*. Insulin increases expression of *GSTP1* through a cis-acting element in intron 1.[619] RA represses transcription of human *GSTP1*, an activity associated with the presence of a consensus TRE in the

promoter of the gene. The Fos-Jun complex binds to this enhancer[616] and is required for the basal level expression of the gene.[688] Xia et al.[619] suggested that the binding of RA to its receptor results in inhibition of transcription of the *GSTP1* gene through protein-protein interaction between the RA-receptor and a positive activation factor. Whether, the RA-receptor binds Fos or Jun is not clear and requires demonstration.

Although both the rat and human class pi genes contain some similar regulatory sequences, such as the ARE/TRE-like elements,[570,599,616] their regulation is distinct. Whereas the induction of rGSTP1 involves the $p21^{ras}$, Fos/Jun pathway and the GPE1 site, the regulation of the human *GSTP1* gene appears to involve a separate pathway and a regulatory sequence located in the first intron of the gene. In addition, the repression of the rat GSTP1 gene involves a number of silencer elements located within the promoter sequence. In the human gene, interaction between factors binding to the NF-κB-like element and the TRE site regulates gene expression,[607] as does the methylation state of the promoter.[687]

C. Tissue-Specific Regulation of GST Subunit Expression

Different GST subunits are expressed in a tissue-specific manner. Table 16 lists information on the tissue-specific expression of the various GST subunits. Tissue-specific regulatory elements were first identified in the promoter of the rat *GSTA2* gene.[573] Immunohistochemistry showed that the rGSTA1 and A2 subunits are specifically expressed in pericentral hepatocytes. Paulson et al.[573] identified enhancer elements, termed hepatic nuclear factor (HNF) elements,[705,706] that confer liver-specific expression on the rat *GSTA2* gene. Sequence analysis of rat *GSTA2* revealed the presence of a HNF-1-like element located between –860 and –850 bp. Deletion of this element from a *GSTA2* -CAT construct resulted in a two-fold decrease in basal expression in HepG2 cell lines. In addition, further deletions abolished all basal activity, indicating the presence of other tissue-specific enhancer elements in the promoter sequence. An HNF-4-like[706] element was also found in *GSTA2* between –775 and –755 bp.[573] A third sequence required for basal expression of *GSTA2* was identified[573] through its homology with the nontissue-specific NLS factor; the NLS factor was previously found to bind a positively acting site in the albumin enhancer.[707] Although the HNF-1-like element was able to function independently when isolated from the GST enhancer, the HNF-4-like and NLS elements could not, but rather required to be combined with other basal elements.

Abramovitz and Listowsky[284] have shown that rGSTM3 is localized primarily in the brain and testis. Subsequently, this research group isolated a clone for the *GSTM3* gene that included approximately 550 bp of DNA 5′ to the transcriptional start site.[708] The promoter region of the gene contains an inverted CCAATT box and consensus SP1 binding sites, but lacks a TATA box in close proximity to the transcriptional start site. In addition, two octamer sequences, 5′-ATTTGCAT-3′, that occur as direct repeats with a 6-bp spacer between them are located between nucleotides –375 and –396. Functional analysis of the rat *GSTM3* promoter region indicated that the octamer repeats were necessary for expression in neural C6 glioma cells and that the *GSTM3* promoter is not functional in either Hep3b or HTC cells. In addition, anti-rGSTM3-3 IgG cross-reacted with a protein in C6 glioma cells, but did not cross-react significantly with protein from other tissues. The introduction of two point mutations in each

TABLE 16
Variations in Constitutive Expression of GST

Example	Species (and strain)	Enzyme and phenotype	Cause	Ref.
Genetic polymorphism	Human	Mu class: 40% of individuals "nulled" for hGSTM1-1	Gene deletion	358, 360, 362
Genetic polymorphism	Human	Mu class: charge variants in enzyme encoded at GSTM1 locus	Allelic variation	43
Genetic polymorphism	Human	Pi class: variation in hGSTP1 at residues 104 and 113	Allelic variation	201
Genetic polymorphism	Human	Theta class: 16% of individuals "nulled" for hGSTT1-1	Gene deletion	44
Interindividual variation	Human	Alpha class: variation in relative amounts of hGSTA1 and hGSTA2 subunits	Unknown	351, 689
Interindividual variation	Human	Alpha class: absence of skin GST9.9 in many individuals	Unknown	355, 690
Strain variation	Rat, EHB	Alpha class: elevated hepatic levels of rGSTA3-5	Unknown	269
Strain variation	Rat, BN	Mu class: alteration in isoelectric point of the rGSTM1 subunit	Unknown	691
Strain variation	Rat, Gunn	Alpha, mu, and pi: increase in rGSTA3, A5, M6*, and P1 in cerebellar cortex	Unknown	692
Strain variation	Mouse, lit/lit	Pi class: loss of hepatic sexual dimorphic expression of mGSTP1-1	GH receptor malfunction	45
Sex-specific expression	Human	Mu class: expression of GST (pI 6.2) in female but not male colon	Unknown	693
Sex-specific expression	Human	Pi class: higher levels of hGSTP1-1 in female skin than in male skin	Unknown	694
Sex-specific expression	Rat, Fischer 344	Alpha class: higher levels of rGSTA2, A3, and A5 in female than male livers	GH and thyroxine	269, 270, 695
Sex-specific expression	Rat, Fischer 344	Alpha class: higher levels of rGSTA1 in male than female livers	GH and thyroxine	695
Sex-specific expresson	Rat, Fischer 344	Mu class: higher levels of rGSTM1 and M2 in male than female livers	GH and thyroxine	520, 695
Sex-specific expression	Mouse, BALB/c	Pi class: higher levels of mGSTP1 in livers of males than females	GH	45, 340, 696
Ontogenic variation	Human	Alpha class: hGSTA1 and/or A2 only observed in kidney 40 weeks postnatally	Unknown	697
Ontogenic variation	Human	Pi class: hGSTP1-1 in fetal liver decreases between first and third trimester	Unknown	698
Ontogenic variation	Rat, Fischer 344	Alpha class: absence of rGSTA1 and A2 in fetal liver; reach adult levels 5 weeks postnatally	Unknown	235, 270, 539, 699
Ontogenic variation	Rat, Fischer 344	Alpha class: high levels of rGSTA5 in fetal liver, sex-specific decrease postnatally (weeks 3–10)	Unknown	270, 699
Ontogenic variation	Rat, Fischer 344	Alpha: high levels of rGSTA4 in fetal liver, modest increase postnatally	Unknown	235, 270
Ontogenic variation	Rat, Fischer 344	Mu class: rGSTM1 found in fetal liver and expression increases rapidly postnatally	Unknown	235, 270
Ontogenic variation	Rat, Fischer 344	Mu class: rGSTM2 not found in fetal liver, expression only observed 3 weeks postnatally	Unknown	235, 270
Ontogenic variation	Rat, Fischer 344	Pi class: rGSTP1 expressed in fetal liver at day 17 but declines thereafter	Unknown	270, 699
Tissue specificity	Human	Alpha class: hGSTA1 and A2 in liver, gastric mucosa, small intestine, adrenals, kidney, testis	Unknown	348, 378, 700–703
Tissue specificity	Human	Mu class: hGSTM2, M3, and M5 expressed at highest levels in skeletal muscle, brain, testis	Unknown	43, 366, 370, 375
Tissue specificity	Human	Mu class: hGSTM4 expressed in skeletal muscle, heart, brain, liver, pancreas	Unknown	188
Tissue specificity	Human	Pi class: hGST P1 expressed in most extrahepatic tissues, also found in biliary epithelium	Unknown	666, 700, 704
Tissue specificity	Rat, Wistar	Alpha class: rGSTA1 subunit only expressed in liver and kidney	Unknown	305
Tissue specificity	Rat, Wistar	Alpha class: rGSTA2 subunit only expressed in liver and small intestine	Unknown	506
Tissue specificity	Rat, Wistar	Alpha class: rGSTA3 in most tissues except small intestine and colon	Unknown	233
Tissue specificity	Rat, Wistar	Alpha class, rGSTA5 in nasal mucosa and epididymis	Unknown	270, 495
Tissue specificity	Rat, Wistar	Alpha class: GST Yl in kidney	Unknown	222
Tissue specificity	Rat, Wistar	Alpha class: GST Ys in spleen	Unknown	271
Tissue specificity	Rat, Wistar	Mu class: rGSTM1 in most tissues except kidney	Unknown	233
Tissue specificity	Rat, Wistar	Mu class: rGSTM2 in most tissues except brain	Unknown	692
Tissue specificity	Rat, Wistar	Mu class: rGSTM3 in brain and testis	Unknown	284
Tissue specificity	Rat, Wistar	Mu class: rGSTM5* and M6* in testis	Unknown	222, 285, 286
Tissue specificity	Rat, Wistar	Pi class: rGSTP1 expressed in most tissues except liver	Unknown	233

of the octamer repeat sequences resulted in a 65% decrease in promoter activity, demonstrating that the element is required for expression in C6 glioma cells. Electrophoretic mobility shift assays using a synthetic oligonucleotide confirmed that C6 glioma, brain, and testis nuclear extracts contain a protein that interacts specifically with the octamer repeat sequence. These results suggest that the octamer repeat sequence is required for tissue-specific expression of the rGSTM3 subunit in C6 glioma cells and is likely to be involved in the expression of *GSTM3* in the brain and testis.

Clearly, further research is required to identify other regulatory elements and *trans*-acting factors involved in tissue-specific expression.

D. Sex-Specific and Ontogenic Regulation

Table 16 shows that GST expression is subject to both sex-specific and ontogenic regulation. Numerous studies have shown that mouse, rat, and human GST are all subject to sex-specific or ontogenic variations, or both, and that class alpha, mu, and pi enzymes are affected. Although little is known about the mechanisms controlling ontogenic variation, limited studies have indicated a role for pituitary growth hormone (GH) and thyroxine in sex-dependent expression in the rat.[695] Northern blot analysis revealed that the steady-state levels of rGSTA1, M1, and M2 mRNAs are approximately 2.5-fold higher in male than in female livers. By contrast, rGSTA2 and A3 mRNAs are between two- and threefold higher in the female than in the male rat liver. Suppression of the male-dominant rGSTA1, M1, and M2 mRNAs was achieved by continuous infusion of GH (mimicking the adult female rat plasma GH levels), thus indicating that feminization of animals represses expression of these subunit genes.[695] Administration of cisplatin, which alters expression of hormonally regulated CYP,[709] causing the depletion of circulating testosterone and modulation of plasma GH profiles, results in repression of rGSTA1 and elevation of rGSTA3 mRNA, further supporting a role for GH in regulation of expression of some rat GST.[500] In the rat, hypophysectomy increased expression of male-dominant rGSTA1, M1, and M2, particularly in females. In addition, treatment with thyroxine, which has feminizing effects on liver CYP expression, suppresses expression of male-dominant rGSTA1 and elevates levels of the female-dominant rGSTA3.[695] These results indicate that the sexual dimorphism observed in the expression patterns of GST enzymes is controlled hormonally. In particular, the pattern of the plasma GH profile, which is sexually dimorphic, determines the constitutive levels of certain GST subunits in the liver. In addition, thyroxine is also important in regulation. Both GH and thyroxine levels are controlled by the anterior pituitary gland, which is in turn hypothalamically regulated. Thus, in effect, the sexual dimorphic control of hepatic GST isoenzymes in the rat is under the control of the hypothalamus.

In the little mouse mutant, which secretes essentially no GH due to a defective receptor for GH-releasing hormone, the sexually dimorphic expression of class pi GST is lost in the liver. As can be seen in Figure 26, the hepatic levels of mGSTP1 and mGSTP2 in male lit/+ and male +/+ mice are substantially higher than in female lit/+ and +/+ mice. However, this sex-specific expression is lost in lit/lit mice and the levels of mGSTP1 in male lit/lit mice are reduced to the same level as seen in female lit/lit mice. The differences in hepatic protein levels are also reflected in GST activity

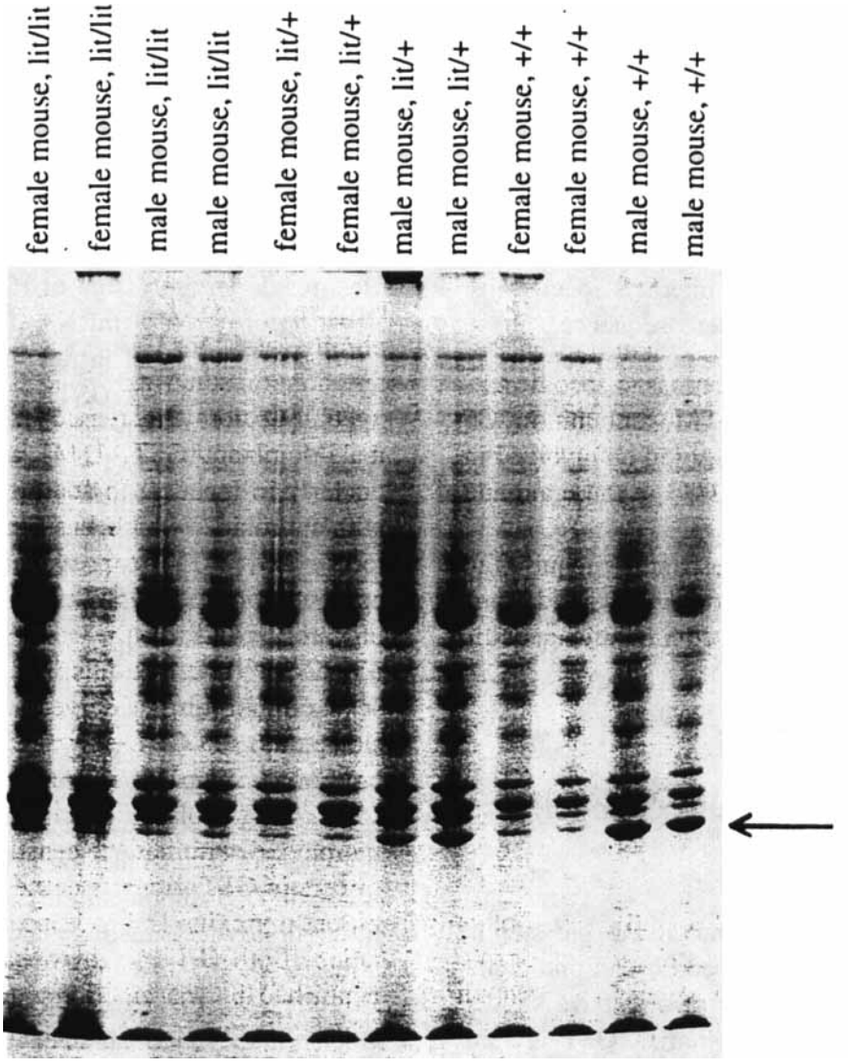


FIGURE 26. Sex-specific control of GST expression in mouse liver. The position of migration of mGSTP1 and mGSTP2 is indicated by the arrow. The gel shows that the levels of class pi GST are similar in hepatic cytosol from male and female lit/lit mice (lanes 1 to 4, numbered from the left), whereas a marked sexual dimorphism in the amount of class pi GST is apparent in livers from lit/+ and +/+ mice (lanes 5 to 12). The GST activities toward ethacrynic acid in hepatic cytosol from male lit/lit, lit/+, and +/+ mice were 0.05, 0.12, and 0.09 μmol/min/mg protein, respectively, whereas the same activities in hepatic cytosol from female lit/lit, lit/+, and +/+ mice were 0.04, 0.04, and 0.03 μmol/min/mg protein, respectively.

toward ethacrynic acid, which is twofold higher in male +/+ and male lit/+ mice than in male lit/lit mice.

Observations that the rat *GSTA2* gene contains a GRE,[566] and that a class mu GST in Syrian hamster is regulated by dexamethasone, suggest that specific enhancer elements may be involved in the hormonal regulation of these and other subunit genes. According to Norris and co-workers,[189] other

enhancer sequences distinct from the GRE may exist. Further work is required to identify both the promoter sequences and hormonally regulated enhancer elements in GST genes.

X. CONTRIBUTION OF GST TO DRUG RESISTANCE

A. Models of Drug Resistance

A large body of literature indicates that the levels of expression of GST contribute significantly to determining the sensitivity of many organisms to chemical insult. In a variety of experimental models, increased tolerance of toxic xenobiotics is associated with increased expression of GST. Examples include (1) fosfomycin resistance in bacteria;[450,451] (2) DDT resistance in insects;[423–425] (3) safeners inducing tolerance of herbicides in plants;[166,167] (4) selective toxicity of different rodent species to aflatoxin B_1;[473] (5) chemoprotection against chemical carcinogenesis in rodents by synthetic antioxidants;[32,541] (6) drug "priming" by the administration of sublethal doses of cytotoxic agents;[489] (7) multidrug-resistant phenotype of preneoplastic hepatocyte nodules in the rat;[710] (8) analyses of tumor cells from patients before and after the onset of clinical drug resistance;[711] (9) selection of resistance to chemotherapeutic agents in tumor cell lines;[712] (10) transfection of GST into mammalian cell lines.[713]

Evidence that GST may be of major importance in conferring resistance to genotoxic carcinogens was first provided by Talalay and his co-workers[337] who demonstrated that GST in mouse liver are induced dramatically by the chemoprotector BHA. Subsequently, many workers have shown that the levels of GST are increased by all chemoprotectors that are classified as blocking agents, suggesting that the transferases actively inhibit the initiation phase of carcinogenesis. The hypothesis that GST are important in providing protection against chemical carcinogens is further supported by their marked overexpression in rat hepatic preneoplastic nodules.[710] These nodules display resistance to a variety of xenobiotics including acetylaminofluorene, adriamycin, aflatoxin B_1, dimethylnitrosamine, and CCl_4. It is worthwhile noting that, although the expression of rGSTP1 differs markedly in livers from animals treated with chemoprotectors and nodule-bearing livers, nonetheless the pattern of expression of the class alpha and mu GST is similar in both resistance models.[301]

The recognition that GST levels are frequently elevated in cell lines selected for resistance to anti-cancer drugs has served as a stimulus to determine the role of GST in protection against chemotherapeutic agents. The early work in this area was pioneered by the laboratories of Cowan, Hickson, and Tew. Thus, many groups have found that GST are overexpressed in a variety of human and rodent cell lines that were selected for resistance *in vitro* to adriamycin, BCNU, chlorambucil, cyclophosphamide, etoposide (VP-16), melphalan, and vincristine. In addition to these cell lines with acquired drug resistance, comparison among related breast, bladder, or colon cell lines, which display different intrinsic levels of resistance toward hepsulfam, mitomycin C, or mitoxantrone, has revealed a correlation between GST expression and the level of drug resistance. As Table 17 shows, the majority of these resistant lines contain elevated levels of class pi GST. However, many of the cells that are resistant to nitrogen mustards contain increased levels of class alpha GST.[719,722,724,725] In two cases, namely, BCNU-resistant rat gliosarcoma 9L-2 cells[452] and ethacrynic acid-resistant MCF-7 human breast tumor

TABLE 17
Altered GST Expression in Drug-Resistant and Drug-Sensitive Cell Lines

Drug	Fold Resistance	Cell line	Cross-resistance	Derived by	Changes in GST	Ref.
Adriamycin	100	MCF-7 human breast (Adr^r)	Actinomycin D, vinblastine	*In vitro* selection	45-fold increase in hGSTP1	714
Adriamycin	32	H69AR human small cell lung	Colchicine, daunomycin	*In vitro* selection	10-fold increase in hGSTP1	715
Adriamycin	75	SW620-ADR human colon	Actinomycin D, puromycin	*In vitro* selection	2-fold increase in hGSTP1	716
Adriamycin	13	Friend erythroleukemia (ARN2)	Mitoxanthrone, vincristine, VP-16	*In vitro* selection	>10-fold increase in mGSTA1 or A2	717
Adriamycin	84	P388 murine leukemia	ns	*In vitro* selection	2.2-fold increase in mGSTP1	718
Adriamycin	200	MatB13762 rat mammary (Adr^r)	Vincristine	*In vitro* selection	5-fold increase in rGSTA3 and P1	719
Arsenic	9	SA7 Chinese hamster ovary	ns	*In vitro* selection	Levels of GSTP1 correlate with resistance	720
BCNU	3.5	9L rat gliosarcoma (9L-2)	CNDP	*In vitro* selection	>2-fold increase in rGSTM1 or M2	452
Bleomycin	0.03	Chinese hamster ovary (BL-10)	ns	Hypersensitive mutant	Sensitivity normalized by hGSTA1	721
CDNB	3	H322 human lung (CDNB^r)	CuOOH	*In vitro* selection	>10-fold increase in hGSTA1 and A2	722
Chlorambucil	15	Walker 256 rat mammary	phosphoramide mustard	*In vitro* selection	>10-fold increase in rGSTA3	723
Chlorambucil	24	Chinese hamster ovary (CHO-Chl^r)	Mechlorethamine, melphalan	*In vitro* selection	>10-fold increase in hamster GST Yc	724
Chlorambucil	>10	Mouse fibroblast 3T3 (N50-4)	ns	*In vitro* selection	>10-fold increase in alpha class GST	725
Cisplatin	18	HeLa human cervix (HeLa-CPR)	ns	*In vitro* selection	6-fold increase in hGSTA1 and A2	716
Cyclophosphamide	19	Yoshida rat sarcoma (YR cyclo)	Phosphoramide mustard	*In vitro* selection	6-fold increase in CDNB activity	726
EA	2.5	MCF-7 human breast (EA^r)	ns	*In vitro* selection	> 10-fold increase in mu-class GST	727
EA	2	HT 29 human colon (HT/M)	ns	*In vitro* selection	3-fold increase in hGSTP1 mRNA	728
Etoposide (VP-16)	14	MCF-7 human breast (VP6E)	Vincristine	*In vitro* selection	>10-fold increase in hGSTP1	729
Hepsulfam	10	MCF-7 human breast	Adriamycin	Comparative study	>10-fold increase in hGSTP1	730
Hepsulfam	8	Hs578T human breast	ns	Comparative study	Levels of hGSTP1 correlate with resistance	730
Melphalan	17	HS-Sultan human plasma cell	ns	*In vitro* selection	1.5-fold increase in hGSTP1	731
Melphalan	10	MatB13762 rat mammary(Mln^r)	BCNU, ionizing radiation	*In vivo* selection	10-fold increase in rGSTA3 and P1	719
Mitomycin C	4.5	SCaBER human bladder	ns	Comparative study	5-fold increase in hGSTP1	732
Mitoxantrone	200	Caco-2 human colon	ns	Comparative study	>6-fold increases in hGSTP1, A1, and A2	733
MNNG	ns	Rat liver endothelial cells (GP9TA)	Adriamycin	*In vivo* selection	10-fold increase in rGSTP1	734
Novantrone	5	MCF-7 human breast (NOV6E)	ns	*In vitro* selection	>10-fold increase in hGSTP1	729
Oxazaphosphorine	6	MCF-7 human breast (MCF/HC)	ns	*In vitro* selection	2.7-fold increase in GST	735
TGF-β1	ns	WB-F344 rat liver epithelial cells	Adriamycin, melphalan	*In vivo* selection	1.5-fold increase in CDNB activity	736
Vincristine	3	MCF-7 human breast (VCR6E)	VP-16	*In vitro* selection	>10-fold increase in hGSTP1	729
Vincristine	11	MCF-7 human breast (VCREMS)	Adriamycin, VP-16	*In vitro* selection	>10-fold increase in hGSTP1	729

Note: BCNU, 1,3-*Bis*(2-chloroethyl)-1-nitrosourea; CNDP, 2-[3-(Chloroethyl)-3-nitrosoureido]-D-dioxyglucopyranose; ns, not stated, VP-16, etoposide; CuOOH, cumene hydroperoxide; EA, ethacrynic acid.

cells,[727] the level of class mu GST increased. In addition to these models of acquired and intrinsic drug resistance, the absence of class alpha GST has been correlated with hypersensitivity to bleomycin in a mutant Chinese hamster ovary cell line.[721] In most of the resistant cell lines, a significant number of detoxification proteins are overexpressed, and therefore it is difficult to be certain that GST, and not a coinduced protein, is responsible for the resistant phenotype.

The use of buthionine sulfoximine to deplete GSH levels is a helpful strategy to demonstrate whether glutathione is involved in drug resistance. Similarly, treatment of drug-resistant cells with GST inhibitors, such as ellagic acid, ethacrynic acid, gossypol, indomethacin, piriprost, sulfasalazine, tienilic acid, and triphenyltin chloride, represents a useful approach to help confirm whether the transferases are responsible for resistance to chemotherapeutic agents.[452,737–742] A series of GSH analogs have been developed by Mulder and coworkers[743] as inhibitors of GST, and the compound (*R*)-5-ethyloxycarbonyl-2-γ-(*S*)-glutamylamino-*N*-2-heptylpentamide has proved to be an effective inhibitor of rat class alpha and mu GST. It remains to be determined whether such GSH analogs can be used to overcome GST-mediated resistance in human tumors.

B. GST Transfection Experiments

Although variable results have been obtained, the most compelling evidence that GST are of importance in drug resistance has been derived from transfection experiments. Such experiments are not as straightforward as they might appear, and the use of different cell lines as well as different expression vectors may give discrepant results. For example, it is distinctly possible that the transfection of GST subunits with antioxidant properties will alter the expression of many genes within the recipient cell, and hence modulate the intrinsic resistance of the cell to drugs; such GST-mediated changes in gene expression are certain to involve heat shock proteins or enzymes involved in oxidative stress responses. In normal mammalian tissues, GST represent a substantial proportion of the cytosolic protein (up to 2.0%), and it would therefore appear essential to achieve high levels of expression of GST following transfection to ensure that false-negative results are not obtained. Also, it should be borne in mind that high levels of GST protein may not equate with high levels of GST activity.[646] In addition to considerations of GST expression, particular care should be taken when selecting the cell line for transfection. As a first requirement, it is important that the recipient cell line should take up the drug of interest, by either passive or active uptake mechanisms. Also, the cells must possess low levels of endogenous GST, and other competing detoxification or repair pathways, to allow the transfected GST to make an impact on the intrinsic resistance mechanisms of the cell line. It is equally important that the cells of study should contain moderate levels of GSH and express the GS-X pump to ensure that the transfected GST can function efficiently. Finally, with certain xenobiotics, metabolic activation is required for toxicity and it will be necessary that the cell contains the appropriate enzymes and co-factors to effect activation of the agent under study. In view of these widely differing criteria for selection of cell lines to be used for transfection experiments, it is possibly not surprising that variable results have been obtained by different research groups. Among the cell lines used for such experiments, COS, NIH-3T3, and MatB cells have, in general, yielded results demonstrating the protective effects

of GST, whereas MCF-7 cells have given generally disappointing results.

The first demonstration that GST can confer resistance against toxic xenobiotics was reported by Fahl and his co-workers,[744] who expressed rGSTA2-2 from the SV40 promoter in COS cells. In a mixed population of cells, they observed a 20- to 30-fold enrichment of GST overexpressing cells following exposure to benz[*a*]pyrene (±)-*anti*-diol epoxide. Later, using cytotoxicity assays, the same laboratory showed that rGSTA2-2 conferred between 1.3- to 2.9-fold resistance on COS cells to chlorambucil and melphalan.[713] Using the same cell line, they also reported that rGSTM1-1 conferred 1.5-fold resistance to cisplatin and hGSTP1-1 conferred 1.3-fold resistance to adriamycin and 1.5-fold resistance to a mixture of 7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo [*a*]pyrene and 7α,8β-dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene.[713] Manoharan et al.[745] also suggested that different GST might provide distinct resistance mechanisms to a specific drug, as COS cells that express both rGSTA2-2 and rGSTM1-1 are 25% or 75% more resistant to chlorambucil than COS cells that express either GST alone. More recently, Gulick and Fahl[458] have shown that *E. coli* expressing rGSTA3-3 are 3.3-fold more resistant to the nitrogen mustard mechlorethamine than nontransformed bacteria.

Similar results to those published by Fahl's laboratory have been obtained independently by other groups of workers. Using NIH-3T3 cells, Nakagawa et al.[746] showed that hGSTP1-1 can confer up to a 3.0-fold resistance to the cytotoxic effects of adriamycin and a 7.9-fold resistance to ethacrynic acid. Black et al.[747] expressed hGSTA1-1 and hGSTP1-1 in *Saccharomyces cerevisiae* and, in this organism, found that hGSTA1-1 can confer 3- to 16-fold resistance to adriamycin and two- to eightfold resistance to chlorambucil, whereas hGSTP1-1 confers two- to tenfold resistance to adriamycin and two- to fivefold resistance to chlorambucil.

To date, the largest increases in GST-mediated resistance to anticancer drugs have been reported by Schecter et al.[748] who obtained a stable transfectant GST subline of MatB cells, using the pSV2neo vector containing the SV40 early region promoter, which stably expressed rGSTA3-3. The clone M49-8 was 6- to 12-fold resistant to melphalan, 10- to 16-fold resistant to mechlorethamine, and 7- to 30-fold more resistant to chlorambucil. In late passages (after 14 months), under continuous selection with G418, GSTA3-3 expression diminished in the transfected MatB cells, and was accompanied by a decrease in resistance to melphalan, mechlorethamine, and chlorambucil. Similar levels of resistance to alkylating agents as those reported by Schecter et al.[748] have been obtained with rGSTA3-3 in NIH-3T3 mouse fibroblast cells.[749]

The possibility that mutant GST can confer greater levels of drug resistance than wild-type enzymes has been explored by Gulick and Fahl.[458] By using random mutagenesis of the region encoding residues 10 to 15 of rGSTA3-3, followed by selection for resistance to mechlorethamine in *E. coli*, these workers isolated mutant transferases with significantly improved catalytic activity toward the nitrogen mustard. Mutant enzymes were isolated that conferred up to 31-fold resistance toward mechlorethamine in *E. coli*, compared with 3.3-fold resistance confered by the wild-type enzyme. The improved catalytic activity for mechlorethamine was accompanied by decreased activity for CDNB and cumene hydroperoxide, suggesting that the mutant rGSTA3-3 may not confer increased resistance against all alkylating agents or organic hydroperoxides.

All the studies described above have employed cytotoxicity rather than genotoxicity as a biological end-point. However, GST may be better suited to provide protection against genotoxic xenobiotics than cytotoxic drugs. Fields et al.[750] have reported that mGSTM1-1 and hGSTP1-1 protect MCF-7 cells against the covalent binding of 4-nitroquinoline-1-oxide to DNA. These workers showed that although mGSTM1-1 and hGSTP1-1 reduced the binding of 4-nitroquinoline-1-oxide to macromolecules in MCF-7 cells by 92 and 70%, respectively, these GST did not protect against the cytotoxicity of 4-nitroquinoline-1-oxide as measured by clonogenic assay. Unfortunately, because of the poor record of GST-transfected MCF-7 cells in giving positive results in clonogenic assays,[751-753] it is not clear whether the disparity between the cytotoxicity and genotoxicity of 4-nitroquinoline-1-oxide is a result specific to this cell line, or a general feature that holds true for all cell lines.

XI. POLYMORPHIC EXPRESSION OF GST: ASSOCIATION WITH DISEASE SUSCEPTIBILITY AND FAILURE OF CHEMOTHERAPY

A. Variable Expression of GST in Experimental Models and Increased Sensitivity to Chemical Insult

Considerable interest exists concerning whether failure to express GST influences susceptibility to disease. As is evident from Table 10, GST are involved in the metabolism of many carcinogens, environmental pollutants, anticancer drugs, and ROS, and it is reasonable to suppose that the absence of specific isoenzymes will have a profound effect on the tolerance of an organism to xenobiotics. The clearest example of a GST null phenotype giving rise to xenobiotic sensitivity is the GT112 inbred strain of maize that lacks an atrazine-metabolizing GST and, through failure to detoxify *S*-chlorotriazines, possesses a markedly increased sensitivity to this class of herbicide.[754] Other strains of maize exist, *bz2*, which lack the GST encoded by the *Bronze-2* gene.[755] The *bz2* plants accumulate cyanidin-3-glucoside in the cytoplasm of tissues and, although it is not known whether they possess increased sensitivity to herbicides, they do exhibit significantly lower levels of activity to the model substrate CDNB.

The evidence supporting the hypothesis that absence of GST results in increased susceptibility to chemical or oxidative stress is less obvious in rodents than in atrazine-sensitive maize GT112. Indeed, the models described involve phenotypic alteration in expression of protein rather than genotypic changes in GST. In inbred strains of mice, marked variation in the expression of class pi GST, due to altered endocrine control, has been observed,[45] but this has not been associated with sensitivity to chemical insult. Also, an increase in the level of rGSTA5 has been noted in the livers of EHB rats[269] and increases in rGSTA3, A4, M6*, and P1 have been noted in the cerebellar cortex of Gunn rats,[692] but again nothing is known about the biological consequences of these alterations in enzyme expression. In the absence of an example of a null GST polymorphism in rodents resulting in sensitivity to xenobiotics, it should be remembered that the selective toxicity of aflatoxin B_1 in the rat and the intrinsic resistance of the mouse to this mycotoxin are attributed entirely to differences in the constitutive expression of orthologous class alpha isoenzymes, namely mGSTA3-3 and rGSTA5-5, in these two species.[325,326,473] With the availability of "gene knock-out" technology, it is expected

that powerful experimental models will become available that will allow a better understanding of the biological significance of GST null phenotypes.

B. Null Polymorphisms and Increased Risk of Cancer

1. Human Health Risk Associated with Deletion of the GSTM1 Gene

The *in vivo* contribution of GST to protection against noxious chemicals is difficult to assess in humans. However, the existence of genetic polymorphisms in the population allows this question to be addressed, at least for a limited number of GST genes, by utilizing molecular epidemiology to show an association between disease and the absence of particular isoenzymes. Although this approach is powerful, it should be pointed out that it does not prove whether an association between GST expression and disease susceptibility is direct or indirect. The fact that GST are part of a complex integrated detoxification system may frustrate attempts to demonstrate association between GST polymorphisms and disease. The ability of certain GST alleles to influence the expression of other genes may represent a significant factor in modulating sensitivity to disease. Furthermore, the overexpression of other genes may be able to compensate for the absence of particular GST isoenzymes.

Interindividual differences in human class mu GST are commonly observed and were first described in the early 1980s.[42,358] Such variation is due either to gene deletion, resulting in failure to express protein, or allelic variation, resulting in production of catalytically active protein with an altered charge. Thus, three common alleles exist at the locus for human GSTM1, namely, *GSTM1*A*, *GSTM1*B*, and *GSTM1*0*, that give rise to the GSTM1A, GSTM1B, and GSTM1 null phenotypes, respectively. The GSTM1a and GSTM1b subunits, encoded by *GSTM1*A* and *GSTM1*B*, have different pI[363] but exhibit closely similar catalytic activities toward model substrates.[365] The frequency of the three GSTM1 alleles varies significantly in different populations. The frequency of *GSTM1*0* homozygosity is 58% in Chinese, 52% in English, 48% in Japanese, and 43% in French nationals, but it is significantly less common in Nigerians. In Nigeria, it is observed in only 22% of the population.[756] Furthermore, the distribution of *GSTM1*B* is also heterogeneous, being found in only 5.8% of Nigerians, but 29% of Chinese, 16% of English, 40% of Japanese, and 9% of French nationals. In certain Micronesian and Polynesian populations, more than 90% of individuals have been found to be nulled for hGSTM1.[43] This variation in *GSTM1* expression among the control population poses significant difficulties for researchers in the selection of suitable control groups to be used for determining the association between GST genotype and disease susceptibility. Considerable care should be taken when selecting controls, because Strange[756] found that the frequency of *GSTM1* null varies in control groups obtained from hospital patients compared with post-mortem samples.

Epidemiological studies suggest that individuals who are homozygous nulled at the *GSTM1* locus may have an increased risk of developing various types of neoplastic disease, including cancer of the bladder, colon, lung, skin, and stomach. Most of the efforts in this area have focused on lung cancer for the reason that hGSTM1a-1a and hGSTM1b-1b are active toward certain epoxides of PAH found in cigarette smoke and other combustion products. Most sig-

nificantly, it has not only been shown that lymphocytes that lack hGSTM1a-1a and hGSTM1b-1b are more prone to epoxide-induced cytogenetic damage,[757] but it has also been shown that a positive association exists between the levels of PAH-DNA adducts formed in human lung and the *GSTM1*0/0* genotype.[758] Similarly, Liu et al.[759] showed that the presence of GSTM1a-1a, or GSTM1a-1b, or GSTM1b-1b in human liver cytosol inhibited the ability of benzo[*a*]pyrene as well as aflatoxin B_1 to form adducts with calf thymus DNA.

Seidegard et al.[760] provided the first evidence that an association exists between the GSTM1 null phenotype and the risk of developing lung cancer when they reported an approximate 1.6-fold increase in the frequency of nulled individuals among patients with lung cancer. Using a *trans*-stilbene oxide enzyme assay to measure GSTM1 activity in leukocytes, they reported that 41% of control individuals were negative for GST activity toward *trans*-stilbene oxide, whereas as many as 65% of lung cancer patients lacked this activity. Subsequent studies by other research groups have not always found a clear relationship between the GSTM1 null phenotype and lung cancer.[761] The reasons are almost certainly multifactorial and may be due to the use of insufficient or inappropriate controls, variations in smoking habits of patients, variable dietary habits of patients recruited into different studies, the presence of environmental factors influencing disease progression, or differences in diagnostic or clinical practice. It has been suggested, possibly due to some type of threshold effect, that high GSTM1 activity (i.e., possession of two copies of *GSTM1*A* or *GSTM1*B*) is associated with a greater decrease in lung cancer risk among heavy than light cigarette smokers.[762] Zhong et al.[763] suggested that GSTM1 may protect against certain types of lung cancer, such as squamous and small cell carcinoma, but not against adenocarcinoma of the lung. The hypothesis that *GSTM1*A* and *GSTM1*B* alleles protect preferentially against squamous cell carcinoma is supported by a study from Finland[764] in which 44% of controls lacked the GSTM1 gene and, although 53% of all lung cancer patients were GSTM1 nulled, the frequency of the *GSTM1*0/0* genotype was as high as 62% in patients with squamous cell carcinoma. In a study of lung cancer patients in Japan, 45% of controls lacked the *GSTM1* gene. However, among patients with lung cancer, 54% of individuals with adenocarcinoma were *GSTM1*0/0,* whereas as many as 63% of squamous and small cell carcinoma patients were *GSTM1*0/0*. When these patients were analyzed in relation to the degree of smoking, the proportion of *GSTM1*0/0* individuals increased in patients with a high smoking index. Other factors that should be considered in the connection between lung cancer and the *GSTM1*0/0* genotype include the antioxidant micronutrient status. Examination of PAH-DNA adduct levels in circulating mononuclear cells of cigarette smokers shows that these are related to serum vitamin E and C levels only in GSTM1-nulled individuals.[765] Thus, although *GSTM1*0/0* individuals appear to be more sensitive to DNA damage from exposure to cigarette smoke, this can be influenced by dietary factors. In lung cancer patients the frequency of sister chromatid exchanges is associated with the *GSTM1*0* allele and is inversely related to vitamin A and selenium intake.[766]

hGSTM1-1 deficiency contributes to individual susceptibility to asbestos-induced pulmonary disease. In a study from North America it was found that among 80 carpenters who showed X-ray abnormalities associated with asbestos exposure, 65% of individuals were *GSTM1*0/0* compared to 52% in a control population of carpenters.[767] These data suggest that individuals nulled

for hGSTM1-1 are more likely to develop nonmalignant asbestos-related disease than those who are not hGSTM1-1 deficient.

A number of groups have found evidence that the *GSTM1*0/0* genotype is a risk factor for bladder cancer. Among cancer patients from England, Daly et al.[768] reported that 85% of 53 patients with bladder cancer were *GSTM1*0/0* compared with 53% in healthy controls and 60% in patient controls. In a study from North America, Bell et al.[769] reported that 61% of 213 white patients with bladder cancer were *GSTM1*0/0* compared with 48% of controls, whilst 50% of 16 black patients with bladder cancer were nulled compared with only 33% of controls; on the basis of these data it was suggested that the *GSTM1*0/0* genotype confers a 70% increased risk of bladder cancer. Examination of 296 bladder cancer patients from Germany has also revealed an increased frequency of *GSTM1*0/0* in affected individuals, although in this case 59.1% of patients were nulled compared with 50.7% of controls;[770] on the basis of these data, Brockmöller et al.[770] proposed that heritable GSTM1 deficiency is responsible for 17% of bladder cancer cases.

Absence of GSTM1 may predispose toward stomach and colon cancer. Using starch-gel electrophoresis, Strange et al.[771] showed a marked increase in the GSTM1 null phenotype from 50% in controls to 67% in a group of 47 patients from England with adenocarcinoma of stomach and colon, suggesting that nulled individuals have an approximately threefold greater risk of developing these malignancies. A similar increased frequency of *GSTM1*0/0* was found in a separate study of patients from Scotland with colon cancer in which 61.1% of 175 patients were nulled compared with 41.8% of controls.[772] Subdivision of these patients into two groups, according to the site of the tumor, revealed that 54.4% of those with distal tumors were *GSTM1*0/0*, whereas 70.8% of those with proximal tumors were *GSTM1*0/0*. This finding suggests that *GSTM1*A* and *GSTM1*B* alleles protect against proximal colon cancer, suggesting that *GSTM1*0/0* individuals have an approximate twofold increased risk of developing this disease.

Skin cancer is another malignancy where the GSTM1 null genotype may confer increased risk of disease. In an extensive study from England of 629 patients with basal cell carcinoma, squamous cell carcinoma, or malignant melanoma, Heagarty et al.[773] found that the frequency of GSTM1*0/0 in patients and controls was similar at 53%. However, in patients with two or more different types of skin tumors, the frequency of GSTM1*0/0 increased from 53% in controls to 71% in patients with multiple tumors. It has been proposed that the protective role of the GSTM1 locus in skin cancer involves antioxidant defenses against ROS generated by UV light, rather than protection against xenobiotics. Another interesting feature of the skin cancer patients with multiple basal cell carcinomas was the unexpected, but significant, decrease in the frequency of *GSTM1*A/B* heterozygotes, suggesting that the possession of both *GSTM1*A* and *GSTM1*B* alleles may have an enhanced protective effect.

2. Human Health Risk Associated with Deletion of the GSTT1 Gene

Besides the null polymorphism at the GSTM1 locus, an additional null polymorphism among class theta GST at theT1 locus occurs commonly. The frequency of *GSTT1*0* homozygosity varies in different populations, being 16% in English, 12% in Germans, 38% in Nigerians and 32% in West Indians.[756] The biological conse-

quences of the GSTT1*0/0 genotype in the human is difficult to predict as this enzyme has both detoxification and toxification activities toward various environmental pollutants. GSTT1-1 will detoxify monohalomethanes and ethylene oxide, but will toxify methylene chloride and other small bifunctional alkylating agents (Table 10). Furthermore, an important difference in the tissue-specific expression of class theta GST in rodents and humans complicates predictions, based on animal models, concerning the health risk associated with the null polymorphism at the GSTT1 locus. Specifically, unlike erythrocytes in rodents, human erythrocytes express hGSTT1-1, and this activity may allow the red cell to sequester reactive conjugates formed in *GSTT1*1* individuals; the red cell has been referred to as a detoxification sink in hGSTT1-positive samples. If this hypothesis is correct, then the erythrocyte hGSTT1-1 will remove bifunctional alkylating agents from the circulation, preventing them from being transported to tissues where, once activated, they can produce genotoxic damage. Support for this notion is provided by a study showing that in a population exposed to 1,3-butadiene, the *GSTT1*0* individuals demonstrated a 16-fold increased frequency of sister chromatid exchange in lymphocytes than *GSTT1*1* individuals.[774] Although this study suggests that the putative role of the erythrocyte as a detoxification sink can protect lymphocytes from 1,3-butadiene in hGSTT1-positive individuals, its ability to protect other cells is less certain. For example, it is unlikely that the sequestration activity of erythrocytes will protect the respiratory tract and lungs from small bifunctional alkylating agents as they are in direct contact with these noxious chemicals. Furthermore, if the capacity of the erythrocyte to remove bifunctional alkylating agents from the circulation is exceeded in *GSTT1*1* homozygotes, then the risk of carcinogenesis in such individuals is likely to be greater than in *GSTT1*0* homozygotes.

Few data have been reported linking the GSTT1 null genotype to cancer susceptibility. Warwick et al.[775] found that the frequency of *GSTT1*0* is unaltered in cervical intraepithelial neoplasia or squamous cell cancer of the cervix. In a study of Australian patients with colorectal cancer, the frequency of GSTT1*0 homozygotes did not differ from controls. However, the nulled individuals were more common in patients diagnosed before 70 years of age than in those diagnosed after 70 years of age,[776] suggesting that the GSTT1 genotype may influence the age of onset of colon cancer.

C. Null Polymorphisms and Failure of Cancer Chemotherapy

A single study by Hall et al.[777] suggests that the absence of GSTM1 is associated with increased success of cancer chemotherapy. These workers found that in a group of 71 children with acute lymphoblastic leukemia, the GSTM1 null phenotype correlated with event-free survival. These patients were all given induction therapy with vincristine, prednisolone, and asparaginase, while continuing therapy involved multiple drugs including 6-mercaptopurine and methotrexate. Among the 71 leukemia patients studied, 44 (62%) were GSTM1 null. However, among the 44 GSTM1 null patients, 36 (82%) remained in remission over 12 to 108 months. Analysis of event-free survival suggests that possession of *GSTM1*A* and *GSTM1*B* alleles represents a threefold risk of relapse. The biochemical basis for this risk of failure of cancer chemotherapy in patients with *GSTM1*A* and *GSTM1*B* alleles is unclear because none of the drugs used by Hall et al.[777] is metabolized by hGSTM1-1. It is, however, pos-

sible that gene-gene interactions occur that might contribute to the failure of chemotherapy and, in this context, it is interesting to note that GSTM1*0/0 individuals express lower amounts of GSTM3 protein in the lung.[778]

It will be important to discover whether success of chemotherapy is associated with other null polymorphisms, particularly *GSTT1*0/0*, or the *CYP1A1* and *CYP2D6* genes.[779]

XII. CONCLUSIONS

The GST comprise a complex supergene family of stress-responsive detoxification proteins. The ability of GST to provide protection appropriate to a diverse range of chemical insults lies in the fact that individual GST genes are each regulated in a distinct fashion and each encodes a protein with unique catalytic activity. In this article the biochemical properties of individual class alpha, mu, pi, sigma, theta, and microsomal GST are reviewed and data are presented showing that these enzymes can detoxify carcinogens, environmental pollutants, therapeutic drugs, and reactive compounds produced by ROS. Certain class theta GST can activate dihaloalkanes and small bifunctional alkylating agents through conjugation with GSH. Knowledge of the activities of individual isoenzymes allows a rational understanding of the biological consequences of GST overexpression and underexpression.

An extremely large number of chemicals, including phenolic antioxidants, Michael reaction acceptors, isothiocyanates, PAH, barbiturates, and glucocorticoids can serve as GST inducing agents. Evidence suggests that these inducers function through a number of *cis*-acting elements, including the ARE (EpRE), XRE, Barbie box, and GRE. The molecular mechanisms responsible for GST induction are largely unknown, and the identity of the transcription factors and signal transduction pathways involved remain uncertain. It is apparent that GST are an important part of an integrated adaptive response mechanism of the cell to chemical stress that involves several detoxification systems. The interdependence between GST regulation and the expression of other detoxification enzymes is also evidenced by the fact that, in certain instances, GST induction is effected by a metabolic cascade initiated by the actions of CYP isoenzymes.

High levels of expression of GST are associated with increased tolerance of cells to noxious chemicals and failure to express GST is associated with increased risk of disease. Increased expression of GST can be advantageous to mammals and many chemoprotectors, both natural and synthetic, are potent inducers of GST activity. By contrast, overexpression of GST in tumors may be disadvantageous to the host as it can be associated with resistance to the anti-cancer drugs BCNU, chlorambucil, mechlorethamine, melphalan, cyclophosphamide, and thiotepa. In humans, absence of a particular class mu transferase, hGSTM1-1, through null polymorphisms in the population, has been associated with predisposition to disease, particularly bladder, colon, and skin cancer. A class theta transferase, hGSTT1-1, is also subject to population polymorphisms but its contribution to disease susceptibility requires further study.

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