The Glutathione Transferase Structural Family Includes a Nuclear Chloride Channel and a Ryanodine Receptor Calcium Release Channel Modulator*

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The ubiquitous glutathione transferases (GSTs) catalyze glutathione conjugation to many compounds and have other diverse functions that continue to be discovered. We noticed sequence similarities between Omega class GSTs and a nuclear chloride channel, NCC27 (CLIC1), and show here that NCC27 belongs to the GST structural family. The structural homology prompted us to investigate whether the human Omega class glutathione transferase GSTO1–1 forms or modulates ion channels. We find that GSTO1–1 modulates ryanodine receptors (RyR), which are calcium channels in the endoplasmic reticulum of various cells. Cardiac RyR2 activity was inhibited by GSTO1–1, whereas skeletal muscle RyR1 activity was potentiated. An enzymatically active conformation of GSTO1–1 was required for inhibition of RyR2, and mutation of the active site cysteine (Cys-32 → Ala) abolished the inhibitory activity. We propose a novel role for GSTO1–1 in protecting cells containing RyR2 from apoptosis induced by Ca2+ mobilization from intracellular stores.

Glutathione transferases (GSTs) are a family of ubiquitous intracellular enzymes that catalyze the conjugation of glutathione to many exogenous and endogenous compounds (1). GSTs are known to have other functions including the binding of bilirubin and carcinogens (2), the isomerization of maleylacetate (3), and the regulation of stress kinases (4), with presumably further roles yet to be discovered. New members of the GST structural family with novel catalytic activities and functions have recently been discovered (5–7). For example, the Omega class glutathione transferase GSTO1–1 has a typical glutathione transferase fold but little enzymatic activity with many conventional substrates (8). GSTO1–1 has a novel active site cysteine that participates in weak thiol transferase reactions. Although the intracellular function of the Omega class GSTs is unknown, a member of the Omega class is over-expressed in a radiation-sensitive tumor (9). We used BLAST searches (10) to identify additional members of the glutathione transferase structural family and were impressed by sequence similarities between GSTO1–1 and the chloride intracellular channel (CLIC) family of proteins, which are thought to form chloride channels in intracellular membranes or to be chloride channel modulators (11, 12). We therefore compared the structure of the CLIC proteins and GSTO1–1 in more detail and found that NCC27 (CLIC1) belongs to the GST structural family. Because of the structural similarity, we also examined the ability of GSTO1–1 to form or modulate ion channels. We find that GSTO1–1 modulates ryanodine receptors (RyRs), which are the calcium release channels in skeletal and cardiac sarcoplasmic reticulum (SR). There is evidence that GSTO1–1 is present in skeletal and cardiac muscle (7) and is thus colocalized with RyRs. RyRs are also located in intracellular membranes of a variety of cells (13) and are expressed in T- and B-lymphocytes (14, 15). GSTO1–1 inhibited cardiac RyR2 channel activity. Modulation of ion channels is a previously undescribed function for a GST. We propose that GSTO1–1 plays a novel role in regulating intracellular [Ca2+]i, potentially protecting cells containing RyR2 from radiation damage (9) and apoptosis induced by Ca2+ mobilization from intracellular stores (16, 17).

EXPERIMENTAL PROCEDURES

Sequence Alignment—Sequences for NCC27 (11), also known as CLIC1 and GSTO1–1 (7), were aligned with CLUSTALW (18) with default settings. Minor manual alterations were introduced into the alignment, taking into consideration both the model and an alignment of other GST family members. Modelling—Modelling was performed with the HOMOLOGY module of the Insight II package (MSI, San Diego, CA) based on the alignment in Fig. 1. Despite the low level of sequence identity (15%), visual inspection of the model confirmed that the NCC27 sequence is compatible with the canonical GST fold. Further validation of the model was derived from applying a THREADING procedure (19) to the NCC27 sequence that scored the highest match against GSTO1–1 when compared with the nonredundant structure data base with a Z score of 2.78. Experimental procedures were described previously (9).

GSTO1–1 Preparation—Recombinant GSTO1–1 was expressed in Escherichia coli after cloning the cDNA into the expression vector pQE 30 (Qiagen, Clifton Hill, Victoria, Australia). The expressed protein has a poly-His tag and was purified by Ni-agarose chromatography (20). The purified protein was dialyzed into 20 mM Tris-HCl, 60 mM NaCl, 5 mM dithiothreitol, pH 8.0. The C32A mutant was created by site-directed mutagenesis and confirmed by DNA sequence analysis. The mutant protein was purified and stored by the same procedures as the wild type enzyme. To block protein thiols, GSTO1–1 was diluted to 2 mg/ml in 20 mM Tris-HCl, 60 mM NaCl, pH 8.0 containing 20 mM N-ethylmaleimide. The protein was incubated at 20 °C for 1 h and then dialyzed extensively against 20 mM Tris-HCl, 60 mM NaCl, pH 8.0 at 4 °C.

Antiserum—Antiserum to human GSTO1–1 was prepared by immu-

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Further details of the alignment are available from Dr. Philip Board at the John Curtin School of Medical Research.
Fig. 1. Alignment between the CLIC protein, NCC27, and GSTO1–1.
Conserved positions between the sequences are indicated by a vertical stroke; conservative replacements (R-K, D-E, P-Y, S-T) are indicated by two vertical dots. Most of these positions are also conserved within the respective CLIC and Omega GST subfamilies. The four amino acid positions that are highly conserved among GSTs are indicated by asterisks. All four of these residues are conserved in the CLIC proteins. Sites showing a pattern of hydrophobicity extending throughout other GST classes are marked with a number sign. Putative secondary structure segments are indicated above the alignment (h, helix; e, strand).

|   | NCC27 | GSTO1-1 | GSTO1-2 | GSTO1-3 |
|---|-------|---------|---------|---------|
| 1 | MAEBRQPQVFLPKGSGDGAKNCNPFCFSGQFLPMVLHGV7FNVTTV | | | |
| 5 | SARSILGKSAPPGVPFSR13YRSMFPCFARRTRLVLKKRAIGNEVINI | | | |
| 47 | DTERTRTQVKGCLP35FLPLLVS-TVEITDNIKEFLAVLCPCFYPK | | | |
| 55 | NLVNPWFMXNPXNVLVPVMLOQLITQLZAIQTYELAEYPQKELL | | | |
| 96 | TALLMPWNATGDLIFPAKFLAFYIMNPSFDNOLSDKILKALVKLVNLYT | | | |
| 105 | DDPYCAQCMELTFLKPVFSQFISQKNED---YAGMLKKEFKEF | | | |
| 146 | SPLLQEVDTASDREVSQSRKPLDGMNLTCDDCNLPKHLKVQVWCYYY | | | |
| 150 | TNL-EVVLWKT----TFFQIQINSIDYLVWFPERLEAMKLHC | | | |
| 196 | GFTIFAPFQGVHRLNSNAYAREFASTPCDDBEIIILAYQKVLKLK | | | |
| 193 | VENT-FKELWMAANKEBDPTVSALMSTEQWQPLEYLYGNGFACVYGL | | | |

**RESULTS**

**Sequence Alignment and Structural Modelling**—Alignment of the human GSTO1–1 sequence and the human chloride channel protein NCC27 (Fig. 1) reveals several similarities, both in length and in the number of conserved and conservatively replaced residues. The similarity is particularly striking in the N-terminal glutathione-binding region, with conservation of a CPF motif that includes the active site cysteine residue of GSTO1–1. There are four amino acid positions that are common to virtually all known glutathione transferases (7). These positions include a cis Pro within the GSH binding site and an Asp, which acts as an N-terminal cap near the start of helix 6. Two Gly residues also appear to be important for structural reasons (8). Conspicuously, all four of these residues are conserved in the CLIC proteins. Additional sites, such as Leu-34, Asp-76, Phe-83, Leu-84, Phe-167, and Leu-168 (Fig. 1, number signs) show a pattern of hydrophobicity that extends throughout other GST classes. Based on the alignment, a tentative three-dimensional structure was predicted by homology modelling (Fig. 2). The model is plausible because there are no uncomplexed buried charges, and most hydrophobic residues are shielded from solvent. The side of helix 3 that forms an interface with helix 4 is quite polar, suggesting that there may be a relative shift between the N- and C-terminal domains with respect to other GST structures (Fig. 2). Both helix 4 and helix 5 are likely to be kinked, with regions of irregular hydrogen bonding. Therefore some differences between the CLIC protein and Omega structures are predicted (7). Modelling GSH into the putative active site reveals that a covalent bond could be formed between the GSH Cys and Cys-24 of the CLIC protein, analogous to that observed in the Omega class GST structure (7). Furthermore, Leu-49, Arg-51, and Arg-29 are able to complex the positive charge on the γ-glutamyl group of GSH, Thus, whereas considerable caution must be exercised when interpreting alignments with limited sequence identity, the sequence of the CLIC pro-

**Single Channel Recording and Analysis**—Single channel recording and analysis have been described (21, 22). Mean current (I), the average of all data points in a record was used as a measure of channel activity, because many bilayers contained more than one active channel. Data are presented in Figs. 3 and 4 as relative mean current (I/Ic, where I is the mean current under test conditions and Ic is the control mean current). Bilayer potential was changed between −40 and +40 mV every 30 s. I/Ic and Ic were measured from 120-s recordings (2 × 30 s at −40 mV and 2 × 30 s at +40 mV) obtained under each condition, i.e. control conditions, for each [GST] (or [buffer], after antibody addition, or after washout. Data is presented as the mean ± S.E., and the numbers of bilayers are given. The number of experiments included in the average data exceeded the number of bilayers because (a) measurements at −40 and +40 mV were included in the average, and (b) the experiment was often repeated on one bilayer.

**Statistics**—The significance of the difference between control and test values was tested (a) using a Student’s t test, either 1- or 2-sided and either for independent or paired data, as appropriate, or (b) using the nonparametric “sign” test (23). Differences were considered to be significant when p < 0.05.
tein is generally consistent with the canonical GST structure, particularly in the N-terminal domain. Additional support for the model comes from the application of an automated THREADING procedure to the NCC27 sequence (19). NCC27 scored the best match with the Omega GST structure, with a Z score of −2.78 when compared with other folds in the nonredundant structure data base.

Ion Channel Modulation by GSTO1–1—The predicted similarities in the structure of the Omega class GSTs and the CLIC proteins led us to examine the possibility that GSTO1–1 may behave like CLICs and act as an ion channel and/or ion channel modulator. Although GSTO1–1 alone did not form ion channels in lipid bilayers under the conditions we used, we found that it modulated RyR channels. GSTO1–1 (21 μg/ml), added to the cis (cytoplasmic) solution, reduced cardiac RyR2 activity by about 50% in 28 of 29 bilayers (Fig. 3, b and c, and Fig. 4, b and c). A 10-fold higher GST concentration (210 μg/ml) caused similar depression of cardiac RyR activity in seven bilayers (Fig. 4b). The Kₘ for inhibition of RyR2 activity in four bilayers that were exposed to a series of GSTO1–1 concentrations was 1 μg/ml (Fig. 4f). The apparent increase in activity as [GSTO1–1] increased from 21 to 210 μg/ml in Fig. 4f was not significant and may have arisen from inclusion of data from different bilayers for the different concentrations. The increase is not seen in the limited data set of Fig. 4f, containing bilayers exposed to each of the three GSTO1–1 concentrations. Control experiments showed that buffer lacking GSTO1–1 did not affect RyR activity (Figs. 3c and 4a). Depression of RyR activity by the GST was independent of cytoplasmic (cis) Ca²⁺ [Ca²⁺] between 10⁻⁵ and 10⁻⁶ M (Fig. 3, b and c, and Fig. 4, b and c) and independent of bilayer potential (therefore average values in Fig. 4 include measurements at −40 and +40 mV).

Covalent modification (oxidation) of the RyR complex by GSTO1–1 was not responsible for the inhibition, because channel activity recovered and was even potentiated above control levels (n = 10) when GSTO1–1 was washed out (Fig. 3b). Normal channel activity could also be restored by addition of polyclonal anti-GSTO1–1 antiserum (n = 7), with potentiation of activity above control levels in each case (Fig. 3c and 4, b and c). These changes in channel activity were a specific effect of the antibody on GSTO1–1 because (a) recovery was not seen when 100 μl of pre-immune serum lacking antibody was added to channels whose activity was depressed by GSTO1–1 (n = 4), and (b) 100 μl of antiserum alone did not affect RyR2 channel activity in the absence of GSTO1–1 (Fig. 4a).

Two other kinds of experiment indicate that inhibition of RyR2 activity by GSTO1–1 is related to its thiol transferase activity. First, when GSTO1–1 was treated with N-ethylmaleimide (GSTO1–1-M), it lost both its enzyme activity and its ability to inhibit RyR2 activity (n = 8) (Figs. 3d and 4d). Indeed channel activity was increased by GSTO1–1-M (Fig. 4d, n = 7). Control-incubated enzyme (GSTO1–1-C; see “Experimental Procedures”) was then applied, and channel activity fell to control levels (Fig. 4d). The depression may have been less than expected because inactive GSTO1–1-M was occupying some of the inhibition sites and preventing GSTO1–1-C binding. In the second type of experiment, GSTO1–1 with a Cys-32 → Ala mutation that removed enzyme activity lost its ability to inhibit RyR2 activity (n = 8) (Figs. 3d and 4d). Indeed, RyR2 channel activity was increased by the mutated GSTO1–1 (n = 4). An increase in RyR2 activity to levels that were greater than before exposure to GSTO1–1 after washout of the enzyme was also seen after addition of antibody and after addition of N-ethylmaleimide-treated enzyme, suggesting that an activating action of GSTO1–1 was unmasked when the inhibitory effect was removed or was not present. Only an excitatory effect of GSTO1–1 was seen in skeletal muscle RyR1 channels, and this was not reversed within 5 min of removing GSTO1–1 (Figs. 3e and 4e).
FIG. 3. GSTO1–1 modulates RyR channels. Current records at −40 mV are shown, as are all-points histograms of the probability (p) of current levels, (pA). GSTO1–1 was added to the cis (cytoplasmic) solution. a, a control experiment showing that RyR2 activity was unaffected by buffer lacking GSTO1–1. In b, RyR2 activity was depressed by GSTO1–1 with 10−6 M cis Ca2+ and then recovered after washout. In c, RyR2 activity was depressed by GSTO1–1 with 10−3 M cis Ca2+ and recovered with anti-GSTO1–1 (a-G). In d, RyR2 activity increased with N-ethylmaleimide-treated GSTO1–1 (G-M) and then declined after adding control-treated GSTO1–1 (G-C). CT, control-treated. In contrast to the decrease in activity of cardiac RyRs exposed to enzymatically active GSTO1–1, e shows an increase in skeletal RyR1 activity with GSTO1–1. Continuous lines, zero current; broken lines, maximum open conductance.

**DISCUSSION**

Early studies of the glutathione transferase family relied on functional similarities to identify different family members. In previous studies we have identified additional members of the GST structural family by sequence alignment-based searches of the expressed sequence tag and GenBank data bases (5, 7). The recently described Zeta and Omega class GSTs were identified by this approach, and although they are clearly members of the GST structural family, they are functionally distinct from previously described GST classes. In the present study we utilized the Omega class GST sequence to search for additional members of the GST structural family, and the search revealed significant sequence similarity with members of the CLIC group of intracellular channel proteins. Detailed examination of an alignment of the GSTO1 and NCC27 (CLIC1) sequences revealed the conservation of several key residues that are conserved throughout the GST structural family. Subsequent homology modelling strongly supported the prediction that NCC27 adopts the canonical GST fold and can be classified as a member of the GST structural family. The formation and modulation of ion channels are novel functions never previously associated with members of the GST family and clearly extend the potential roles of this superfamily.

The observation that CLIC proteins probably adopt a GST fold and share a similar N-terminal extension and ‘active site’ motif with GSTO1 suggested that we should investigate the capacity of an Omega class GST to form or modulate ion channels. GSTO1–1 did not form channels under the conditions we used. However, because GSTO1–1 is strongly expressed in both skeletal and cardiac muscle (7), we examined its capacity to modulate RyRs. Our results clearly indicated that GSTO1–1 is able to either inhibit or potentiate RyR calcium channels. The inhibition we observed (a) does not depend on an oxidation reaction, (b) requires an active enzyme conformation, and (c) is seen only in RyR2. Activation of RyRs is independent of enzyme activity and is seen in both RyR1 and RyR2. The results suggest that RyR2 has two binding sites for GSTO1–1 and that enzyme binding to one site activates the channel, whereas enzyme binding to the second site inhibits the channel. The RyR has a very large cytoplasmic domain with multiple ligand binding sites, and there are several examples of ligands with dual effects on the channel because ligands can bind to more than one site. Examples are Ca2+ (21), ATP (24), and peptides that correspond to parts of the II-III loop of the dihydropyridine receptor (25).

Ion channel modulation is a novel and unrecognized role for a GST; this is the first report of modulation of RyRs by a GST. RyR channels are regulated by many factors including oxidation and reduction reactions (26). GSTO1–1 provides an additional mechanism by which redox state might be conveyed to RyRs. The present study was designed to examine the influence of GSTO1–1 on RyR2 activity. The RyR is also activated by ATP and dihydropyridine receptor agonists (25). Therefore, the absence of modulation of RyR2 activity by other ligands in the presence of GSTO1–1 suggests that the inhibitory effects of GSTO1–1 on RyR2 activity are specific for the GSTO1–1 interaction with the RyR. Early studies suggested that RyR activity is regulated by Ca2+ and by ATP (24). The results presented here suggest that GSTO1–1 provides an additional mechanism by which redox state might be conveyed to RyRs.
to the channels. Cytoplasmic [Ca\textsuperscript{2+}] increases during oxidative stress, partly through oxidative activation of RyRs (26). An increase in [GSTO1–1] during oxidative stress could protect RyR2 from oxidation-induced activation in all cells expressing this RyR isoform. Because CLIC proteins also form or modulate ion channels (11, 12) and have a structure similar to that of GSTs, it may be that ion channel modulation is a common property of this superfamily. It may be significant that Jun N-terminal kinase signaling is regulated by GST Pi binding (4, 27) and that the mitogen-activated protein kinase ERK7 binds to CLIC 3 (12), an intracellular chloride channel protein shown here to be a putative member of the GST structural family by its strong sequence similarity to NCC27/CLIC 1. Because cardiac RyR2s form macromolecular complexes that include protein kinase A (28), the possibility that the modulating effects of GSTO1–1 may be mediated by interactions with the RyR2-associated protein kinase deserves further investigation. GST O1 may be associated with the RyR2–

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