Electrophilic Prostaglandins and Lipid Aldehydes Repress
Redox-sensitive Transcription Factors p53 and Hypoxia-inducible
Factor by Impairing the Selenoprotein Thioredoxin Reductase*

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Tumor suppressor p53 exhibits an enigmatic phenotype in cells exposed to electrophilic, cyclopentenone prostaglandins of the A and J series. Namely, cells harboring a wild-type p53 gene accumulate p53 protein that is conformationally and functionally impaired. This occurs via an unknown molecular mechanism. We report that electrophilic cyclopentenone prostaglandins covalently modify and inhibit thioredoxin reductase, a selenoprotein that governs p53 and other redox-sensitive transcription factors. This mechanism accounts fully for the unusual p53 phenotype in cells exposed to electrophilic prostaglandins. Based on this mechanism we derived, tested, and affirmed several predictions regarding the kinetics of p53 inactivation; the protective effects of selenium; the structure-activity relationships for inhibition of thioredoxin reductase and impairment of p53 by electrophilic lipids; the susceptibility of hypoxia-inducible factor to inactivation by electrophilic prostaglandins; and the equivalence of chemical inactivation of p53 to deletion of a p53 allele. Chemical precepts dictate that other electrophilic agents should also inhibit thioredoxin reductase and impair its governance of redox-sensitive proteins. Our results provide a novel framework to understand how endogenous and exogenous electrophiles might participate in carcinogenesis; how selenoproteins and selenium might confer protection against cancer; how certain tumors might acquire their paradoxical p53 phenotype; and how chronic inflammation might heighten the risk for cancer.

Cyclopentenone prostaglandins (PG),1 of the A and J series impair the conformation and function of tumor suppressor p53 by a novel, but unknown, mechanism of action (1, 2). Cyclopentenone PG penetrate cells and accumulate in the cytosol and nucleus (3) where they can react covalently with other molecules via their electrophilic β-carbon (4). Few of the proximal molecular targets of these PG are established (5–7). There are two formal hypotheses to explain how electrophilic PG might inactivate p53. First, they might act directly, via covalent reaction with p53 itself. Second, they might act indirectly, via covalent reaction with regulatory proteins that govern p53 conformation and function. A direct mechanism of action is incompatible with our observation that PGA1 and PGA2 antagonize only the apoptosis mediated by p53 (1), but not the cell-cycle arrest. These PG should antagonize all functions mediated by p53 if their molecular mechanism of action involved its modification directly. Accordingly, we sought candidate proteins consistent with an indirect molecular mechanism of action. Thioredoxin reductase (TrxR) is notable from biological and chemical perspectives. Biologically, TrxR-Trx cycling modulates sulfhydryl-disulfide isomerization reactions that govern the conformation and function of p53, as well as several other redox sensitive transcription factors, like NFκB and hypoxia-inducible factor (HIF) (8–10). Trr1, the yeast ortholog of TrxR, is essential for transcription by p53 expressed ectopically in yeast (11, 12). Chemically, TrxR is a selenoprotein. Selenocysteine residues are typically more nucleophilic than cysteine under comparable conditions. Chemical precepts dictate that electrophilic agents, like cyclopentenone PG, should react readily with selenoproteins under conditions encountered in cells.

Here we report that: (i) a prototypical PGA analog forms a covalent adduct with TrxR; (ii) analogous to the cyclopentenone PG, several representative, naturally occurring or synthetic aldehydes and ketones with electrophilic β-carbons (15-keto-PG, 4-hydroxy-2-nonenal, and ethacrynic acid) impair p53 conformation and function, indirectly, via inhibition of TrxR; (iii) other redox-sensitive transcription factors governed by TrxR-Trx cycling, e.g. HIF, are also susceptible to inactivation by lipid aldehydes and ketones with electrophilic β-carbons; (iv) supplementation of cell culture medium with inorganic Se spares p53 from inactivation by lipid electrophiles; (v) impairment of p53 by lipid electrophiles is comparable in severity to loss of one allele of the p53 gene. Our results provide a novel framework to understand how these agents and numerous chemically related, endogenous and exogenous electrophiles might participate in carcinogenesis; how selenoproteins and dietary selenium may confer protection against cancer (13); how cells might acquire an unusual and unexplained p53 phenotype observed in some tumors (14–17); and how chronic inflammation might heighten the risk for cancer (18).

EXPERIMENTAL PROCEDURES

Materials—We used Dulbecco’s modified Eagle’s medium and McCoy’s 5A medium and supplements (Invitrogen); prostaglandins (Cayman Chemicals); Auranofin (ICN Biomedicals); cobalt chloride and...
etoposide (Sigma); malondialdehyde (Fluka); 4-hydroxy-2-nonenal (Oxis International, Inc.); protease inhibitor mixture and FuGene-6 transfection reagent (Roche Molecular Biochemicals); enhanced chemiluminescence reagents (Amersham Biosciences); luciferase reporter lysis buffer and reporter detection reagents (Promega); monoclonal antibodies directed against p53 (Pab240, Santa Cruz; Pab1620 (Ab5), Oncogene Sciences); polyclonal antibodies against TrxR (Upstate Biotechnology), and p53 (FL-395-G, Santa Cruz); horseradish peroxidase-conjugated secondary antibodies; protein A/G PLUS-agarose (Santa Cruz Biotechnology); neutralin-conjugated beads (Pierce); Ac-DEVD-conjugated secondary antibodies; protein A/G PLUS-agarose (Santa Cruz Biotechnology); neutralin-conjugated beads (Pierce); Asp-DEVD-conjugated secondary antibodies; protein A/G PLUS-agarose (Santa Cruz Biotechnology); neutralin-conjugated beads (Pierce); Ac-DEVD-conjugated secondary antibodies; protein A/G PLUS-agarose (Santa Cruz Biotechnology); neutralin-conjugated beads (Pierce).

Cell Culture—We maintained HCT 116 p53+/−, p53−/− and p53−/− (ref. 20, gift of B. Vogelstein) cells in McCoy’s 5A medium and RKO cells (gift of M. Meuth, Institute for Cancer Studies, University of Sheffield, Sheffield, UK) in Dulbecco’s modified Eagle’s medium at 37 °C in a humidified incubator with 5% CO2. We supplemented media with 2 mM t-glutamine, 1 mM sodium pyruvate, 50 units/ml penicillin and streptomycin, and 10% (v/v) fetal bovine serum. In certain experiments, cells were metabolically labeled with 100 μCi of 35Se, obtained from the University of Missouri Research Reactor, for 48 h to ensure that selenoproteins were labeled to steady state.

Isolation of Proteins Labeled by PGA1-ABP—For Neutravidin sequencing, we treated RKO and HCT 116 cells with 60 μg PGA1-ABP for 4 h, or as described in the text. We lysed cells in 250 mM sucrose/50 mM Tris, pH 7.4/25 mM KC1/5 mM MgCl2/1 mM EDTA/1× Complete™ protease inhibitor/2 mM NaF2/2 mM sodium orthovanadate. We sonicated the lysate twice for 5 s at 4 °C. After centrifugation at 13,000 × g, we incubated samples containing 200 μg of total cell lysate for 16 h at 4 °C with 100 μl of neutralin beads in 1 ml of PBS with 0.4% Tween 20. We centrifuged the samples at 500 × g for 5 min to isolate the neutralin-biotin complexes. We washed the beads 5 times with 1 ml of PBS/0.4% Tween 20. We fractionated samples by SDS-PAGE and detected the biotinylated proteins with streptavidin-horseradish peroxidase. We also reprobed the membranes with antibodies directed against Trx, TrxA, p53, p50/p105 of NFκB, and IKKα to determine whether they adhered to the neutralin beads.

Immunoprecipitation of p53—We lysed cells and incubated 200 μg of total cell lysate for 16 h at 4 °C with 1 μg of either Pab240 or Pab1620, antibodies that specifically recognize p53 in its mutant or wild-type conformation, respectively (21). We added 20 μl of protein A/G PLUS-agarose in 1 ml of PBS with 0.4% Tween 20. We centrifuged the samples at 500 × g for 5 min to isolate the antigen-antibody immune complexes. We washed the immunoprecipitate twice with 1 ml of PBS/0.4% Tween 20. We fractionated samples by SDS-PAGE and measured the amount of conformationally mutant or wild-type p53 in the immunoprecipitated hybridization with a separate anti-p53 polyclonal antibody (FL-395).

p53 and HIF-1 Transcriptional Activity—We transfected 105 RKO cells per well with 1 μg of p53-Luc or p2.1 and 50 ng of pCMV β-galactosidase activity in the supernatant for 15 min at 4 °C and then lysed cells at 4 °C in 1 ml of reporter lysis buffer. We aspirated media, washed cells with PBS (pH 7.4) at 4 °C, and then lysed cells at 4 °C in 100 μl of PBS for 5 min to prepare the lysates for the progress curves.

RESULTS

To determine whether electrophilic PGs react with TrxR or other proteins we used PGA1 amidopentyl biotin (PGA1-ABP). PGA1-ABP retains the α, β-unsaturated ketone substituent and the electrophilic β-carbon of PGA1. Its C1 biotin amide, instead of a C1 carboxyl group, facilitates the detection of any covalent adducts it might form with proteins (Ref. 6) (Fig. 1).

To calibrate the utility of PGA1-ABP, we examined its interaction with IKKα, a protein putatively modified by cyclopentenone PG (7). We incubated intact RKO and HCT 116 colon cancer cells with PGA1-ABP (60 μM) for 4 h; sequestered any proteins with biotin epitopes on Neutravidin beads; fractionated these same biotinylated proteins by SDS-PAGE; and identified them immunochemically. Cells contained ~15 proteins labeled de novo with PGA1-ABP under these conditions; two of these proteins were IKKα (Fig. 2) and the p50/p105 subunit of NFκB (data not shown). Our data are the first direct evidence that cyclopentenone PG do covalently modify cellular IKK, as hypothesized (7), and they suggest that PGA1-ABP is useful for isolating and identifying proteins that react with cyclopentenone PG.

Accordingly, we determined if PGA1-ABP reacted with TrxR, the strongest candidate molecule for an indirect mechanism of action that leads to impairment of p53. RKO cells and two HCT 116 cell lines contained a protein modified covalently by PGA1-ABP and identified as TrxR immunochemically with anti-TrxR antibody (Fig. 2A, lanes 3). The fact that HCT 116 p53+/− and HCT 116 p53−/− cells each contained this ~56-kDa protein excludes the possibility that it is a p53-PGA1-ABP adduct that migrates more slowly than p53 during fractionation by SDS-PAGE (Fig. 2A, lanes 3). Incubation of cells with PGA1 alone, or amidopentyl biotin alone, did not generate proteins with biotin epitopes inserted de novo (Fig. 2A, lanes 2 and 4). Thus, the biotin epitope on the 56-kDa TrxR protein and other cellular proteins originates from their covalent reaction with PGA1-ABP, not its hydrolysis products in cells. We exploited the fact that TrxR is a selenoprotein to strengthen our conclusion that it forms an adduct with PGA1-ABP. We metabolically labeled RKO and HCT 116 cells with 75Se to incorporate it into their selenoproteins; repeated the previous experiment; and found a ~75Se-labeled, 56-kDa protein recognized by anti-TrxR antibody among the proteins sequestered on neutralin beads (Fig. 2B).

RKO cells and HCT 116 p53−/− cells that are haplosufficient in p53 contained barely detectible amounts of p53 covalently modified by PGA1-ABP when we conducted experiments analogous to those described above. In corresponding experiments in which we immunoprecipitated p53 with anti-p53 antibodies; fractionated the precipitate by SDS-PAGE; and probed with neutralin-horseradish peroxidase, we found no detectable biotinylated p53 adduct (data not shown). Thus, PGA1-ABP does not react to an appreciable extent with p53, itself, in intact cells. As expected, the HCT 116 p53−/− cells that lack p53 did not contain any modified protein corresponding to p53.
In addition to TrxR, we examined Trx, the substrate of TrxR. RKO cells contained a 12-kDa species labeled by PGA1-ABP and identified as Trx with anti-Trx antibody (data not shown). The 12-kDa species also immunoprecipitated with anti-Trx antibodies and reacted positively with streptavidin-horseradish peroxidase, consistent with its annotation as a Trx:PGA1-ABP adduct.

Several representative electrophilic lipids also inhibited p53 transactivation, p53 transactivation, p53 transactivation with a similar rank order of potency (Fig. 3). 4-Hydroxy-2-nonalen (4-HNE), a decomposition product of linoleic or arachidonic acid hydroperoxides was the most potent inhibitor followed by J- and A-series cyclopentenone PG; ethacrynic acid, and 15-keto PGF2α. Under our experimental conditions malondialdehyde and PGB1 were inactive, as expected, because exogenously added malondialdehyde does not penetrate cell membranes readily and PGB1 has an inert β-carbon.

We investigated the kinetic features of p53 inactivation by PGA1 to assess their compatibility with inhibition of TrxR. We exposed RKO cells to 50 μM etoposide for 6 h to initiate genomic damage and time-dependent accumulation of wild-type p53. We added PGA1 simultaneously with etoposide at t = 0 h or at 1, 2 and 4 h after the addition of etoposide. PGA1 impaired p53 transcription maximally when present throughout the entire 6-h duration of the experiment. When added at intervals after etoposide, PGA1 impaired p53 transcription proportionately to exposure time (Fig. 4A). For example, when present only for the final two h, t = 4–6 h, PGA1 did not impair p53 transactivation or conformation significantly (95% versus 100%).

TrxR is a selenoprotein whose cellular steady-state level depends on selenium availability (23, 24). Most tissue culture media is partially deficient in selenium (−0.1 μM). Tumor suppressor p53 was less vulnerable to impairment by PGA1 when cells were grown in media supplemented with 1 μM inorganic Se. Half-maximal impairment of p53 required exposure to −3-fold more PGA1 (IC50 = 60 μM PGA1) in cells grown with supplemental selenium versus cells with no supplementation (IC50 = 20 μM PGA1) (Fig. 4B).

Auranofin is chemically unrelated to cyclopentenone PG or other electrophilic lipids, but it is an inhibitor of TrxR activity (23, 25). Auranofin impaired the conformation of p53 and transcription by p53 and HIF (Fig. 4C), analogous to the electrophilic lipids depicted in Fig. 3.

Bunz and colleagues recently established that p53 haplosufficiency is proportional to p53-mediated apoptosis in vitro using a panel of isogenic HCT 116 cells in which p53 alleles were disrupted experimentally (20). We used these same cell lines to compare the functional consequences of p53 inactivation by electrophilic agents versus the functional consequences of genetic deletion of p53 alleles. Consistent with previous results (20) amethopterin induced apoptosis proportional to p53 haplosufficiency (caspase-3 activity in HCT 116 p53−/− > HCT 116 p53+/− > HCT 116 p53−/− > HCT 116 p53−/−) (Fig. 5, bars to right). When we incubated the HCT 116 p53−/− cells with amethopterin plus PGA2, the PGA2 antagonized apoptosis in a concentration-dependent manner (Fig. 5, bars to left). Apoptosis in HCT 116 p53+/− cells treated with 6–20 μM PGA1 plus amethopterin corresponded approximately to apoptosis in the HCT 116 p53−/− cells treated with amethopterin alone. In other words, chemical impairment of p53 approximates the loss of at least one allele of p53.

DISCUSSION

We recently discovered that electrophilic cyclopentenone PG impair the p53 tumor suppressor by a novel mechanism that is distinct from mutation of the p53 gene or functional inactivation of p53 by oncoproteins like mdm-2. Since our initial report (1), we have sought the precise molecular mechanism responsible for this effect. Here we report that cyclopentenone PG act by covalently modifying and inhibiting TrxR. This indirect mechanism can account for the p53 phenotype in cells exposed to cyclopentenone PG, as well as other representative electrophilic lipids.

To develop our mechanism-of-action hypothesis, we integrated three independent observations: (i) PGA1 and PGA2 impair the conformation, transactivation, and function of p53 (1); (ii) PGA1-ABP reacts covalently with TrxR and Trx (Fig. 2); and (iii) TrxR-Trx coupling maintains p53 and several other redox-sensitive proteins and transcription factors in an active state (8–10). Collectively, these data suggest a model with several testable predictions. First, our model predicts that many other chemical agents with an α,β-unsaturated carbonyl and accessible, electrophilic β-carbons should impair p53 conformation and function. Second, these chemical agents should impair p53 transcription and p53 conformation and inhibit TrxR activity with the same rank order of potency, if they act...
indirectly via TrxR. Third, these agents should impair transactivation by other redox-sensitive transcription factors, e.g., hypoxia-inducible factor (10, 26) with the same rank order of potency with which they impair TrxR and p53. Our results affirm each of these predictions. Our model also predicts that PGA₁ will impair p53 only as it accumulates during the initial, early stage of the cellular response to DNA damage, but not later, after it has assumed a transcriptionally active, wild-type conformation. By inhibiting the disulfide reductase activity of TrxR-Trx, PGA₁ should prevent assembly of p53 into a mature conformation, but it should not convert p53 from an active to an inactive conformation. Kinetic experiments affirmed this prediction. Last, the molecular mechanism of action we propose can resolve a paradox. Namely, A-series PG antagonize p53-mediated apoptosis but not cell-cycle arrest. These effects are fully compatible with inhibition of TrxR. Inhibition of TrxR-Trx cycling deranges the assembly of p53 into a transcriptionally competent form; this manifests as antagonism of p53-mediated transcription. Lastly, the molecular mechanism of action we propose resolves a paradox. Namely, A-series PG antagonize p53-mediated apoptosis but not cell-cycle arrest. These effects are fully compatible with inhibition of TrxR. Inhibition of TrxR-Trx cycling deranges the assembly of p53 into a transcriptionally competent form; this manifests as antagonism of p53-mediated transcription.

FIG. 3. Spectrum of electrophilic lipids that inactivate p53, HIF-1, and TrxR. A, electrophilic lipids attenuate p53 activity as measured by luciferase reporter constructs in RKO cells in a dose-dependent manner. Electrophiles used include 4-HNE (filled square), Δ12-PGJ₂ (filled triangle), 15-dideoxy-Δ12, Δ14-PGA₁ (inverted filled triangle), PGA₁ (filled diamond), 15-keto-PGF₂₀ (filled circle), 15-keto-PGE₂ (open inverted triangle), PGB₁ (open triangle), and malondialdehyde (open circle). B, these lipids also result in a change in conformation of p53 to the mutant conformation. C, the lipids attenuate HIF-1 transcriptional activity with a similar rank order of potency to p53. D, electrophilic lipids attenuate TrxR activity as measured by Trx-dependent NADPH oxidase activity in RKO cell lysates.

Our mechanistic framework is supported, but not necessarily proven, by our data. Notably, our framework aligns well with yeast genetic experiments indicating that TrxR is essential for transcription by p53 (11, 12). In addition to its effects on TrxR, we observed that PGA₁-APB binds covalently to thioredoxin, the substrate of TrxR. TrxR and Trx are vital components of a regulatory cycle and they act coordinately to maintain p53 conformation and function. Biologically, the reductase activity of TrxR maintains Trx in a reduced state so that it is competent to function as a sulphydryl-disulfide isomerase (8). It is possible that covalent binding to, and direct inactivation of Trx is also important for p53 inactivation. In other words, electrophilic lipids inhibit Trx directly, via irreversible, covalent binding and indirectly via their effects on TrxR.

Certain a,β-unsaturated carbonyl compounds with electrophilic carbons are known risk factors for cancer, e.g., acrolein, malondialdehyde, and 4-hydroxy-2-nonenal. Their carcinogenic mechanism is best understood in terms of their direct interaction with DNA (27–29). Our data and model provide a new molecular basis for appreciating their carcinogenic effects. Aside from these well established carcinogens, many chemically complex a,β-unsaturated ketones and a,β-unsaturated aldehydes are considered safer because they have low rates of reaction with DNA and reduced glutathione (30). Dipple and colleagues have termed these agents “stealth carcinogens” (31) because the unusual elements of this phenotype occur in tumors. Our data and model provide a new molecular basis for appreciating and reassessing the safety of such compounds. The cyclopentenone PG provoke an unusual and distinctive phenotype typified by accumulation of p53 protein in an abnormal conformation that cannot support DNA binding and transcription.

We have tested a set of representative electrophilic chemicals that include agents derived from the cyclooxygenase pathway (malondialdehyde, metabolites of prostaglandins, e.g., 15-keto-PGF₂₀, and dehydration products, e.g., PGA₁ or Δ12-PGJ₂) and agents derived from the lipoxygenase pathways (e.g., 4-HNE generated by decomposition of hydroperoxycyclooctadienic acids. Based on chemical precepts, we anticipate that electrophilic carbons on numerous other compounds would confer a similar ability to inhibit TrxR. Cells can encounter electrophilic chemicals via environmental exposure, dietary exposure, or normal metabolic processes. We draw special attention to inflammation as one of these processes. As part of their normal host-defense function, inflammation inevitably exposes proximal epithelial and stromal cells to substances with mutagenic potential in vitro (18). Individual eicosanoids with a,β-unsaturated ketone substituents like PGA₁ or PGA₂ may not occur in μM concentrations at a site of inflammation. However, inflammatory exudate contains a blend of electrophiles typified by a,β-unsaturated aldehydes derived from eicosanoid biosynthesis or lipid peroxidation (4-HNE); a,β-unsaturated ketones derived from eicosanoid metabolism (15-keto-PGF₂₀, 15-keto-PGE₂, 5-, 12-, and 15-oxo-ETE); and a,β-unsaturated ketones derived from albumin dehydrating PGE₂ to PGA₁ and PGD₂ to Δ12-PGJ₂ and 15-deoxy-Δ12-PGJ₃ (32–35). Thus, inflammation likely exposes cells to a mixture of electrophiles in quantities sufficient to impair TrxR. Note that 4-HNE, a common product of lipid peroxidation, potently inactivates the selenoprotein TrxR. The level of endogenous 4-HNE in tissues ranges from 0.1 to 3.0 μM and increases to −10 μM in conditions of oxidative stress (36).
Although purely speculative at this point, our mechanistic framework aligns well with the lipid mediator class switching hypothesis recently proposed by Serhan and colleagues (37). It has been suggested that J-series cyclopentenone PG are present during resolution phases of inflammation and attenuate the inflammatory response (33). Electrophilic lipoxins would also be present and perhaps act through a common mechanism involving TrxR inhibition.

The same electrophilic cyclopentenone PG and lipid aldehydes that impair conformation and repress transcription by p53 can also repress transcription and antagonize the effects of NFκB (7, 38–40). This may also occur via an irreversible, covalent modification of proteins. For instance, cyclopentenone PG of the A and J series or 4-HNE can form adducts with IKK (36). The fact that electrophilic lipids act indirectly via a selenoprotein may have implications for cancer prevention. For instance, our model predicts that selenium supplementation of culture medium should maintain TrxR activity and thereby spare p53 from inactivation by electrophilic lipids.

We affirmed this prediction. Clark and colleagues have reported that supplementation of dietary selenium lowers the risk of prostate, colon, and certain other cancers (41). The molecular basis for this phenomenon, especially the role of selenoproteins, is uncertain. Our observation that selenium spares an important tumor suppressor, p53, provides an explicit mechanistic framework to understand how dietary selenium confers protection against cancer. Approximately 50–60% of cancer patients have tumors harboring mutations or deletions of p53. These patients typically have a poorer prognosis than patients with tumors harboring wild-type p53 (20, 42). Likewise, not all mutations are equally pernicious; certain classes may be worse than others. In particular, mutations associated with an altered conformation of p53 protein correlate with significantly shorter survival and poorer prognosis in patients with colorectal cancer (43, 44). We draw attention to reports about colon, breast, and neuroblastoma tumors with a wild-type p53 gene that paradoxically express a dysfunctional p53 protein with a mutant conformation (14, 15, 17, 45–48). The latency model of p53 function (49), in its current form, does not account for the peculiar p53 phenotype described in these reports. We can recapitulate this unusual and unexplained p53 phenotype in cells by impairing their TrxR-Trx, or related disulfide reductases, in its emergence.

In summary, various electrophilic lipids have the capacity to repress transactivation by several redox-responsive transcription factors by covalently modifying regulatory proteins in the
pathways, IKK in the case of the NFκB pathways and TrxR-Trx in the case of p53 and HIF.

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