Genotoxic Exposure Is Associated with Alterations in Glucose Uptake and Metabolism

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ABSTRACT

Recent observations suggest that growth factor withdrawal can promote cell death in part through modulation of basic cellular bioenergetic pathways, including inhibition of glucose uptake and glycolytic metabolism. Whether DNA damage-initiated cell death pathways also involve bioenergetic deregulation has not been studied previously. Subtractive suppressive hybridization was used to identify changes in gene expression in murine cells after exposure to genotoxic stimuli, including cisplatin, etoposide, and γ-radiation. Among the genes identified in this screen were several that regulate glycolytic metabolism. Enzymes that catalyze key regulatory steps of glycolysis, including hexokinase, phosphofructokinase, and pyruvate kinase, appeared to be coordinately down-regulated by genotoxic exposure. Northern blotting confirmed that these changes in gene expression occur within 4 h of exposure to several DNA-damaging agents. Genotoxic exposure was found to similarly inhibit expression of both glut-1 and glut-3, genes that encode critical regulators of glucose uptake. Direct measurement of glycolytic rate and of oxygen consumption confirmed that genotoxic exposure resulted in suppression of both anaerobic and aerobic metabolism. Many of these metabolic changes mimic those observed after growth factor withdrawal. Together, these observations suggest that multiple apoptotic triggers, including growth factor withdrawal and genotoxic exposure, suppress cellular bioenergetic pathways. Mitochondrial responses to the resulting rapid decrease in metabolic substrates may play an important role in initiation of apoptotic cell death.

INTRODUCTION

The cellular responses to genotoxic damage, including cell cycle arrest, DNA repair, and apoptotic cell death, are critical for the maintenance of genomic integrity (1, 2). Defects in these responses may play important roles in the development of human cancers and in the acquisition of therapeutic resistance. Carcinogenesis requires the accumulation of multiple mutations and in most cancers involves gross chromosomal rearrangement with both gains and losses of large segments of the genome (3). Resistance to the programmed cell death pathways that are normally triggered by aberrant replicative cycles is therefore thought to be essential in the derivation of many solid tumors. Many anticancer therapies, including radiotherapy and most chemotherapeutics, function directly or indirectly as DNA-damaging agents, and resistance to these agents has been associated with inhibition of programmed cell death pathways (4).

The molecular pathways from DNA damage to apoptotic commitment are incompletely understood. Although the p53 protein plays a central role in coordinating many responses to DNA damage, p53-independent induction of apoptosis after DNA damage has also been reported in many systems (5, 6). Therapeutic resistance to DNA-damaging agents can derive from overexpression of genes encoding apoptotic resistance factors, such as Bcl-2 or Bcl-xL (7, 8). These Bcl-2 family members function in the outer membrane of mitochondria to inhibit the loss of mitochondrial homeostasis resulting in cytochrome c release and apoptotic initiation (9). The nature of the signaling pathway from nuclear genomic damage to mitochondrial response has not been fully characterized.

Recent data have implicated changes in uptake and utilization of glucose in the mitochondrially dependent apoptotic pathway initiated by growth factor withdrawal (10). Restriction of growth factor availability from lymphocytes in culture and in vivo results in progressive cellular atrophy and cell death. Cellular atrophy is most evident in cells in which the apoptotic response has been inhibited by overexpression of an antiapoptotic Bcl-2 family member (11). Cellular atrophy is associated with down-regulated expression of the glut-1 gene, encoding a cell surface glucose uptake transporter, with decreased cellular ATP levels, and with rapid inhibition of expression of HK1 and PFK1, key regulators of glycolytic metabolism (10, 11). Growth factor receptor signaling may promote cell growth and survival in part by stimulating continued glucose uptake and glycolytic metabolism.

Down-regulation of glycolytic rate results in a decrease in the availability of substrates for oxidative phosphorylation. One of the functions of antiapoptotic Bcl-2 family members appears to be maintenance of ATP/ADP exchange across the mitochondrial membrane under conditions of stress, including growth factor withdrawal (12). Growth factor withdrawal in IL-3-dependent cells leads to a deficiency in the ability to exchange mitochondrial ATP for cytoplasmic ADP, with subsequent mitochondrial swelling, loss of mitochondrial membrane potential, and loss of outer mitochondrial membrane integrity. Bcl-xL expression can maintain mitochondrial ATP/ADP exchange and prevent the subsequent alterations associated with the induction of programmed cell death (12). Maintenance of adenine nucleotide exchange by Bcl-xL may facilitate integration of cytoplasmic (glycolytic) and mitochondrial (oxidative) metabolism. This continued integration may be critical in preventing mitochondrial alterations associated with the initiation of programmed cell death after rapid decreases in the rate of glycolysis.

Whether suppression of glycolytic metabolism is associated only with extrinsic apoptotic induction, such as mediated by growth factor withdrawal, or represents part of a more general apoptotic response has not been determined. In particular, the changes in bioenergetic regulation initiated by genotoxic damage, and their association with apoptotic induction, have not been characterized. We initiated a screen to identify changes in gene expression after exposure to cisplatin, a potent genotoxic agent, by subtractive suppressive hybridization. Among the many differentially expressed transcripts identified as either up-regulated or down-regulated after cisplatin exposure were a number involved in the regulation of glycolytic metabolism. Here we report that exposure to multiple DNA-damaging agents is associated with marked down-regulation of cellular bioenergetic pathways, with inhibition of expression of genes encoding rate-limiting factors in glycolysis and factors responsible for glucose uptake by cells. Many of these effects appear to parallel metabolic alterations.

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2 The abbreviations used are: HK, hexokinase; IL, interleukin; PFK, phosphofructokinase.
observed on apoptotic induction by growth factor withdrawal, suggesting a common bioenergetic response pathway.

MATERIALS AND METHODS

Cell Culture and Drug Exposure. FL5.12 cells are an IL-3-dependent hematopoietic precursor line derived from murine fetal liver (13). Transfection of FL5.12 with pSSV-Bcl-x<sub>L</sub> and subsequent selection to generate FL5.Bcl-x<sub>L</sub> cells has been described previously (14). FL5.Bcl-x<sub>L</sub> cells were cultured at 37°C in RPMI 1640 containing 10% FCS, 20 mM HEPES, 2 mM glutamine, 1 g/ml geneticin, 50 μg/ml β-mercaptoethanol, and 10% WEHI-3B supernatant as a source of IL-3. Unless otherwise noted, chemotherapeutic concentrations (5 μg/ml cisplatin, 10 μg/ml etoposide, or 0.1 μg/ml vincristine) were chosen based on previous cytotoxicity data for the parental lines and Bcl-x<sub>L</sub>-transfected (15). All γ radiation was delivered from a single cesium source emitting 2.86 Gy/min.

Centrifugal Elutriation. Elutriation was performed using a JE-6B elutriation system (Beckman Instruments) according to the manufacturer’s instructions. FL5.Bcl-x<sub>L</sub> cells (5 × 10<sup>6</sup>) were loaded into the centrifuge at a rotor speed of 3200 rpm and a flow rate of 25 ml/min. Rotor speed was decreased in 100 rpm increments, and 50-m1 fractions were collected at each interval. Fractions were split immediately for analysis of cell cycle profile and RNA preparation and for culture, either with or without 5 μg/ml cisplatin. Synchronized populations with or without cisplatin were used for RNA preparation and cell cycle analysis at time points <22 h after elutriation. RNA preparation was performed using TRIzol reagent (Life Technologies, Inc., Rockville, MD) according to the manufacturer’s instructions. Cell cycle analysis was performed by propidium iodide staining and flow cytometry as described previously (15).

Subtractive Suppressive Hybridization. Subtractive suppressive hybridization was performed using the PCR-Select cDNA Subtraction Kit (Clontech, Palo Alto, CA) according to the manufacturer’s instructions. In brief, total cellular RNA from cisplatin-treated, G<sub>2</sub>-phase-arrested cells and untreated G<sub>2</sub> phase cycling cells was used as a template for double-stranded cDNA synthesis. cDNA from cisplatin-treated and untreated cells was used as a tester and driver, respectively, to identify up-regulated genes and in the reverse arrangement, to identify down-regulated genes. Both cDNA populations were digested with Rsal, and tester cDNA was ligated to adapters 1 and 2 in two separate reactions. These ligated populations were heat denatured and hybridized with molar excess of denatured driver cDNA lacking adapters. The two hybridization reactions were then mixed, and PCR was performed using primers complementary to adapters 1 and 2. cDNAs over-represented in the tester population were further enriched by a second round of subtractive hybridization with excess driver cDNA.

Products of this initial screen were directly cloned into Topo-TA (Invitrogen, Carlsbad, CA) and transformed into Escherichia coli. Randomly selected batches of 96 colonies were inoculated onto a nylon membrane and lysed, and the DNA was fixed to the membrane. These membranes were then probed with <sup>32</sup>P-labeled tester and driver cDNA, as well as with subtracted or reverse subtracted cDNA probes. Over 2000 clones were screened using this technique.

Northern Blotting. Total cellular RNA was prepared using TRIzol reagent (Life Technologies, Inc.) according to the manufacturer’s instructions. Equal amounts of RNA, quantitated by spectrophotometry, were run on 1% agarose gels and transferred to a nitrocellulose filter. Blots were hybridized with <sup>32</sup>P-labeled probes derived by random priming of DNA fragments or by polynucleotide kinase end-labeling for the 55 RNA oligonucleotide probe (5’aaagctcaagccgctcgtat3’). The probe for pyruvate kinase was derived from the gene fragment cloned in the screen. Probes for glut-1, glut-3, HK1, HK2, PFK1, and α-enolase were amplified from total cellular RNA by RT-PCR. The primers used included: 5’-ggcgcgactgtcgcagcagc-3’ and 5’-acttgtgggtggttggtgatc-3’ for glut-1, 5’-ctcctgttcctgggatgcct-3’ and 5’-ccgcaagaaagtgcgagtt-3’ for glut-3, 5’-aaagtgctcggctcagtac-3’ and 5’-aaagtgctcggctcagtac-3’ for HK1, 5’-ctcctgttcctgggatgcct-3’ and 5’-ctcctgttcctgggatgcct-3’ for HK2, 5’-ctcctgttcctgggatgcct-3’ and 5’-ctcctgttcctgggatgcct-3’ for PFK1, and 5’-ctcctgttcctgggatgcct-3’ and 5’-ctcctgttcctgggatgcct-3’ for α-enolase. The 18S rRNA probe was purchased from Ambion, Inc. (Austin, TX).

RESULTS

Subtractive Suppressive Hybridization Reveals Changes in Expression of Glycolytic Regulators after Cisplatin Exposure. We have demonstrated previously that the lymphocytic cell line FL5.12 undergoes rapid apoptosis after exposure to 5 μg/ml cisplatin (15). Stable transfection of FL5.12 cells with a vector driving Bcl-x<sub>L</sub> expression greatly increased resistance to cisplatin and DNA-damaging agents. These cells were used as a system in which to evaluate changes in gene expression associated with cellular responses to DNA damage without the confounding variable of cell death. Exposure of FL5.Bcl-x<sub>L</sub> cells to cisplatin is associated with cell cycle arrest in the G<sub>2</sub> phase of the cell cycle (15). Comparison of gene expression in cisplatin-treated, G<sub>2</sub>-arrested cells with unsynchronized cycling cells might result in the isolation of genes associated with the G<sub>2</sub> phase of the cell cycle rather than genes associated with the cellular response to genotoxic exposure. To enrich for the latter class of genes, gene expression was compared in proliferating cells within the G<sub>2</sub> phase of the cell cycle and in cells arrested recently in the G<sub>2</sub> phase of the cell cycle after cisplatin exposure. Centrifugal elutriation of an unsynchronized population of FL5.Bcl-x<sub>L</sub> cells was performed to enrich for cells in distinct phases of the cell cycle. Pilot experiments demonstrated that FL5.Bcl-x<sub>L</sub> cells isolated from the G<sub>2</sub> phase of the cell cycle, exposed to 5 μg/ml cisplatin, arrest in G<sub>2</sub> after ~20 h (data not shown). To isolate RNA from cells shortly after cell cycle arrest, isolated G<sub>2</sub> cells were exposed to 5 μg/ml cisplatin and cultured for 22 h (Fig. 1). Subtractive suppressive hybridization was used to compare gene expression in these G<sub>2</sub>-arrested cells to that of untreated cycling cells isolated in the G<sub>2</sub> phase from the same elutriation experiment (Fig. 1, B and C).

Western Blotting. Whole cell lysates were prepared in radioimmunoprecipitation assay buffer, and protein concentration was determined by the Bio-Rad Protein Assay (Bio-Rad Laboratories, Hercules, CA). Samples normalized for protein content were run on 14% polyacrylamide gels (Invitrogen) and electrophoretically transferred to nitrocellulose. Filters were probed sequentially with anti-Glut-1 antibody sc-7903 (Santa Cruz Biotechnology, Santa Cruz, CA), anti-Glut-3 antibody sc-7582 (Santa Cruz Biotechnology), and anti-β-actin antibody AC-15 (Sigma, St. Louis, MO). Blots were developed using an enhanced chemiluminescence kit (Amersham/Pharmacia) according to the manufacturer’s instructions.

Measurement of Glycolytic Rate. Determination of glycolytic rate was dependent on the conversion of 5<sup>-3</sup>HD-glucose to H<sub>2</sub>O. To describe previously (10, 16). Synthesis of radiolabeled H<sub>2</sub>O is dependent on conversion of 2-phosphoglycerate to phosphoenolpyruvate in the glycolytic pathway. Briefly, 1 × 10<sup>6</sup> cells were washed and resuspended in 500 μl of Krebs buffer [25 mM NaHCO<sub>3</sub>, 115 mM NaCl, 2 mM KCl, 2 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, and 0.25% BSA (pH 7.4)] for 30 min in 5% CO<sub>2</sub> at 37°C. Cells were then pelleted and resuspended in 500 μl of Krebs buffer containing 1 mM glucose and 10 μCi 5<sup>-3</sup>HD-glucose for 60 min in the same conditions. Aliquots (100 μl) of each sample were added to 50 ml of 0.2 N HCl in open 500-ml centrifuge tubes. These tubes were placed upright in scintillation vials containing 1 ml H<sub>2</sub>O. The vials were sealed and permitted to equilibrate for ≥24 h at room temperature. The amount of <sup>3</sup>H retained within the centrifuge tube and the amount that had diffused out by evaporation and condensation into the surrounding H<sub>2</sub>O were determined separately. 5<sup>-3</sup>HD-glucose and H<sub>2</sub>O standards were included in each experiment, permitting the calculation of the rate of conversion in each experimental sample, as described previously (17). All experiments were performed in triplicate.

Measurement of Oxygen Consumption. Aliquots of 4 × 10<sup>6</sup> cells in 4.5 ml of media were introduced into a functionally airtight Warburg chamber at 37°C, equipped with a polarographic O<sub>2</sub> electrode. The rate of decline in oxygen tension in the closed system is directly proportional to cellular O<sub>2</sub> consumption. ΔPO<sub>2</sub>(torr)/Δt(min) was continuously recorded over 10 min and was used to calculate respiratory rate as described previously (18). All experiments were performed in triplicate.
This screen identified 23 transcripts that were up-regulated by cisplatin and 17 transcripts that were down-regulated. Among the genes found to be down-regulated by genotoxic exposure were α-enolase, pyruvate kinase, and lactate dehydrogenase, enzymes catalyzing the last three biochemical steps in cytoplasmic glycolysis. Pyruvate kinase, a rate-limiting regulator of glycolysis, drives the conversion of phosphoenolpyruvate to pyruvate, which can then be incorporated into acetyl-CoA, a substrate for the tricarboxylic acid cycle and subsequent oxidative degradation to CO2 and H2O in mitochondria. It was possible that the down-regulation of pyruvate kinase expression was unique to cisplatin exposure. However, Northern blotting demonstrates that this inhibition is found consistently in the cell populations shown in B and C was compared, representing G2 phase cells in the absence (B) or presence (C) of cisplatin.

Expression of Glucose Transporters Is Strongly Repressed after Exposure to DNA-damaging Agents. The glut-1 and glut-3 genes encode cell surface proteins important in regulating glucose uptake by cells. Down-regulation of the glut-1 gene after IL-3 withdrawal in FL5.12 cells has been implicated in growth factor withdrawal-induced metabolic alterations and apoptotic cell death (10). It is possible that inhibition of glucose uptake after growth factor withdrawal is specific to that apoptotic signal. Alternatively, suppression of glucose uptake and of anaerobic glycolysis may represent a common pathway initiated by multiple apoptotic triggers. Consistent with the latter hypothesis, rapid inhibition of both the glut-1 and glut-3 mRNA was observed after exposure to either cisplatin or etoposide (Fig. 3). Glut-1 and glut-3 mRNA levels in response to either growth factor withdrawal or genotoxic exposure were strongly suppressed within 4 h, well before onset of either cell cycle arrest or apoptosis after any of these treatments. Notably, glut-1 and glut-3 mRNA levels were relatively maintained in response to vincristine, which also induces growth arrest in these cells (Fig. 3).

To evaluate whether the observed decrease in glucose transporter gene expression correlated with decreased protein level, Western blotting was performed using anti-Glut-1 and anti-Glut-3 antibodies. A decrease in both Glut-1 and Glut-3 protein levels was evident after exposure to cytotoxic agents or IL-3 withdrawal (Fig. 4). As expected, the decrease in protein levels occurred over a slower time course than the observed decrease in mRNA (compare Figs. 3 and 4).

Rates of Both Glycolysis and Oxidative Metabolism Are Decreased after Genotoxic Exposure. The observed down-regulation of key regulators of glucose uptake and glucose metabolism suggested that DNA damage may inhibit the ability of the cell to use glucose through glycolysis. To measure the rate of glycolysis in cells before and after genotoxic exposure, we examined the rate of conversion of 5-3H glucose to 3H2O. The conversion of 5-3H glucose to 3H2O is dependent on the metabolic breakdown of glucose through nine steps of glycolysis to phosphoenolpyruvate, the immediate precursor of pyruvate. The rate of glycolysis was found to be suppressed after cisplatin, etoposide, vincristine, or growth factor withdrawal, consistent with the observed down-regulated expression of metabolic regulators (Fig. 5).

To determine the effect of glycolytic suppression on mitochondrial function, the rate of oxygen consumption was examined. Because
oxygen serves as the final electron acceptor in the electron transport chain (being reduced to water), the rate of oxygen consumption reflects the rate of mitochondrial oxidative phosphorylation. FL5.Bcl-xL cells were incubated with 5 μg/ml cisplatin, 10 μg/ml etoposide, or 0.1 μg/ml vincristine or were washed and cultured in media lacking IL-3. At the indicated times, cells were harvested for RNA extraction and Northern blotting. The blot was sequentially hybridized to probes for each of the indicated genes. Between hybridizations, the blot was stripped using boiling distilled water, and completeness of stripping was verified by exposing the stripped blot to film.

**DISCUSSION**

Cells demonstrate a coordinated bioenergetic response to genotoxic exposure that results in the down-regulation of both anaerobic and aerobic metabolism. Exposure to multiple agents that are known to induce DNA damage via a variety of mechanisms results in the decreased expression of multiple genes involved in glucose uptake and glycolysis. The down-regulation of glycolytic gene expression is accompanied by a functional impairment in glucose utilization. This disruption in anaerobic metabolism is associated with an inhibition of mitochondrial function as measured by a decrease in the rate of oxygen consumption. This mitochondrial response to the altered bioenergetics after DNA damage may play an important role in the initiation of programmed cell death.

Cytochrome c redistribution from the mitochondria to the cytosol has been implicated in the cell death pathway after multiple apoptotic stimuli, including both radiation and genotoxic drugs (19). Both cytochrome c redistribution and apoptosis are prevented by Bcl-2 protein expression (19–21). Bcl-2 proteins are thought to inhibit cell death at least in part through their ability to prevent mitochondrial...
changes in glucose metabolism may be part of the common pathway that leads to mitochondrial dysfunction, cytochrome c redistribution, and the initiation of apoptosis.

Anaerobic metabolism in the cytosol is intimately linked to mitochondrial function. Oxidative phosphorylation and mitochondrial function are necessary for the efficient regeneration of NAD from NADH that is required for glycolysis to continue. Additionally, both pyruvate and reducing equivalents derived from glycolysis serve as the substrates that enable mitochondria to perform oxidative phosphorylation and regulate their own homeostasis. The majority of active processes carried out in mitochondria, including the control of mitochondrial volume homeostasis, requires the presence of a potential across the inner mitochondrial membrane (24, 25). When oxidative phosphorylation becomes limited, a resultant disruption in mitochondrial volume homeostasis has been proposed to be responsible for a loss of outer mitochondrial membrane integrity, cytochrome c redistribution, and the induction of apoptosis (21).

A decreased ability to use glucose may be the point of integration that connects specific cellular stress responses to the apoptotic machinery through the mitochondria and cytochrome c. As in the case of growth factor withdrawal, we have found that DNA-damaging agents initiate a characteristic set of alterations in basic bioenergetic pathways, including decreased expression of the principal regulators of glucose uptake and glycolytic metabolism, as well as a functional down-regulation of both anaerobic and aerobic metabolism. The similarity in the metabolic effects of apoptotic initiation by growth factor withdrawal and by genotoxic exposure suggests that this response plays a central role in the cellular response to apoptotic initiation.

Maintenance of glycolytic metabolism is important not only to the preservation of ATP generation but also for the maintenance of the hexose monophosphate pathway, a critical generator of NADPH in the cell. Among other functions, NADPH is essential for the maintenance of reduced glutathione. Glutathione is a critical intracellular antioxidant and may protect cells against apoptotic cell death through the preservation of protein sulfhydryl groups in a reduced state (26). Administration of bifunctional thiol-reactive agents, which mimic formation of covalent disulfide bridges, has been associated with apoptotic induction, whereas monofunctional thiol-reactive agents appear to have a protective function (27, 28).

The regulation of glucose utilization is complex, and the exact mechanism of glycolytic inhibition may vary between DNA damage, growth factor withdrawal, and other cell death-inducing stimuli. In addition to the transcriptional control of glucose transporters and glycolytic enzymes observed here, a variety of other mechanisms may disrupt glycolysis. Glucose transport into the cell is limited by the levels of various glucose transporters at the cell surface. Although some glucose transporters, such as Glut-1, appear to be controlled by the amount of transporter expressed, insulin-dependent glucose transport is regulated by the translocation of intracellular Glut-4 to the cell surface (29). Intracellular trafficking may represent another means to regulate glucose utilization in response to apoptotic stimuli. Notably, glycolytic rate was significantly affected by vincristine exposure, despite relatively minimal effects on the expression of genes encoding regulators of glucose uptake and metabolism.

Glycolytic enzyme activity can also be regulated by post-translational mechanisms. The reaction catalyzed by PFK1 exerts the most control over the rate of glycolysis in mammalian cells. PFK1 enzyme activity is under complex allosteric regulation that involves cellular adenine nucleotide concentrations in addition to the levels of another metaboite, fructose-2,6-bisphosphate (30, 31). Fructose-2,6-bisphosphate levels are regulated by enzyme phosphorylation, indicating a target for regulation by cellular signal transduction pathways. Therefore, although genotoxic damage appears to affect bioenergetic pathways through altered expression of important metabolic genes, the
cellular response to other agents may intersect the metabolic pathways differently, reflecting distinct upstream signal transduction. This hypothesis is supported by the observation that vincristine treatment resulted in an inhibition of metabolism similar to that observed after genotoxic damage and growth factor withdrawal, despite little evident change in metabolic gene expression.

The observation that decreased glucose utilization may represent a central pathway of apoptotic response has important implications for our understanding of cancer therapy. The great majority of neoplastic cells relies principally on glycolytic metabolism. Cancer cells maintain a high glycolytic rate despite the presence of adequate oxygen in their environment, a phenomenon known as the Warburg effect (32). The transformation event leading to altered metabolism may have implications for the therapeutic sensitivity of a particular tumor. Differences in the mechanisms leading to altered glycolytic dependence in various tumors may differentially affect tumor sensitivity to various anticancer agents. Studies of neoplastic cells have identified altered expression of genes involved in glucose utilization (33–35), and overexpression of genes involved in glucose utilization has been shown to inhibit cell death (10, 23). A better understanding of both how bioenergetic pathways are altered in specific neoplasms and how different agents inhibit metabolism and result in tumor cell death may lead to better targeting of and improved therapeutic response to antineoplastic regimens.

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