We report that a decrease in facilitative glucose transporter (GLUT1) expression and reduced glucose transport trigger apoptosis in the murine blastocyst. Inhibition of GLUT1 expression either by high glucose conditions or with antisense oligodeoxynucleotides significantly lowers protein expression and function of GLUT1 and as a result induces a high rate of apoptosis at the blastocyst stage. Similar to wild-type mice, embryos from streptozotocin-induced diabetic Bax+/− mice experienced a significant decrease in glucose transport compared with embryos from non-diabetic Bax−/− mice. However, despite this decrease, these blastocysts demonstrate significantly fewer apoptotic nuclei as compared with blastocysts from hyperglycemic wild-type mice. This decrease in preimplantation apoptosis correlates with a decrease in resorptions and malformations among the infants of the hyperglycemic Bax−/− mice versus the Bax+/+ and +/− mice. These findings suggest that hyperglycemia by decreasing glucose transport acts as a cell death signal to trigger a BAX-dependent apoptotic cascade in the murine blastocyst. This work also supports the hypothesis that increased apoptosis at a blastocyst stage because of maternal hyperglycemia may result in loss of key progenitor cells and manifest as a resorption or malformation, two adverse pregnancy outcomes more common in diabetic women.

In prior studies, it has been shown that maternal hyperglycemia results in down-regulation of the embryonic facilitative glucose transporters (GLUT), GLUT1, GLUT2, and GLUT3, at the blastocyst stage of mouse development (1). Culturing two-cell embryos for 72 h in high concentrations of glucose (30 or 52 mM) likewise causes a decrease in the expression of these facilitative transporters at the mRNA and protein levels. This decrease in transporter expression leads to a significant drop in intraembryonic free glucose levels in blastocysts obtained from mice made hyperglycemic by streptozotocin injection or after culturing two-cell embryos from normal mice in high glucose. Blastocysts cultured under similar conditions also experience a 6-fold increase in expression of the proapoptotic protein BAX, as compared with controls and undergo increased apoptosis (2). Approximately 40% of all nuclei from embryos from hyperglycemic mothers showed evidence of terminal dUTP nick-end labeling or TUNEL-positive staining compared with less than 10% among controls. This apoptotic event requires BAX expression because blastocysts recovered from diabetic Bax−/− mice are resistant to the hyperglycemia-induced apoptosis. Similarly, the hyperglycemia-induced event is inhibited partially with either the caspase inhibitor z-Val-Ala-Asp-fluoromethylketone (zVAD-FMK), or the ceramide synthase inhibitor, fumonisin B1, strongly suggesting that these apoptosis-associated pathways are involved. Apoptosis at this developmental stage may manifest later in pregnancy as a malformation or, if a significant cell loss occurs, as a miscarriage. Both these adverse pregnancy outcomes occur more frequently in infants of diabetic women (3–5) and thus hyperglycemia-induced apoptosis at this preimplantation stage may explain the increased incidence of these pregnancy complications.

In these experiments, we hypothesize that the hyperglycemia-induced decrease in glucose transport is responsible for triggering apoptosis. This phenomenon has been described in other cell systems (6–9). To test this hypothesis, we investigated the role of presumed upstream and downstream components. First, we examined whether blocking GLUT1 expression with antisense oligonucleotides at the blastocyst stage leads to apoptosis. This would suggest that decreased intracellular glucose and not hyperglycemia per se triggers the death cascade. Second, we examined whether BAX expression is downstream of glucose transport using a Bax null model. In agreement with our initial hypothesis, we would predict that BAX expression is downstream of glucose transport and thus maternal hyperglycemia would have the same effect of decreasing transport in embryos from Bax−/− mice as seen in embryos from Bax+/+ mice. However, these embryos because of BAX deficiency would not undergo apoptosis.

We also hypothesize that a glucose-induced increase in apoptosis at this developmental stage may manifest later in pregnancy as a malformation or, if a significant cell loss occurs, as a miscarriage. To test this hypothesis we examined the effect of maternal diabetes in the Bax-deficient mice on fetal malformations and pregnancy resorptions. We know from previous work that lack of BAX expression protects the blastocyst from glucose-induced apoptosis (2). Thus, if this preimplantation event manifests later in pregnancy as a miscarriage or malformation,
these Bax null mice should experience fewer reproductive complications of maternal hyperglycemia.

**EXPERIMENTAL PROCEDURES**

**Embryo Recovery and Culture**—Embryos were recovered as described previously (1). In brief, female mice (B6 × SJL F1, Jackson Laboratories, Bar Harbor, ME) of 4–6 weeks of age were given free access to food and water and were maintained on a 12:12 h light/dark cycle. Superoxoluation was achieved with an intraperitoneal injection of 10 IU/pregnant mare serum gonadotropin (Sigma Chemical) followed later by 10 IU/animal of human chorionic gonadotropin (hCG, Sigma Chemical). Female mice were mated with males of proven fertility overnight after hCG injection. Mating was confirmed by identification of a vaginal plug.

Animals were killed by cervical dislocation at 48 h after hCG administration and mating. Two- and four-cell embryos were obtained by flushing dissected uterine horns and oviducts as described previously. The embryos were then immediately placed in human tubal fluid (HTF) medium (Irving Scientific) containing 0.25% BSA (Sigma, Fraction V) and cultured at 37 °C in an atmosphere of 5% CO2, 5% O2, and 95% N2 for 24 h. Four-cell embryos were exposed to 0.01% lysolecithin for 30 min and then cultured for a further 48 h in one of the following conditions: D-glucose, 52 mm glucose, 5 μM GLUT1 sense oligonucleotide (5′-ATGAGGCCCCAGCGAGAAG), or 5 μM GLUT1 antisense oligonucleotide (5′-CTTCTGTCGTGCTGCTGAT). The oligodeoxynucleotides were modified to contain phosphorothioate linkages. In a previous study, this GLUT1 antisense oligonucleotide had been used successfully in a preimplantation model to decrease protein expression (10).

**Western Analysis to Quantitate Embryo GLUT1 Protein**—Blastocysts were collected in groups of 200, added to 2× sample buffer, subjected to 7.5% SDS-polyacrylamide gel electrophoresis and transferred to nitrocellulose. GLUT1 was then detected using a polyclonal mouse GLUT1 antibody (1:500, gift of Dr. Mike Mueckler, Washington University School of Medicine). 125I-Labeled goat anti-rabbit IgG was used as the secondary antibody. Radioactive bands were quantitated using a PhosphorImager (Molecular Dynamics).

**Immunofluorescence Labeling to Quantitate Protein Expression**—Immunofluorescence staining techniques have been described for embryonic preparations previously (1). All labeling was performed in microdroplets. Blastocysts were fixed in 3% neutral buffered formaldehyde for 30 min and then permeabilized with 0.1% Tween 20 for 10 min. The embryos were then blocked by incubating for 60 min in 20% donkey serum in phosphate-buffered saline containing 0.1% Tween 20 (PBS/BSA). Embryos were then washed three times for 10 min each in PBS/BSA, incubated in the affinity-purified primary antibody (polyclonal anti-mouse GLUT1) at a dilution of 15 μg/ml for 60 min. The embryos were then washed three times for 10 min each in PBS/BSA and incubated with the secondary antibody, fluorescein isothiocyanate (FITC)-labeled goat anti-rabbit IgG (Chemicon, Temecula, CA) at a concentration of 1:80 followed by propidium iodide at a concentration of 0.01 mg/ml for 20 min. Propidium iodide stains all nuclei red. Finally the embryos were washed three times for 10 min each in PBS/BSA and mounted in drops of Vectashield (Vector Labs, Burlingame, CA) under a supported coverslip. Fluorescence was detected with a Bio-Rad MRC-600 laser-scanning confocal microscope. Confocal images were taken at ×63 magnification. Total fluorescence per embryo was expressed as a number/area using NIH image (version 1.60). Similar fluorescence ratios were derived for preimmune serum images and subtracted from the GLUT1 images to generate a total fluorescence value. These experiments were performed in triplicate with 7–10 blastocysts per group for each experiment.

**2-Deoxyglucose Uptake and Free Glucose Assay**—To confirm that the antisense oligonucleotide blocked GLUT1 function as well as expression, glucose uptake was measured using a nonradioactive microanalytic procedure described previously (1, 11). In brief, blastocysts after 72 h of culture were incubated at 25 °C in 200 μl 2-deoxyglucose (DG) for 15 min, washed in DG- and BSA-free buffer for 1 min, and then were quick-frozen on a glass slide. After freeze-drying overnight, the embryos were extracted in microliter volumes under oil and assayed for DG and DGP as described previously. The final measurements are expressed as picromoles per embryo per 15 min. Experiments were performed in triplicate on 10–15 individual embryos per group for each experiment. For the intrablastocystic glucose measurements, embryos were treated in the same manner as above and free glucose levels were measured on individual blastocysts as described previously (1, 11).

**Terminal DUTP Nick End Labeling (TUNEL) Assays to Detect Apoptosis in Blastocysts**—This technique has been described previously for murine blastocysts (2, 12). Fixed blastocysts were counterstained with propidium iodide to label all nuclear DNA and fragmented DNA was end-labeled with FITC-labeled DUTP using terminal transferase (cell death in situ kit, Roche Molecular Biochemicals). The embryos were then observed using confocal immunofluorescent microscopy (Bio-Rad MRC-600). A complete z-series was performed for each blastocyst to ensure that each nucleus was sampled and counted. The degree of apoptosis is expressed as % TUNEL-positive nuclei (green channel) per total nuclei (red channel) per embryo. These experiments were performed in triplicate with 7–10 blastocysts per group for each experiment.

**Induction of Hyperglycemia in Mice and Preimplantation Studies**—Bax−/−, −/+ and +/+ female mice were made hyperglycemic by a single intraperitoneal injection of streptozotocin (Sigma) dissolved in sodium citrate, pH 4.4, at a dose of 190 mg/kg as described previously (1, 13). Blood glucose levels were checked with tail blood using a HemoCue B-glucose analyzer (Angelholm, Sweden) at least four days following the injection. Blood glucose levels of greater than 200 mg/dl were considered hyperglycemic. The hyperglycemic and non-hyperglycemic control mice were superovulated and mated with either Bax−/− males (for the Bax+/− and −/− females) or Bax+/+ males (for the Bax+/− females). Bax−/− males are infertile, and thus Bax heterozygote males must be mated with Bax null females (14). Embryos were recovered 24 h after mating for glucose uptake experiments. For glucose uptake measurements, the blastocysts were fixed in 3% parafomaldehyde, permeabilized with 0.1% Tween 20 and assayed for apoptosis by TUNEL as described.

**Recovery of Day 14 Embryos and Analysis of Morphologic Changes**—Embryos from matings of hyperglycemic or control Bax−/− or −/+ females with Bax−/− or Bax+/− females were recovered on day 14 of gestation counting the day of plug as day 0. The mice were anesthetized with a lethal dose of pentobarbital, and the abdomen was opened immediately. The uterus was removed and examined for resorption sites and fetuses. The fetuses were freed of membranes and examined carefully under a dissecting microscope for evidence of external anomalies. The following morphologic criteria were examined: body rotation, closure of the neural tube, and appearance of heart, head, mouth, and abdominal wall. Embryos were categorized as morphologically normal or as showing minor or major malformations as described previously (15). Normal embryos exhibited correct body flexure and closure of both the anterior and posterior neural pole. Embryos were classified as having a minor malformation if they exhibited a small malrotation or a delayed closure of a single neural pole. Embryos were recorded as having a major malformation if they demonstrated severe malrotation, an abnormally open neural tube, or a cardiac or other gross malformation. An average malformation score was calculated for each experimental condition, where normal embryos and embryos with minor and major malformations were assigned individual scores of 0, 1, and 10 respectively.

Because Bax−/− mice had to be mated with Bax+/− males, only 50% of the fetuses should have the null genotype. To determine whether the malformed fetuses among these litters demonstrated a Bax+/− or −/− genotype, malformed fetuses in these litters were genotyped using the standard protocol for genotyping tail DNA with polymerase chain reaction (14).

**Statistical Analysis—**Differences between the four groups (L-glucose, D-glucose, sense, and antisense) among protein expression, glucose uptake, and percent TUNEL staining were compared by one-way analysis of variance (ANOVA) coupled with Fisher test (Statview 4.5). Differences between the diabetic and non-diabetic Bax genotypes among glucose transport, TUNEL staining, and resorption/malformation rates also were compared by ANOVA coupled with the Fisher test. Results are expressed as means ± S.E. of at least three separate experiments.

**RESULTS**

**Antisense Oligoprobe Treatment Successfully Decreases GLUT1 Protein Expression and Function**—By Western blot analysis, protein expression of GLUT1 was significantly lowered in response to antisense oligonucleotide exposure as compared with sense or L-glucose control. There was a significant 46 ± 11% drop in protein expression in the antisense group as compared with the sense group. There was a significant 33 ± 13% drop in protein expression in the D-glucose versus L-glucose group. (n = 3 experiments with 280 embryos in each group for...
Antisense oligoprobe decreases GLUT1 protein expression. A, blastocysts cultured from a 2-cell stage in either 5-μM sense oligoprobe (S), 5-μM antisense oligoprobe (AS), 52 mM L-glucose (LG) or 52 mM D-glucose (DG) were subjected to 7.5% SDS-polyacrylamide gel electrophoresis. Each sample represents 280 embryos. PC or positive control represents purified erythrocyte transporter GLUT1. B, fixed blastocysts cultured under one of the four conditions listed in A were stained with propidium iodide (red channel) and GLUT1 polyclonal primary antibody with an FITC-labeled secondary antibody (green channel) and visualized by confocal immunofluorescent microscopy.

Each experiment, Fig. 1A). These findings were confirmed by detection of less GLUT1 protein in antisense-treated blastocysts by confocal immunofluorescence microscopy (Fig. 1B).

The decrease in protein expression among the embryos exposed to antisense oligoprobe correlated with a significant decrease in nonradioactive 2-deoxyglucose uptake into single mouse blastocysts using microfluorometric assays combined with enzymatic cycling reactions (1.254 ± 0.077 pmol/embryo/15 min antisense (n = 32 embryos) versus 1.795 ± 0.12 pmol/embryo/15 min sense (n = 35). Embryos cultured in D-glucose demonstrated a similar decrease as compared with L-glucose controls (2.045 ± 0.067 pmol/embryo/15 min antisense (n = 35 embryos) versus 1.644 ± 0.070 pmol/embryo/15 min sense (n = 33 embryos)) (Fig. 2).

The decrease in 2-deoxyglucose uptake correlated with a significant decrease in intraembryonic free glucose levels. Embryos cultured in antisense oligoprobe demonstrated 36% less free glucose than the embryos cultured in sense oligoprobe (41.8 ± 4 fmol/embryo AS, n = 13) versus 64.8 ± 5 fmol/embryo sense (S, n = 13).

Antisense Treatment Induces Apoptosis—Culturing embryos in the presence of GLUT1 antisense oligopropes (n = 10 embryos) induced a high rate of apoptosis (46 ± 6% TUNEL-positive nuclei/total nuclei/embryo) at the blastocyst stage as compared with embryos exposed to sense (7 ± 2%, n = 6) or control media with 52 mM L-glucose (5 ± 1%, n = 8). This high TUNEL-positive percentage was significantly higher than control conditions (p < 0.001) but was not significantly different from embryos cultured in 52 mM D-glucose (47 ± 5%, n = 7) (Fig. 3, A and B).

Lack of BAX Does Not Affect Glucose Transport but Does Protect Against Apoptosis—Embryos obtained from streptozotocin-induced diabetic Bax−/− mice experience a significant decrease in glucose transport (0.265 ± 0.027 pmol/embryo/15 min) compared with embryos from non-diabetic Bax−/− mice (0.633 ± 0.133). This decrease in glucose transport in a diabetic state was not significantly different from that seen among embryos from diabetic versus non-diabetic wild-type mice (diabetic, 0.278 ± 0.038 versus control, 0.528 ± 0.062 pmol/embryo/15 min; Fig. 4).

Despite this decrease in glucose transport, blastocysts from hyperglycemic Bax−/− mice fail to show any evidence of apoptosis. Blastocysts from diabetic Bax−/− mice demonstrated 7.6 ± 2.0% TUNEL-positive nuclei/total nuclei/embryo (n = 7) as compared with non-diabetic Bax−/− mice with 5.0 ± 1% (n = 15). In contrast, wild-type mice made diabetic with streptozotocin demonstrated a significant increase in apoptotic nuclei versus non-diabetic (48.5 ± 5.6% diabetic, n = 7; 62 ± 1.6% control, n = 10) (Fig. 5, A and B).

Lack of Bax Expression Protects Against Diabetic Embryopathy—As shown in Table I, E14 embryos from Bax−/− mice made hyperglycemic with streptozotocin demonstrated a significantly lower rate of resorptions and malformations as compared with E14 embryos from diabetic Bax+/− or +/+ mice. Using ANOVA, a significantly higher percent of Bax−/− or Bax+/− embryos demonstrate malformations than Bax−/+ embryos (p < 0.001). Moreover, the severity of the malformations from the diabetic Bax−/− mice was significantly lower than the heterozygote or wild-type mice as reflected by the malformation score. These malformations included micrognathia, omphalocele, cranial abnormality/neural tube defect, or malrotation in that order of descending frequency. Non-diabetic mice of all genotypes demonstrated similar low rates of resorption and malformation.

DISCUSSION

These experiments demonstrate that decreased expression of GLUT1 in the mouse blastocyst caused by exposure to GLUT1
antisense oligonucleotide probes results in decreased glucose transport and an increase in apoptosis. In addition, hyperglycemia in the Bax^{2/-} mother causes a decrease in embryonic glucose transport at the blastocyst stage as is seen in wild-type Bax^{+/+} mice. The embryos lacking BAX expression, however, fail to undergo apoptosis. These findings demonstrate that this apoptotic event experienced in conditions of hyperglycemia is triggered by a decrease in glucose transporter expression. Previously, we have shown in two separate reports that hyperglycemia leads to apoptosis (2) and concurrently to decreased transporter expression (1). These findings clarify that the two events are not unrelated parallel responses to hyperglycemia and reveal that the decrease in glucose transport caused by hyperglycemia directly triggers a downstream BAX-dependent apoptotic event. This conclusion is significant because the majority of studies reported, which relate diabetes and hyperglycemia to apoptosis, assume that the high glucose triggers programmed cell death by accumulation of intracellular glucose levels or glucotoxicity (16–18). Several studies in a number of different cell types have shown, in accordance with our findings, that decreased transport and metabolism of glucose modulate programmed cell death (Refs. 6, 19, and 20 and reviewed in Ref. 21). Three cell death paradigms exist that link a decrease in glucose transport to apoptosis. These include 1) glucose deprivation-induced ATP depletion and stimulation of the mitochondrial death pathway cascade (7, 22), 2) glucose deprivation-induced oxidative stress and triggering of BAX-associated events including the JNK/MAPK signaling pathways (8, 23–27), and 3) hypoglycemia-regulated expression of HIF-1α, stabilization of p53 leading to an increase in p53-associated apoptosis (28, 29).

In this embryonic model, it is possible that low levels of ATP because of decreased glucose utilization may be responsible for triggering apoptosis. At a blastocyst stage embryonic energy metabolism changes from the use of pyruvate via the Krebs cycle and oxidative phosphorylation to the use of glucose via glycolysis to generate lactate (30–32). This switch is believed to be because of anaerobic conditions that occur at this time of implantation and result in less efficient production of ATP (33–35). This physiologic decrease in ATP production coupled with the hyperglycemia-induced decrease in glucose transport and thus glucose utilization seen in embryos exposed to hyperglycemia may act to trigger apoptosis via this paradigm.

Altered embryonic redox state may also play a role in high glucose-induced embryonic apoptosis. In postimplantation models of diabetes-induced malformations, it has been shown that antioxidants such as N-acetylcysteine (36), butylated hydroxytoluene (37), and vitamins C (38) and E (15) reduce the incidence of anomalies by decreasing oxygen-free radicals during organogenesis. Two factors are different in the blastocyst model. First, we are looking at a preimplantation event, prior to organogenesis. Second, postimplantation models support intracellular hyperglycemia, not hypoglycemia as the cause of
is determined by the exacerbated imbalance between pro-oxidant factors and those factors that scavenge them in response to hyperglycemia (9). As a result of this oxidative stress, expression of the anti-apoptotic gene Bcl-2 decreases while BAX expression increases, and DNA fragmentation occurs, thus linking oxidative stress to apoptosis in this system. These events were reversed by antioxidants and did not occur in retinal endothelial cells. It is possible that the same mechanisms are at work in the blastocyst model, and experiments are needed to determine whether these apoptotic events are reversible by antioxidants.

Finally, expression of HIF-1α in response to intracellular hypoglycemia may play a role at this stage of development. In embryonic stem cells, Carmeiliet et al. (28) have shown that hypoglycemia or hypoxia-induced expression or HIF-1α result in reduced proliferation and increased apoptosis (28). This adaptation is not seen in ES cells deficient in HIF-1α expression; however, apoptosis is induced by other agents such as cytokines. Other studies have shown that in response to hypoxia or hypoglycemia, HIF-1α accumulates and directly associates with and stabilizes active wild-type p53 (29). It is possible then that this increase in p53 protein is responsible for the apoptosis demonstrated in our blastocyst model. We have preliminary data to suggest that p53 may be involved in hyperglycemia-induced apoptosis in the blastocyst as p53−/− blastocysts fail to demonstrate increased TUNEL-positive nuclei in response to hyperglycemia.2 Further studies are needed to determine whether this is related to HIF-1α effects.

These studies also strongly suggest that this glucose-triggered apoptosis is responsible in part for diabetes-associated malformations and late resorptions because the diabetic Bax−/− mouse failed to demonstrate the adverse pregnancy outcomes seen in the Bax+/+ and +/- mice. One emerging hypothesis for the etiology of some diabetes-associated malformations is hyperglycemia-induced apoptosis. In models of both pre- and postimplantation diabetic anomalies, apoptosis has been detected in the tissues destined to show evidence of malformations (2, 40, 41). Although the mechanisms are not identical for these two different time points in development, the theme is the same; hyperglycemia of maternal diabetes triggers exaggerated programmed cell death in the developing murine embryo resulting in congenital malformations in the postimplantation models. It appears that elevated glucose levels disturb expression of regulatory genes in embryonic development and cell cycle progression resulting in premature cell death of progenitor cells and subsequently defective morphogenesis. In the postimplantation diabetic models, alterations in apoptotic pathway-related gene expression, specifically the transcription factor Pax-3, directly result in neural tube, musculoskeletal, and cardiac defects (40). Two downstream targets of Pax-3, cdc46, and Dep-1, have been determined (42, 43); however, the

\[ \text{TABLE I} \]

| Genotype | N | Implantation Sites | Resorptions % | Malformations % | Score |
|----------|---|--------------------|---------------|-----------------|-------|
| Diabetic | Bax+/− | 3 | 34 | 3 | 8 ± 3 | 0.4 |
|          | Bax+/− | 5 | 38 | 9 ± 3 | 57 ± 7 | 4.0 |
|          | Bax+/− | 5 | 33 | 46 ± 10 | 39 ± 9 | 4.5 |
| Non-diabetic | Bax−/− | 4 | 27 | 1 | 0 | 0 |
|          | Bax+/− | 5 | 47 | 4 ± 2 | 1 | 0.3 |
|          | Bax+/− | 5 | 53 | 5 ± 1 | 2 | 0.2 |

* p < 0.001 versus diabetic Bax−/−.

increased oxygen-free radicals. Similar to our blastocyst model, hyperglycemia also has been shown to induce a down-regulation of glucose transporters leading to glucose deprivation in retinal capillary pericytes (39). High initial intracellular glucose levels in this condition lead to accelerated elimination of reactive oxygen species generated by glucose auto-oxidation and by the increased NADH/NAD⁺ ratio (9). Intracellular glucose levels then drop rapidly as glucose transporter expression decreases in response to the hyperglycemia. As a result of these rapid changes, reduced glutathione levels are depleted, and expression of GSH peroxidase is increased. These data indicate that the increased susceptibility of pericytes to oxidative stress...
upstream regulators of Pax-3 expression by hyperglycemia are not yet clear. The mechanisms clarifying apoptosis-induced malformations in these models have yet to be determined.

This is the first time preimplantation apoptotic events have been linked to malformations and late resorptions. Although this BAX dependent effect may in part be because of postimplantation anti-apoptotic events, we predict that these pregnancy outcomes are in large part because of the drastic preimplantation differences seen between the genotypes. This work supports our hypothesis that the increased programmed cell death at this stage of development results in loss of key progenitor cells in the embryo and in turn this event manifests later in pregnancy as a pregnancy loss or congenital malformation. Both these pregnancy outcomes are more common in women with insulin-dependent diabetes mellitus, and these findings may provide one possible explanation for this increased incidence.
Decreased Glucose Transporter Expression Triggers BAX-dependent Apoptosis in the Murine Blastocyst
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J. Biol. Chem. 2000, 275:40252-40257. doi: 10.1074/jbc.M005508200 originally published online September 19, 2000

Access the most updated version of this article at doi: 10.1074/jbc.M005508200

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