The 31-kDa Caspase-generated Cleavage Product of p130\textsuperscript{cas} Functions as a Transcriptional Repressor of E2A in Apoptotic Cells*  

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In response to integrin receptor binding to the extracellular matrix, the multidomain docking protein p130\textsuperscript{cas} (Crk-associated substrate) activates various signaling cascades modulating such cellular processes as proliferation, migration, and apoptosis. During apoptosis, caspase-mediated cleavage of p130\textsuperscript{cas} generated a C-terminal 31-kDa fragment (31-kDa) and promoted morphological changes characteristic of apoptosis, including loss of focal adhesions, cell rounding, and nuclear condensation and fragmentation. By contrast, a p130\textsuperscript{cas} D748E mutant, which was unable to produce 31-kDa, attenuated the disassembly of focal adhesions at the bottom of the cell. 31-kDa contains a helix-loop-helix (HLH) domain that shows greater sequence homology with Id proteins than with basic HLH proteins, which enabled heterodimerization with E2A. Once coupled to E2A, 31-kDa was translocated to the cell nucleus, where it inhibited E2A-mediated p21\textsuperscript{Waf1/Cip1} transcription. Moreover, overexpression of 31-kDa led to cell death that could be inhibited by treatment with the caspase inhibitor ZVAD-fluoromethyl ketone or by ectopic expression of E2A or p21\textsuperscript{Waf1/Cip1}. These data suggest that during etoposide-induced apoptosis, 31-kDa promotes caspase-mediated cell death by inhibiting E2A-mediated activation of p21\textsuperscript{Waf1/Cip1} transcription.

Caspase-mediated cleavage of various components of focal adhesion complexes disrupts cell extracellular matrix (ECM) and cell-cell contacts and is a hallmark of apoptosis (1–6); conversely, maintenance of such contacts is an important cell survival factor (1, 7, 8). The targets of caspase-mediated cleavage within focal adhesion complexes include p130\textsuperscript{cas} (4), Hef1 (5), Fak (6), Src (9), and paxillin (10). The C-terminal cleavage fragment of FAK, which resembles a natural variant of FRNK (FAK-related non-kinase), inhibits FAK activity by preventing its localization at focal adhesions (11), where FAK-mediated survival signals are transduced via tyrosine phosphorylation of p130\textsuperscript{cas} and subsequent coupling of p130\textsuperscript{cas} and Crk. In that regard, overexpression of p130 protects cells from apoptosis (12–14), whereas inhibition of p130\textsuperscript{cas} phosphorylation or overexpression of dominant negative forms of p130\textsuperscript{cas} (15–17) induces apoptosis. Moreover, caspase-mediated cleavage of p130\textsuperscript{cas} is closely associated with apoptosis induced by a variety of agents (4, 5, 10, 14, 16, 18, 19). We previously showed that cleavage of p130\textsuperscript{cas} by caspase yields an active 31-kDa C-terminal fragment (31-kDa) that is regulated by tyrosine phosphorylation and contributes to the disassembly of focal adhesion complexes, thereby interrupting survival signals from the ECM. Conversely, uncleavable p130\textsuperscript{cas} attenuates the disassembly of focal adhesion complexes and the progression of apoptosis (4, 18). Hef1, another Cas family focal adhesion protein, undergoes similar caspase-mediated cleavage during apoptosis (5), resulting in the generation of 3 fragments, among which the 28-kDa fragment is highly conserved among Cas family members. This fragment also contains a HLH domain that mediates dimerization with a limited number of basic (b) HLH proteins (20) and contributes to the induction of apoptosis (19).

The bHLH family of transcription factors is crucially involved in such fundamental processes as cell growth, differentiation, development, and survival. These proteins can be divided into several classes based on their tissue distribution, DNA binding properties, and structural features (21). The ubiquitously expressed class A bHLH proteins, often referred to as E proteins, consist of E2-2, HEB, and E2A (21), which serve as partners within heterodimers with tissue-specific classes of bHLH proteins (22). E2A encodes two alternatively spliced products, E12 and E47 (21, 23), which are >80% identical and bind to the same E-box sequence (CANNTG). DNA binding by E2A proteins is abolished by the Id proteins (Id1–4), which serve as dominant-negative inhibitors (24–27). Ids dimerize with E2A, but the resultant heterodimers cannot bind to DNA because Ids lack a DNA binding domain. Consequently, Id and E2A play opposing roles in regulating cell function (24, 28–31). In NIH 3T3 cells, for example, E2A causes growth arrest (30) that is mediated by up-regulation of p21\textsuperscript{Waf1/Cip1} (31–33). Such E2A-mediated p21\textsuperscript{Waf1/Cip1} transcription is inhibited by Id proteins due to formation of the aforementioned inactive heterodimers.

Evidence suggests that E2A proteins protect cells against apoptosis (28, 34). For instance, ectopic expression of Id3, which abolishes E2A activity, leads to the induction of caspase-dependent apoptosis. This finding is consistent with the absence of B-lineage cells in E2A−/− mice and indicates that at least one function of E2A is to maintain cell viability (35, 36). Furthermore, E2A suppresses activation of caspase-3 and protects cells from apoptosis induced by activation of alternative death pathways, such as those activated by death domain-
FIG. 1. Proteolytic cleavage of p130\textsuperscript{cas} and identification of a putative HLH domain in 31-kDa. A, HeLa cells were exposed to 40 μM etoposide for the indicated time periods. Cell lysates were then subjected to immunoblot analysis using anti-Cas mAb, anti-FAK mAb, or anti-lamin B polyAb. The blot was then reprobed with anti-tubulin mAb to verify equal loading of protein. Molecular mass standards are indicated by small arrowheads on the right. B, the following regions within p130\textsuperscript{cas} are indicated: the SH3 domain (SH3), the proline-rich sequence (Pro), the substrate domain (YXXP, tyrosine phosphorylation sites), the serine-rich domain (SR), the Src binding site (SBS), and a putative HLH. Two cleavage sites are indicated by closed arrowheads. The 31-kDa fragment generated by caspase-3-catalyzed cleavage during etoposide-induced apoptosis is indicated; also illustrated is the immunogen for anti-Cas mAb.

C, alignment of p130\textsuperscript{cas}, Id, and bHLH based on the original description of the HLH motif (33). Conserved sequences matching the initially described consensus are boxed in black. Additional sequences conserved in p130\textsuperscript{cas} and Ids are boxed in gray.

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containing proteins through a Bcl-2-independent mechanism (34). At the present time, the number of caspase isofoms activated in the absence of E2A and the targets of E2A that mediate this anti-apoptotic effect are unknown. The fact that 31-kDa contains a HLH domain similar to that of Id proteins and E47 or treated with 40 μM etoposide (Sigma) for selected time periods. After transient transfection, the incidence of cell death was determined by nuclear condensation, and fragmentation was observed under a fluorescence microscope after Hoechst staining. Calculated were the percentages of cells exhibiting a rounded, shrunk morphology in the presence or absence of caspase inhibitor ZVAD-fluromethyl ketone. This assay was repeated three times.

In Vitro Protein-Protein Interaction Assays—Fusion proteins constructed of GST and 31-kDa or its mutants were expressed in Escherichia coli and purified by adsorption onto glutathione-Sepharose 4B beads (Amersham Biosciences). 35S-Labeled E47 and E12 were generated by in vitro transcription and translation using a TNT kit (Promega). The radiolabeled translation mixture was incubated with 10 μg each of the GST fusion proteins bound to the beads in binding buffer (50 mM HEPES (pH 7.5), 150 mM NaCl, 0.1% Tween, 1 mM EDTA, 2.5 mM EGTA, 10% glycerol, 1 mM dithiothreitol, 0.1 mM NaVO₄, 1 mM phenylmethylsulfonyl fluoride, and protease inhibitors). The beads were then washed extensively in the same buffer, after which the adsorbed proteins were separated on SDS-PAGE and visualized by autoradiography.

Immunoblotting—Cell extracts were prepared as described by Kook et al. (4). Proteins were separated by electrophoresis in a 10% acrylamide gel, after which Western blots were probed with anti-Cas mAb, anti-paxillin mAb, anti-Cas mAb, anti-p21 mAb, or anti-E2A antibody. Fluorescein isothiocyanate- and TRITC-conjugated goat anti-mouse and anti-rabbit secondary antibodies were used to visualize the antibodies. The derived from the exogenous gene was detected with a 1:200 dilution of antibody. Overexpressed E47 detected with a 1:50 dilution of antibody, whereas overexpressed E47 from the exogenous gene was detected with a 1:200 dilution of antibody. Fluorescein isothiocyanate and TRITC-conjugated goat anti-mouse and anti-rabbit secondary antibodies were used to visualize the primary Abs. Nuclei were visualized with Hoechst dye 33258 (Sigma).

Electrophoretic Mobility Shift Assays—For electrophoretic mobility shift assays, double-stranded oligonucleotides derived from the 5′-GCTGCGAAGC-3′ (the EcoRV site is underlined) were labeled with 7[32P]dATP using T4 polynucleotide kinase (New England Biolabs). Nuclear extracts from HeLa cells transiently transfected with expression constructs encoding E47 were prepared as described previously (22), after which they were mixed with selected doses of GST 31-kDa protein in a 10-μl final volume and incubated at 37 °C for 20 min. Binding and electrophoretic conditions were as described previously (27).
RESULTS

31-kDa Shows Higher Homology with Id Family Than bHLH Proteins—During etoposide-induced apoptosis, caspase-mediated cleavage of p130\(^{\text{cas}}\) yields 31-kDa (4). In HeLa cells 31-kDa was first detected after 12 h of etoposide treatment, after which its level continued to rise for an additional 36 h (Fig. 1A). In untreated control cells, by contrast, 31-kDa was barely detectable. The appearance of the p130\(^{\text{cas}}\) cleavage product correlated well with reductions in the levels of two other caspase-3 substrates, FAK and lamin B (Fig. 1A).

The amino acid sequence of 31-kDa is highly conserved among all members of the Cas protein family and contains an HLH domain that mediates homo- or heterodimerization with other HLH-containing proteins (19, 20). Notably, however, sequence alignment of several HLH proteins indicated that 31-kDa possesses substantially greater sequence homology with Id family proteins than with bHLH proteins such as E2A (E12/E47) and MyoD (Fig. 1C). The lack of a basic region responsible for DNA binding suggests that, like Id proteins, 31-kDa antagonizes the activity of bHLH proteins by sequestering them into an inactive state.

Translocation of 31-kDa from the Cytosol into the Nucleus—To determine the cellular distribution of 31-kDa, HeLa cells transiently transfected with a FLAG-tagged 31-kDa construct were exposed to 40 \(\mu\)M etoposide for the indicated periods. Cell lysates were immunoprecipitated with anti-Cas mAb followed by immunoblotting with anti-E47 polyAb. E, the intensity of the band corresponding to the immunoprecipitated E47 in panel D was quantified by densitometry.

**Fig. 3.** Association of 31-kDa with E47 during etoposide-induced apoptosis. A, recombinant GST-31-kDa fusion proteins overexpressed in E. coli were immobilized on glutathione-Sepharose beads, after which GST pull-down assays were carried out by incubating the beads with \(^{[35]}\)Smethylated in vitro-translated E47 and E12. Bound proteins were separated by SDS-PAGE and visualized by autoradiography. The Coomassie Blue-stained gel in the lower panel shows the integrity and equal loading of the GST-fusion proteins. B, HeLa cells were transiently co-transfected with expression plasmids containing E47 and FLAG-tagged 31-kDa. After 36 h cell lysates were immunoprecipitated (IP) using anti-FLAG mAb and visualized with anti-E47 Ab. IB, immunoblot. C, HeLa cell lysate exposed to 40 \(\mu\)M etoposide were subjected to immunoblot analysis with anti-E47 polyAb. D, HeLa cells transiently transfected with E47 were exposed to 40 \(\mu\)M etoposide for the indicated periods. Cell lysates were immunoprecipitated with anti-Cas mAb followed by immunoblotting with anti-E47 polyAb. E, the intensity of the band corresponding to the immunoprecipitated E47 in panel D was quantified by densitometry.

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This nuclear localization of 31-kDa led us to investigate whether the fragment interacts with transcription factors such as E2A. In vitro protein-protein interaction assays clearly showed that a GST-31-kDa fusion protein, but not GST alone, bound to in vitro–translated [35S]E47 and [35S]E12, yielding specific bands on autoradiography (Fig. 3A), which suggests 31-kDa interacts directly with both E47 and E12. To test whether 31-kDa interacts with E47 in vivo, FLAG-tagged 31-kDa and E47 were co-expressed in HeLa cells, after which the cell lysates were subjected to co-immunoprecipitation using selected doses of anti-FLAG mAb, and the resultant precipitate was visualized with anti-E47 Ab. That E47 was found to associate with FLAG-tagged 31-kDa (Fig. 3B) indicates 31-kDa directly interacts with E47 in vivo as well as in vitro.

To assess the biological relevance of interaction between 31-kDa and E47, we evaluated the extent to which they interact during apoptosis. HeLa cells expressed only low levels of endogenous E47, and that expression remained constant during etoposide-induced apoptosis (Fig. 3C). HeLa cells transiently transfected with E47 alone were exposed to 40 μM etoposide for the indicated times, after which the cell lysates were subjected to immunoprecipitation with anti-Cas mAb and then visualized using anti-E47 Ab. Notably, although E47 was barely detectable in the immune complexes from untreated control cells, its increased association with 31-kDa was readily apparent in etoposide-treated cells (Fig. 3, D and E), suggesting that the interaction between 31-kDa and E47 mainly occurs during apoptosis.

31-kDa Represses E2A-mediated p21Waf1/Cip1 Gene Transcription by Inhibiting DNA Binding of E2A—Given that 31-kDa and E2A co-localize in the nucleus, where they directly interact with one another, we next examined the extent to which 31-kDa affects E2A activity when co-expressed in cells. For these experiments, E2A and/or 31-kDa were co-transfected...
into either HeLa or C3H10T1/2 cells with (μE2-E5)₄-luciferase (Fig. 4A) or p21₆Galactosidase promoter-luciferase (Fig. 4, B and C) reporter genes. As expected, cells expressing E2A (E47 or E12) generated high levels of (μE2-E5)₄ luciferase activity. When E2A and 31-kDa were co-expressed, however, (μE2-E5)₄ luciferase activity was dose-dependently repressed. A similar 31-kDa-dependent repression was observed in the p21Waf1/Cip1 promoter-luciferase reporter gene assays, confirming that 31-kDa functions as an antagonist of E2A activity.

To determine whether 31-kDa would also inhibit expression of endogenous p21Waf1/Cip1, HeLa cells were transfected with E47 alone or with 31-kDa or Id2, after which p21Waf1/Cip1 expression was examined by immunostaining (Fig. 4D). Transfection with E47 clearly induced endogenous p21Waf1/Cip1 expression, but that expression was abolished by co-transfection of either 31-kDa or Id2. Given its shared homology with Id family proteins, it seems likely that 31-kDa inhibited E2A activity by forming inactive heterodimers (E2A-31-kDa) incapable of binding to DNA. To test that hypothesis, electrophoretic mobility shift assays were carried using a ³²P-labeled E-box probe of the p21Waf1/Cip1 promoter, nuclear extracts from the E47-transfected cells (E47 nuclear extracts), and a GST-31-kDa fusion protein (Fig. 4E). Incubation of the E47 nuclear extracts with the ³²P-labeled E-box probe generated the predicted E47 homodimer that efficiently bound to the E-box site. No binding activity was observed when E47 nuclear extracts were co-incubated with Id2 proteins, however. Moreover, as increasing amounts of GST-31-kDa were added to the reaction mixture containing the ³²P-labeled E-box probe and the E47 nuclear extract, the formation of DNA-bound E47 homodimeric

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**Fig. 5.** The HLH domain of 31-kDa is essential for full functional activity. A, schematic representation of various 31-kDa mutants. B, interaction of ³⁵S-labeled, in vitro-translated E47 and its deletion mutants with GST-31-kDa fusion proteins. The upper panel shows E47 protein retained by GST-31-kDa beads. The Coomassie Blue-stained gel in the lower panel confirms the integrity and equal loading of the GST fusion proteins. C, C3H10T1/2 cells were co-transfected with p21₆Galactosidase promoter-Luc reporter genes, E47, and 31-kDa or its mutants. β-Galactosidase activity was determined and used to normalize the luciferase activity. D, HeLa cells were transiently transfected GFP-p130cas, 31WT, or 31H12. Twelve hours after transfection cells were evaluated by immunostaining with an anti-GFP Ab. Hoechst staining was used as a nuclear marker; arrowheads indicate focal adhesions.
complexes gradually declined. Thus, 31-kDa appears to repress E2A activity by combining with it to form inactive heterodimers incapable of binding to DNA.

**Inhibition of E47 Activity by 31-kDa Is Mediated by Its HLH Domain**—To determine whether the 31-kDa HLH domain is necessary for its repressor activity, we first analyzed the ability of several 31-kDa deletion mutants to interact with E47 in vitro (Fig. 5, A and B). The full-length fragment (31WT) as well as fragments truncated at the N terminus and/or C terminus (31ΔN, 31ΔC, and 31HLH) were all able to interact with E47. Unfortunately, we were not able to evaluate the interaction between 31H12 (an HLH point mutant) and E47 because of the instability of GST-31H12 during protein purification. Still, deletion of the bHLH domain of E47 (E47ΔHLH) abolished its interaction with full-length 31-kDa. In addition, both the full-length fragment and the N and C terminus deletion mutants inhibited E47 transactivating activity, whereas 31H12 lacked the ability to inhibit E47 activity (Fig. 5C). Taken together,
these findings indicate that 31-kDa interacts with E47 via its HLH domain and that the HLH domain is required for the inhibitory function of the fragment.

The importance of the HLH domain for nuclear localization of 31-kDa was demonstrated by transfecting three fusion proteins, GFP-p130\textsuperscript{cas}, GFP-31-kDa, and GFP-31H12, into HeLa cells. Subsequent immunostaining with anti-GFP Ab revealed that a point mutation within the HLH domain (31H12) significantly inhibited translocation of 31-kDa from the cytoplasm to the nucleus (Fig. 5D).

31-kDa Is Sufficient to Induce Cell Death—To examine the effect of 31-kDa generation during etoposide-induced apoptosis, HeLa cells transfected with GFP constructs of either 31-kDa, p130\textsuperscript{cas} (wild-type), or p130\textsuperscript{cas}D748E, which is an uncleavable p130\textsuperscript{cas} point mutant (see Fig. 1B), were incubated with 40 \(\mu\)M etoposide for 24 h (Fig. 6A). Focal adhesions were observed at the bottoms of cells expressing p130\textsuperscript{cas}D748E but were lost from the bottoms of p130\textsuperscript{cas} transfectants and were instead localized at the cell periphery. 31-kDa transfectants displayed a complete loss of focal adhesion, which led to cell rounding, and nuclear condensation and fragmentation were also apparent. These results suggest that generation of 31-kDa through cleavage of p130\textsuperscript{cas} by caspase-3 may accelerate the disassembly of focal adhesions and the progression of etoposide-induced apoptosis.

The recent findings that the 28-kDa HEF1 fragment, which has a high sequence homology with 31-kDa, causes apoptosis and that mutation of its HLH domain significantly diminishes that effect (5, 19) raises the possibility that 31-kDa may have the ability to directly induce apoptosis. Consistent with that idea, when HeLa cells were transiently transfected with GFP-p130\textsuperscript{cas} or GFP-31-kDa, the GFP-31-kDa transfectants rounded up became refractile and floated off the plate. By contrast, cells transfected with empty vector remained normal with respect to their morphology and their ability to adhere to the plate (Fig. 6B). Immunostaining with anti-paxillin Ab revealed that the bottoms of GFP-31-kDa transfectants had fewer focal adhesions than those of GFP-p130\textsuperscript{cas} transfectants (Fig. 6C), perhaps as a result of their disassembly. As compared with cells expressing empty vector or wild-type p130\textsuperscript{cas}, a much higher percentage of cells expressing GFP-31-kDa or GFP-31H12H exhibited a morphology characteristic of apoptosis (Fig. 6D). These morphological changes were dose-dependently inhibited by the caspase inhibitor ZVAD-fluoromethyl ketone (Fig. 6E), which lends additional support to the idea that 31-kDa itself promotes caspase-mediated cell death.

Ectopic Expression of E2A and p21\textsuperscript{Waf1/Cip1} Can Rescue HeLa Cells from 31-kDa-induced Cell Death—Several lines of evidence suggest that E2A suppresses caspase-3 activation and protects cells from apoptosis (28, 29, 34). In addition, E2A activates transcription of p21\textsuperscript{Waf1/Cip1}, which is generally protective against apoptosis (39–43). During etoposide-induced apoptosis, the interaction of 31-kDa and E2A inhibited E2A-mediated p21\textsuperscript{Waf1/Cip1} transcription. This led us to ask whether overexpression of E2A or p21\textsuperscript{Waf1/Cip1} could rescue cells from 31-kDa-induced cell death. For this experiment HeLa cells were co-transfected with GFP-31-kDa and E2A (Fig. 7A) or p21\textsuperscript{Waf1/Cip1} (Fig. 7B). That transfectants expressing either E2A or p21\textsuperscript{Waf1/Cip1} exhibited less susceptibility to 31-kDa-induced cell death than cells transfected with empty vector suggests 31-kDa promotes cell death by repressing E2A-mediated p21\textsuperscript{Waf1/Cip1} transcription.

DISCUSSION

Displacement of epithelial and endothelial cells from the ECM causes them to undergo apoptosis ("anoikis") (1, 44), whereas adhesion to ECM suppresses apoptosis in mammary epithelial cells (1, 45). Cell attachment to ECM is mediated by focal adhesion complexes that link the cytoskeleton to the ECM and/or to other cells; detachment from ECM during apoptosis is promoted by caspase-mediated disassembly of these focal adhesion complexes, which is in turn closely associated with the morphological changes characteristic of apoptosis. Furthermore, because focal adhesion complexes also serve as molecular adaptors and signal transducers, their disruption may impede survival signaling or even constitute a death signal that actively contributes to apoptotic processes (2–4, 12, 13, 15, 46).

Caspase-mediated cleavage of p130\textsuperscript{cas} and the accompanying disassembly of focal adhesion complexes serve to prevent transmission of survival signals from the ECM and leads to apoptosis (4, 12, 13, 15). In addition, we previously showed that p130\textsuperscript{cas} is a substrate for caspase-3 and that its cleavage yields 31-kDa, which contributes to the loss of focal adhesion complexes and promotes apoptosis. Conversely, expression of an uncleavable p130\textsuperscript{cas} mutant attenuates the disassembly of focal adhesion complexes and the progression of apoptosis (4). Similarly, in the present study, expression of uncleavable p130\textsuperscript{cas}D748E inhibited the disassembly of focal adhesions at the bottoms of cells, whereas expression of 31-kDa elicited a complete loss of focal adhesion, cell rounding, and nuclear condensation and fragmentation during etoposide-induced apoptosis (Fig. 6A). It, thus, appears that cleavage of p130\textsuperscript{cas} to...
generate 31-kDa plays a central role in the progression of apoptosis.

Another Cas family protein, HEF1, is similarly cleaved by a
caspase into 55-, 65-, and 28-kDa fragments (19). Among those,
the 28-kDa fragment contains a HLH domain and contributes to
the induction of apoptosis. Because the amino acid sequence
of the 28-kDa HEF1 fragment is 74% similar and 57% identical
to that of 31-kDa (47), it would be reasonable to predict that the
latter also facilitates the progression of apoptosis (5, 19). And,
indeed, overexpression of 31-kDa caused the loss of cell-ECM
and cell-cell contacts and transition from a flat to a round cell
morphology, all of which are characteristic of the cleavage of
and cell death is consistent with those earlier reports. Thus, 31-kDa
likely contributes to cell death by repressing E2A-mediated
p21Waf1/Cip1 transcription. However, it remains to be deter-
mined whether 31-kDa-induced decreases in the activities of E2A and p21Waf1/Cip1
are a direct cause of cell death.

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