Hepatocyte Growth Factor/Scatter Factor Inhibits UVB-induced Apoptosis of Human Keratinocytes but Not of Keratinocyte-derived Cell Lines via the Phosphatidylinositol 3-Kinase/AKT Pathway*

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Michael Mildner†, Leopold Eckhart‡, Barbara Lengauer†, and Erwin Tschachler§§†
From the †Division of Immunology, Allergy and Infectious Diseases, Department of Dermatology, Vienna Medical School, Währinger Gürtel 18-20, A-1090 Vienna, Austria and the §Centre de Recherches et d’Investigations Epidérmiques et Sensorielles, 29521 Neuilly Seine, France

Acute irreparable UV-induced DNA damage leads to apoptosis of epidermal keratinocytes (KC) and the formation of sunburn cells, whereas less severely damaged cells survive but harbor the potential of tumor formation. Here we report that hepatocyte growth factor/scatter factor (HGF/SF) prevents UVB-induced apoptosis in primary KC cultured in vitro. When we analyzed the signaling pathways initiated by the HGF/SF receptor c-met, we found that the phosphatidylinositol (PI) 3-kinase and its downstream-element AKT and the mitogen-activated protein (MAP) kinase were activated. Inhibition of PI 3-kinase led to a complete abrogation of the anti-apoptotic effect of HGF/SF, whereas blockade of the MAP kinase pathway had no effect. In contrast to the observation with primary KC, HGF/SF could not enhance survival after UVB irradiation of HaCaT and A431 cell lines, despite the fact that in these cells the PI 3-kinase and MAP kinase pathways were also activated by HGF/SF. Cell cycle analysis of KC revealed a G2/M arrest after UVB irradiation and a complete loss of proliferating cells. Because HGF/SF in the skin is produced by dermal fibroblasts, our findings suggest that the HGF/SF-mediated rescue of KC from apoptosis represents an important paracrine loop by which UVB-damaged KC can be kept alive to maintain the epidermal barrier function but cannot further proliferate, thereby preventing the induction of epithelial skin tumors.

HGF/SF1 derived from mesenchymal cells is a multifunctional cytokine that has been shown to have a variety of effects on cells of different origin. It was first identified as a potent mitogen for hepatocytes (1, 2), and more recently it was shown to promote cell motility and proliferation of KC, melanocytes, and kidney epithelial cells (for review see Ref. 3). Furthermore, HGF/SF is able to induce scattering of cells (4) and their invasion into extracellular matrix (5), thereby promoting tumor metastasis (6, 7). Recently HGF/SF has been shown to promote or inhibit apoptosis depending on the cell type. For example, in the renal epithelial cell line HKC, HGF/SF acts as a survival factor after serum withdrawal (8, 9); it inhibits hepatocyte apoptosis in Fas-induced fulminant hepatic failure in a mouse model (10) but is able to induce apoptosis of sarcoma 180 cells (11).

The receptor for HGF/SF is a heterodimeric tyrosine kinase encoded by the c-met proto-oncogene, consisting of a 50-kDa extracellular α-subunit and a 145-kDa transmembrane β-subunit (12). c-met signaling is mediated by autophosphorylation on Tyr1349 and Tyr1356 of the β-subunit, which leads to a strong up-regulation of its kinase activity (13). As a result, a multi-functional docking site for adaptor molecules on the C-terminal tail of the β-subunit becomes phosphorylated at the tyrosine residues on position Tyr1349 and Tyr1356. Their phosphorylation leads to interaction of c-met with several cytoplasmic signal transducers. This occurs either directly, such as with the PI 3-kinase, or indirectly via molecular adapters such as Grb2 (14), She (15), or Gab1 (7), activating the MAP kinase (16) and the STAT-3 pathways (17). The MAP kinase pathway has been shown to be responsible for cell growth (14), whereas the phosphorylation of STAT-3 and the resulting nuclear signaling is required for triggering differentiation for branching morphogenesis (17). The PI 3-kinase pathway is responsible for cell scattering by inducing the loss of intercellular junctions and cell migration (18). This pathway has recently been shown to also be involved in the anti-apoptotic activity of HGF/SF in renal tubular epithelial cell line (19), in hepatocytes (20), and in NIH 3T3 fibroblasts (21).

For the skin, UV irradiation is the most important DNA damaging stimulus and represents the major risk factor for the development of epithelial skin tumors (22). Whereas mild UV-induced damage induces DNA repair, severe UV exposure leads to irreparable DNA damage resulting in KC apoptosis and the formation of sunburn cells (23, 24). It has been suggested that this UV-induced apoptosis contributes to the homeostasis of the epidermis and helps to prevent skin cancer by preferentially eliminating DNA-damaged KC (25). However, because a substantial loss of keratinocytes would result in a life-threatening damage of the skin barrier function, we are interested in mechanisms that counteract UV-induced KC apoptosis. In the present study we demonstrate that HGF/SF inhibits UV-induced apoptosis of KC and arrests them irreversibly in the G2/M phase of the cell cycle.

MATERIALS AND METHODS

Cell Culture—KC derived from normal neonatal foreskin of single donors were purchased from Clonetics (San Diego, CA). They were cultured at low calcium concentrations in KC growth medium (Clonetics) provided by the supplier (0.15 mM). The epidermoid cell line A431 and the KC-derived cell line HaCaT (26) were cultured in either KC growth medium or in RPMI 1640 (In vitrogen) supplemented with 10% fetal bovine serum (PAA, Linz, Austria), 25 mM L-glutamine (Invitro-
gen), and 1% penicillin/streptomycin (Invitrogen). 12–15 h before irradiation, KC were changed to KC basic medium (KBM; Clonetics) without growth factors. The cell lines were either changed to serum-free conditions in RPMI 1640 or to KBM. After irradiation, the culture was continued in KBM or RPMI 1640, respectively, with or without HGF/SF (20 ng/ml; R & D Systems, Minneapolis, MN). All tissue culture was performed at 37 °C in 5% CO₂ and 95% air.

**UV Irradiation**—For irradiation experiments 1 × 10⁴ cells/well were seeded in 12-well plates (Costar, Cambridge, MA) and cultured overnight in KBM or RPMI 1640 without serum. Prior to irradiation, the cells were washed twice with phosphate-buffered saline, pH 7.4 (Invitrogen). UVB irradiation was carried out as described previously (27). As a light source a Mutzhas Supersun 5000-type solar simulator (Mutzhas, Munich, Germany) filtered for the emission of UVB (290–330 nm) was used. Energy output was monitored with a IL-1700 radiometer (International Light, Newburyport, MA). Energy output was 0.7 mW/cm² at a tube to target distance of 30 cm. The cells were irradiated with 8, 16, 24, and 32 mJ/cm² of UVB under a thin layer of phosphate-buffered saline at 25 °C. For some experiments the cells were also irradiated at 4 °C. For each experiment, control cells were treated identically, except for the exposure to UV light. Immediately after irradiation phosphate-buffered saline was removed, and prewarmed basic medium or with or without HGF/SF was added. The cells were followed up to 5 days after irradiation.

**Apoptosis Detection Assays**—To quantify the extent of cell death, nonadherent cells were washed off with phosphate-buffered saline. After fixation in methanol, the remaining adherent cells were stained with methylene blue (Sigma; 0.5% in methanol). Excess methylene blue was washed out with distilled water, and the culture wells were evaluated with an inverted microscope for the presence of adherent cells. The activity of caspase-3 in cell lysates was determined according to a published protocol (28), using the synthetic caspase-3 substrate Ac-DEVD-pNA (Calbiochem, La Jolla, CA). Color development was measured on an enzyme-linked immunosorbent assay reader at 405 nm. Nucleosome release into the cytoplasm was measured with an enzyme-linked immunosorbent assay according to the manufacturer’s instructions (Roche Molecular Biochemicals).

**Western Blot Analysis**—Western blot analysis was performed as described previously (29). Briefly, 10⁴ cells were lysed in 1% Nonidet P-40 lysis buffer. After quantification with the micro-β protein quantification kit (Pierce), the proteins were size fractionated by PAGE through an 8–18% gradient gel (Amersham Biosciences) and transferred onto nitrocellulose membranes (Schleicher & Schuell). Immunodetection was performed with an anti-phospho-AKT (1 μg/ml, New England Biolabs, Beverly, MA), anti-phospho-MAP (1 μg/ml, Upstate Biotechnologies, Lake Placid, NY), and anti-c-met (1 μg/ml, Upstate Biotechnologies) monoclonal antibody, followed by a horseradish peroxidase-conjugated sheep anti-mouse IgG antisera (1:10000; Amersham Biosciences). In parallel an identical blot was reacted to an irrelevant isotype-matched monoclonal antibody as negative control. The reaction products were detected by chemiluminescence with the ECL kit (Amersham Biosciences) according to the manufacturer’s instructions. Blots were quantified using the Gel-Pro Analyzer 3.1 software.

**Inhibition of Kinases**—For the inhibition of the PI 3-kinase and MAP kinase, KC were treated with the PI 3-kinase inhibitors wortmannin (1 μM; Sigma) or LY294002 (5 μM; Sigma) or with the MAP kinase inhibitor PD98059 (5 μM; Biomol, Vienna, Austria) for 1 h prior to exposure to UVB. After UVB irradiation the prewarmed KBM was also supplemented with the kinase inhibitors. 15 h after irradiation, the cells were assayed for apoptotic cell death by light microscopy, nucleosome release, and caspase-3 activation.

**Cell Cycle Analysis**—24 and 48 h after UVB irradiation cells were incubated with bromodeoxyuridine, and 2 h later cell cycle analysis was performed using the BrdU-Flow kit (Becton Dickinson, Vienna, Austria) according to the manufacturer’s instructions.

**RESULTS**

**UV-induced Apoptosis of KC, but Not of A431 and HaCaT Cells**—Is Inhibited by HGF/SF—As shown in Fig. 1 irradiation with 16 mJ/cm² induced cell death of KC (Fig. 1B) and the KC-derived cell lines A431 (Fig. 1E) and HaCaT (Fig. 1H). The addition of 20 ng/ml HGF/SF inhibited cell death and detachment of KC (Fig. 1C), whereas no inhibition was seen with A431 (Fig. 1F) and HaCaT (Fig. 1G) cells. The induction of caspase-3 activity (Fig. 2A) and the release of nucleosomes into the cytoplasm (Fig. 2C) confirmed that both KC and KC-derived cell lines died by apoptosis. The addition of HGF/SF to UV-irradiated KC prevented nucleosome release (Fig. 2D) and caspase activation (Fig. 2B) but had no such effect on A431 (Fig. 2, B and D) and HaCaT cells (Fig. 2, B and D). The fact that HGF/SF-treated KC remained viable after UV exposure throughout the observation period of up to 5 days proved that HGF/SF was indeed able to block rather than delay apoptosis (data not shown). Inhibition of UVB-induced apoptosis in KC could be observed at HGF/SF doses as low as 1 ng/ml (Fig. 3A) and also occurred when the factor was added 2 h after exposure to UVB. No inhibition of apoptosis was observed when HGF/SF was added 4 h after UV exposure (Fig. 3B).

**The Anti-apoptotic Effect of HGF/SF Is Mediated by Signaling via PI 3-Kinase**—Three different signaling pathways, i.e. the PI 3-kinase, the MAP kinase, and the STAT-3 pathways are involved in HGF/SF signaling. Blockade of the PI 3-kinase pathway by wortmannin (Fig. 4, c and d) or LY294002 (Fig. 4, e and f) completely abolished the anti-apoptotic effect of HGF/SF after UVB irradiation (Fig. 4, d and f). By contrast, the MAP kinase inhibitor PD98059 had no effect on the prevention of UVB-induced cell death (Fig. 4, g and h). As expected from these results, wortmannin and LY294002 blocked the release of nucleosomes into the cytoplasm (Fig. 5A) and the activation of caspase-3 (Fig. 5B), whereas addition of PD98059 had no such effect. Thus HGF/SF transduces the anti-apoptotic signal via the PI 3-kinase pathway.

**c-met Is Functionally Active in Both KC and KC-derived Cell Lines**—Because A431 and HaCaT cells were not protected from UVB-induced apoptosis by HGF/SF, we asked whether these cell lines express the receptor for HGF/SF, c-met. When we analyzed the expression of c-met in KC and A431 and HaCaT cells, proteins of identical sizes, i.e. 190 and 145 kDa under nonreducing conditions and 145 and 95 kDa under reducing conditions, were detected in primary KC and both cell lines (Fig. 6). Sequence analysis of the c-met receptor revealed no differences in the sequence of the multifunctional docking site (YVH/IVN/V¹⁵⁰) between KC and KC cell lines (data not shown). To test whether c-met was functional in the KC-derived cell lines, we analyzed the phosphorylation status of AKT and MAP kinase in these cells and KC after HGF/SF stimulation. We found a strong induction of phosphorylation of both kinases in

![Fig. 1](http://www.jbc.org/)

**FIG. 1.** HGF/SF inhibits UVB-induced cell death in KC but not in KC-derived cell lines. To demonstrate the extent of apoptosis, dead cells were washed off, and surviving cells were fixed and stained with methylene blue solution 15 h after UVB irradiation. Non-irradiated cells showed no morphological changes (a, d, and g). Strong induction of cell death could be observed in KC (b), A431 (e), and HaCaT (h) after exposure to 16 mJ/cm² UVB. The addition of 20 ng/ml HGF/SF to KC (c) completely blocked UVB-induced cell death, whereas it showed no effect on the prevention of apoptosis in A431 (f) and HaCaT cells (i). One representative experiment of five is shown.
HaCaT (Fig. 7, bottom left panel) and A431 (Fig. 7, bottom right panel) cells as well as in KC (Fig. 7, top panel). The maximal induction of AKT phosphorylation was 7.4-fold in HaCaT, 4.4-fold in A431 cells, and 51-fold in KC. For MAP kinase phosphorylation, the induction was 29.8-fold in HaCaT, 10.3-fold in A431 cells, and 19-fold in KC. When the maximal levels of induction were compared between the three cell types, we found that AKT phosphorylation was 2 and 13 times stronger in KC.

FIG. 2. HGF/SF inhibits UVB-induced histone release and the activation of caspase-3 in KC but not in KC-derived cell lines. At different time points after UVB irradiation, the cell lysates were tested for caspase-3 activity (A and B) and histone release (C and D). Exposure to UVB led to caspase-3 activation (A) and nucleosome release (C) in both KC and KC-derived cell lines. The addition of HGF/SF blocked this effect in KC but not in A431 and HaCaT cells (B and D). One representative experiment of five is shown. The error bars represent one standard deviation calculated from three replicates for each set of values.

FIG. 3. Dose- and time-dependent inhibition of UVB-induced apoptosis in KC. Different concentrations of HGF/SF were added after UVB irradiation of KC. Nucleosome release of KC is depicted in A. As shown in B, the anti-apoptotic effect of HGF/SF was observed even when it was added 2 h after UVB irradiation. 4 h after exposure to UVB, the protective effect of HGF/SF was lost. One representative experiment of two is shown. The error bars represent one standard deviation calculated from three replicates for each set of values.

HaCaT (Fig. 7, bottom left panel) and A431 (Fig. 7, bottom right panel) cells as well as in KC (Fig. 7, top panel). The maximal induction of AKT phosphorylation was 7.4-fold in HaCaT, 4.4-fold in A431, and 51-fold in KC. For MAP kinase phosphorylation, the induction was 29.8-fold in HaCaT, 10.3-fold in A431 cells, and 19-fold in KC. When the maximal levels of induction were compared between the three cell types, we found that AKT phosphorylation was 2 and 13 times stronger in KC.

FIG. 4. HGF/SF prevents KC apoptosis via the PI 3-kinase pathway. The addition of the PI 3-kinase inhibitors wortmannin (c and d) or LY294002 (e and f) abrogated the anti-apoptotic effect of HGF/SF on KC (d and f). The addition of the MAP kinase inhibitor PD98059 (g and h) did not neutralize the anti-apoptotic effect of HGF/SF. a and b depict UV-irradiated KC without and with addition of HGF/SF, respectively. One representative experiment of two is shown.
HGF/SF Inhibits UVB-induced Apoptosis of KC

**Discussion**

Apoptosis is the consequence of a genetically determined cell death program that can be initiated by a number of stimuli such as growth factor withdrawal, signaling through apoptotic receptors, or cell damaging stress (for review see Ref. 30). Induction of apoptosis by DNA damaging agents plays a central role in the elimination of genetically altered cells, contributing to the inhibition of tumor development (23). In the skin UV irradiation is the most relevant DNA damaging stimulus and represents the major risk factor for the development of epithelial skin tumors (22). Whereas mild UV-induced damage induces DNA repair, severe UV exposure leads to irreparable DNA damage resulting in KC apoptosis and the formation of sunburn cells (23, 24).

In the present study, we demonstrate that UVB-induced apoptosis of human KC in primary culture is completely inhibited by HGF/SF in the absence of other growth factors. In contrast to primary KC, identical treatment had no effect on the survival of the two autonomously growing KC-derived cell lines HaCaT and A431. In our experiments, we identified the PI 3-kinase/AKT pathway as the one responsible for conferring UV resistance to KC, i.e. both wortmannin and LY294002 completely abolished the anti-apoptotic effect of HGF/SF. This part of our data complements recent data by others who have extensively studied the role of PI 3-kinase/AKT signaling in apoptosis in epithelial keratinocytes (18, 19) and in immortalized human keratinocyte cell lines (18, 20).

Our finding that HGF/SF, although protecting KC, could not prevent apoptosis of A431 and HaCaT cells was unexpected because Tang et al. (32) have recently reported that activating the PI 3-kinase pathway via β1 integrin protects A431 cells from apoptosis. Our data exclude the possibility that the lack of...
FIG. 8. Cell cycle arrest of KC after UVB irradiation with or without HGF/SF. Untreated KC and A431 cells show a normal distribution of the different stages of the cell cycle (A) that is not altered by addition of HGF/SF (B). UVB irradiation led to cell cycle arrest and a loss of the proliferative capacity in KC but not in A431 cells (C). In contrast to A431 cells, the addition of HGF/SF led to the survival of irradiated KC but showed a loss of cells in the S phase and an increase in the G2/M phase (D) comparable with the UV-only treated cells (C).
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UV-induced KC apoptosis by itself cannot merely be regarded as a harmful event but is thought to help reduce or prevent skin carcinogenesis (25, 45). Protection of KC by the inhibition of apoptosis might therefore be a double-edged sword potentially favoring the survival of cells with DNA damage. A possibility to circumvent such a harmful scenario would be that HGF/SF-protected KC enter a postmitotic state. We could show in our experiments that KC protected by HGF/SF do not further proliferate in vitro. If this holds true in vivo, these cells would be removed from the replicating population, thereby reducing the risk of transformation while keeping them alive and thus maintaining the integrity of the skin barrier. With regard to the differences observed between cells in primary culture and cell lines bearing p53 mutations, it is tempting to speculate that HGF/SF might preferentially protect nontransformed KC in vivo while leaving transformed cells to be eliminated by UV irradiation, implying a possible beneficial effect of strong UV irradiation in the removal of precancerous epithelial skin lesions.

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