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Cutaneous epidermal growth factor receptor system following ultraviolet irradiation: exploring the role of molecular mechanisms

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Summary

Background/purpose: The epidermal growth factor receptor (EGFR) pathway appears to be essential in many cutaneous disorders. It is well established that ultraviolet (UV) irradiation activates the EGFR in the animal and human skin; however, the molecular mechanisms involved in such activation remain unclear. Our aim is to review and analyse them.

Methods: Computerized search and selection of original papers in the MEDLINE database (PubMed) from 1988 to 2009 were performed. Systematic analysis and breakdown of the information selected were carried out.

Results: Full manuscripts were retrieved for 32 citations. It was proven that UV light acts directly and indirectly on EGFR (ErbB1/ErbB2) and on numerous intermediaries of extracellular and intracellular signalling. The most closely observed changes imply concentrations and/or molecular activity of the reactive oxygen species group, hydrogen peroxide, matrix metalloproteinases, p38MAPKinase, p21WAF1, p53, signal transducers and activators of transcription 3 and telomerase.

Conclusion: Our results help to clarify the working and importance of the UV-EGFR system in the human skin.

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Epidermal growth factor (EGF) and related proteins are potent mitogens in tissues of ectodermal origin, especially the skin and the cornea. They perform by means of autocrine, paracrine and endocrine routes activating its specific transmembrane receptor [epidermal growth factor receptor (EGFR)], also known confusingly as ErbB, ErbB1 and HER1, and to a lesser extent with the rest of the receptors of the same family: ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4). Upon activation by ligand, EGFR undergoes a transition from an inactive monomeric form to an active homodimer. EGFR dimerization stimulates its intrinsic intracellular activity, and as a result, autophosphorylation of several tyrosine residues occurs in the C-terminal domain of EGFRs. Downstream signalling proteins initiate several signal transduction cascades, particularly the MAPK, AKT and JNK pathways, leading to DNA synthesis and cell proliferation, as well as modulation of cell migration, adhesion and immune response. Mitogen-activated protein (MAP) kinases (MAPKs) respond to extracellular stimuli and mitogens. To date, six different groups of MAPKs have been characterized in mammals. The most important are the Extracellular signal-regulated kinases (ERK1, ERK2), c-Jun N-terminal kinases (JNKs) (MAPK8, MAPK9 and MAPK10), also known as stress-activated protein kinases (SAPKs) and p38 isoforms (MAPK11, MAPK12, MAPK13 and MAPK14). The ERK1/2 (also known as classical MAP kinase) signalling pathway is preferentially activated in response to growth factors, while both JNK and p38 signalling pathways are responsive to stress stimuli, such as cytokines and ultraviolet (UV) irradiation, and are involved in cell differentiation and apoptosis. The MAPK/ERK pathway is a very complex signal transduction and includes many protein components. One effect of MAPK activation is to alter the translation of mRNA to proteins. MAPK can phosphorylate c-myc and also regulates the transcription of the c-fos gene. Finally, the AKT protein family (also called protein kinase B), and particularly Akt1, are involved in cellular survival pathways by inhibiting apoptotic processes, and are therefore a key protein in tissue growth (1–6).

Cutaneous EGF signalling pathway involves the basal and suprabasal layers of the epidermis, sebaceous glands and the outer root sheath of the hair follicles. EGFR immunoreactivity can be localized throughout the epidermis in normal skin, although it is more accentuated in the basal cell layer. Epidermal keratinocytes are a rich source of EGFR ligands, such as EGF, TGF-α, amphiregulin, epiregulin and other EGF-like factors. Apart from direct activation by specific ligands, heterologous ligand, the dependent and independent mechanisms are also at work, as demonstrated by observation that the stimulation of a

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number of G-protein-coupled receptors result in EGFR activation, influenced via matrix metalloproteinases (MMP). EGFR-mediated proliferation and migration appear crucial in skin wound healing (7, 8).

UV radiation has been recognized as a major initiator and promoter of skin cancer. The component in sunlight that contributes most to human skin malignancy is UVB (280–320 nm) and, to a lesser extent, UVA (320–400 nm), whereas the high-energy UVC (100–280 nm) is absorbed by the earth's upper atmosphere. It is well known that UV irradiation activates EGFR and a number of other cell surface receptors through reactive oxygen species (ROS). The generation of ROS secondary to EGFR activation appears to lead to the reversible inactivation of some enzymes. Moreover, an increased EGFR activation is observed within minutes after exposure to UV light in cultured keratinocytes and in normal skin. UV irradiation excites aromatic residues, causing them to disrupt nearby disulphide bridges. The EGFR is rich in aromatic residues near the disulphide bridge and UV light generates ROS, which readily reacts with conserved cysteine residues in the active site of the protein–tyrosine phosphatases (PTP) (7, 8).

Material and methods

To summarize and quantify current evidence about the cutaneous EGFR system after UV irradiation, we conducted a systematic review of the literature from the MEDLINE database (PubMed) from 1988 to 2009. The search for and selection of abstracts were performed by two independent investigators (PMC and MTS), validating concordance using the Kappa index (κ). Key words and descriptors used were: Epidermal growth factor/EGF/epidermal growth factor receptor/EGFR/ultraviolet/UV/ultraviolet irradiation/photobiology/phototherapy/laser/laser therapy.

Results

The search strategy yielded 89 potentially relevant citations. After a careful reading of the corresponding abstracts, 57 articles that did not adjust to the aims of the study were rejected. Concordance in abstract search was $\kappa = 1$, while concordance in abstract selection was $\kappa = 0.79$. Discrepancies in selection were evaluated by agreement between both investigators. Full manuscripts were retrieved for 32 citations (9–40). The findings and results of the selected full articles are later outlined successively.

At the end of the 1980s, Yang and colleagues examined whether 8-methoxy-psoralen (8MOP) alone, or in combination with UVA (320–400 nm), influences the expression of the human EGFR gene in a human keratinocyte cell line. They found that 8MOP alone, and to a lesser extent PUVA, induce a striking increase in cellular levels of the EGFR gene at the transcriptional level (9). Furthermore, this exposure of the A431 human epidermal cell line to PUVA causes a dramatic inhibition of the stimulated EGFR system. Mermelstein *et al.* (10) suggest that PUVA-induced serine phosphorylation may mediate EGFR activity, and alterations in EGFR function may contribute to the therapeutic efficacy of PUVA in photo-chemotherapy. In the 1990s, using a KB human epithelial cell line, the inhibition of EGF binding was temperature dependent and occurred immediately following UVA light exposure, and appeared to be due to a decrease in the number of EGFR. In KB cells, EGFR binding is followed by its rapid receptosomal internalization and degradation, as we found previously in the MDA-MB-231 cell line after EGF stimulation (4, 5). Photoactivated psoralens also inhibited the internalization of EGF, but had no apparent effect on EGF metabolism. The results indicate that the cell surface membrane may be an important target for the photoactive psoralens, in agreement with many findings suggesting that the cell surface membrane is an important target for chemical photosensitizers (11).

Binding and degradation of EGF have been studied in human fibroblasts and human keratinocytes after UVA, observing a dose-dependent reduction in EGF binding. EGF binding was more affected by UVA in fibroblasts than in keratinocytes. In both cell types, the effect of UVA appeared to be related to a reduction in the affinity of the EGFR for EGF. Kinetic studies indicated that EGF is more rapidly internalized by keratinocytes than by fibroblasts, and that UVA exposure resulted in a slower decay of EGF intracellular content. UVA radiation brings about important changes in EGF processing and might participate in the light-induced degenerative processes of the skin (12). UVB injury increases prostaglandin synthesis through a tyrosine kinase-dependent pathway in response to EGFR system activation. The data indicate that antioxidant depletion induced by UVB results in tyrosine phosphorylation and activation of the EGFR (photophosphorylation). This activation may subsequently trigger epidermal phospholipase soon after UVB exposure (13). On the other hand, Laskin studied the cellular and molecular mechanisms in photochemical sensitization, as well as the mechanism of action of psoralens and UVA. Psoralens, which are potent photosensitizers, appear to induce reactions, which include alterations in epidermal cell growth and differentiation due to interactions with the EGFR system. In addition, because photoactivated psoralens modulate epidermal cell growth and differentiation, the ability of these compounds to modify the functions of the EGFR may underlie their biological activity as chemical photosensitizers (14). The importance of the EGFR system in skin photodynamic therapy (PDT) is complex and warrants a separate chapter (15).

Subsequently, Coffer and colleagues have revealed that UV illumination rapidly activates both the EGFR and the insulin receptor, as shown by the tyrosine phosphorylation of these receptors. They demonstrate that this activation is due to auto-phosphorylation as it only occurs in cells containing receptors with a functional kinase domain. They also demonstrate that in cells expressing a mutant 'kinase-dead' receptor, the UV response is inhibited, blocking MAPK activation and transcriptional inductions. Furthermore, prior stimulation of cells with UV appears to reduce further responsiveness to the addition of growth factor, suggesting a common signalling pathway. These data prove the critical significance of receptor-mediated events in regulating the response of the cells to UV exposure (16). Huang *et al.* demonstrate that UVC irradiation causes the tyrosine

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phosphorylation of EGFR in mouse NIH 3T3 fibroblasts and HC11 mouse cells. The activation of EGFR by UV is mimicked by hydrogen peroxide (H_2O_2), suggesting that ROS may function upstream of EGFR activation (17). Also, Lirvall and colleagues found that human keratinocytes display a higher basal level of EGFR mobility than human skin fibroblasts. The effect of UVB on fibroblast receptors is abolished by the prior addition of superoxide dismutase and catalase, concluding that UVB radiation of fibroblasts and keratinocytes can thus affect the biophysical properties of EGFR. The discovery that the addition of antioxidant enzymes prevented the UVB effect in fibroblasts may indicate the involvement of ROS (18).

In 1996, Rosette and Karin demonstrated that exposure to UV light induced clustering and internalization of EGFR, TNF-R and IL-1-R. Whereas the activation of each receptor alone resulted in the modest activation of c-Jun amino-terminal protein kinase (JNK), co-administration of EGF, IL-1 and TNF results in a strong synergistic response equal to that caused by exposure to UV light. UV light may perturb the cell surface or alter receptor conformation, thereby subverting signalling pathways normally used by growth factors and cytokines (19). On the other hand, Assefa and colleagues show in HaCaT cell line that UVB light is a JNK/SAPK family potent inducer of MAPK, but only a weak activator of ERKs. EGF causes rapid induction of both JNK and ERK signalling pathways, and the down-modulation of the EGF signalling pathway by EGF pre-treatment inhibits UVB-induced JNK1 activation. Prior UVB irradiation of the cells decreased the level of ERK2 activation by a subsequent EGF treatment, but this sensitized the cells and allowed for the activation of JNK1 after a re-challenge with either UVB or EGF (20). Subsequently, Peus *et al.* have shown that exposure of human keratinocytes to physiological doses of UVB radiation activates EGFR/ERK1, ERK2 and p38 signalling pathways via ROS. The authors showed that UVB exposure increases intra- and extracellular H_2O_2 production rapidly in a time-dependent manner. The findings establish a sequence of events after UV irradiation: H_2O_2 generation, EGFR phosphorylation and ERK activation (21). Moreover, the specific EGFR inhibitor, PD153035, markedly decreases UVB-induced phosphorylation of EGFR, ERK1 and ERK2, whereas p38 activation is unaffected. The data suggest that ligand-independent phosphorylation of EGFR and likely dependent downstream signalling pathways regulate cellular defence mechanisms that are important for cell survival following oxidative stress (22). Wan and colleagues show that UV-induced expression of Gadd45 (growth arrest and DNA damage protein) is mediated by an oxidant-sensitive pathway in cultured human keratinocytes and in human skin *in vivo*. Gadd45 interacts with other proteins implicated in stress responses, including p21WAF1 and p38 kinase. EGFR activation by UV is a prerequisite for the subsequent activation of NADPH oxidase and the generation of ROS. PD168393, another potent EGFR inhibitor, blocks UV-induced Gadd45 α expression. Moreover, UV irradiation activates PI 3-kinase/AKT survival pathway via EGFR in human skin *in vivo* (23, 24). The role of PDT to inhibit EGFR pathway has been shown *in vitro* and *in vivo* (25).

In 2001, Rea and Rice studied the modulation of telomerase activity in SIK human epidermal cell line (neoplastic keratinocytes) in a culture treated with EGF. In the presence of EGF, telomerase activity is maximal approximately 12 days after inoculation and then decreases considerably at confluence. In the absence of EGF, telomerase activity is increased by UV exposure, despite its suppressive effect on keratinocyte growth (26). To gain an insight into the transformation of epidermal cells into squamous carcinoma cells (SCC), Dazard and colleagues compared the response with UVB radiation of normal human epidermal keratinocytes vs. SCC. The implication of the changes in gene profile in keratinocytes appears widely related with EGFR system activity (27). On the other hand, EGFR activation is vital in the induction of cyclooxygenase-2 (COX-2) in HaCaT keratinocytes after UVB. COX-2 converts arachidonic acid into prostaglandins, responsible for inflammatory effects. Because selective inhibition of this enzyme suppressed the induction of skin tumours in mice by UV, and as UVB has been shown to induce the expression of COX-2 in skin and cells, COX-2 may be crucial for EGFR-related photocarcinogenesis of the skin (28). In skin, UVA photocarcinogenesis has shown a delayed and sustained activation of ERK. Significantly, the delayed and sustained ERK activation provide a survival signal to human HaCaT keratinocytes, which may serve as an important mechanism for cell transformation and potential skin carcinogenesis *in vivo* caused by UVA exposure (29).

In 2005, El-Abaseri and colleagues indicated the importance of the chemoprevention of UV light-induced skin tumorigenesis by the inhibition of EGFR. The UV-induced activation of EGFR promotes skin tumorigenesis by suppressing cell death, augmenting cell proliferation and accelerating epidermal hyperplasia in response to UV. These results suggest that EGFR may be an appropriate target for the chemoprevention of UV-induced skin cancer (30). In addition, they found that UV irradiation induces keratinocyte proliferation and epidermal hyperplasia through the activation of the epidermal growth factor receptor. EGFR is rapidly activated in mouse epidermis following exposure to UV, as detected by the phosphorylation of EGFR on tyrosine residues. Moreover, p53 and p21WAF1 appear to be implicated (31). Canguilhem and colleagues show that the RhoB gene, encoding a small GTPase, is involved in EGFR trafficking, cytoskeletal organization, cell transformation and survival. Inhibition of UVB-induced EGFR activation prevents RhoB protein expression and AKT phosphorylation. RhoB seems to be essential in regulating keratinocyte cell survival after UVB exposure, suggesting its potential effect in photocarcinogenesis (32). Xu *et al.* (2006), demonstrate that UV irradiation rapidly increases tyrosine of EGFR in human skin. EGFR-dependent signalling pathways drive an increased expression of MMP, whose actions fragment collagen and elastin fibres (primary structural protein components in skin connective tissue). They report that EGFR activation by UV irradiation results from the oxidative inhibition of RPTP-κ (receptor –tyrosine phosphatases-κ). RPTP-κ directly counters intrinsic EGFR tyrosine kinase activity, thereby maintaining EGFR in an inactive state. Reversible oxidative inactivation of RPTP-κ activity by UV irradiation shifts the kinase–phosphatase balance

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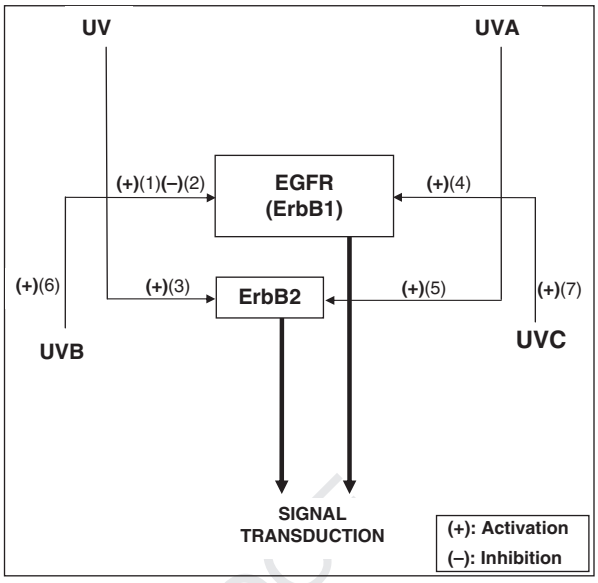
in favour of EGFR activation (33). Madson and colleagues demonstrate that UV-induced activation of ErbB2 (HER2/neu) regulates the response of the skin to UV. Inhibition or knockdown of ErbB2 before UV irradiation suppresses cell proliferation, cell survival and inflammation following UV light. In addition ErbB2 is necessary for the UV-induced expression of numerous proinflammatory genes that are regulated by the transcription factors nuclear factor-κB and Comp, and diverse enzymes and chemokines (34). It is also proven that EGFR is not activated in cells exposed to UVA in the absence of extracellular photosensitizers, and extracellular generation of H_2O_2 is responsible for the activation of EGFR by UVA irradiation (35). In skin-derived cancer cell lines, UV light may block the EGFR signalling pathway upregulating p21WAF1 (36). Signal transducer and activator of transcription 3 (Stat3) is a latent cytoplasmic protein that conveys signals to the nucleus upon stimulation with EGF and other growth factors and cytokines. It appears that EGFR system activity leads to Stat3 activation. Stat3 seems to favour skin wound healing, keratinocyte migration, hair follicle growth and resistance to UV-induced apoptosis (37).

Recently Han and colleagues have found that induction of ErbB2 by UVA irradiation plays a key role in the malignant transformation of keratinocytes. Exposure of keratinocytes to UVA has been reported previously to lead to the activation of a variety of EGFR, and ErbB2 activation is involved in skin oncogenesis (38). Very recent studies have revealed that UV-induced EGFR signal transactivation is dependent on proligand shedding by activated MMP in skin cancer cell lines (39). Moreover, UVB irradiation generates platelet-activating factor receptor (PAFR) with agonist formation involving EGFR-mediated ROS (40).

In brief, Fig. 1 illustrates the articles (references), which directly study the activity of the EGFR after UV irradiation, while Fig. 2 shows the principal molecular mechanisms investigated following UV irradiation.



(*) References
(1): 9, 16, 19, 23, 30, 31, 33, 39
(2): 36
(3): 34
(4): 25, 35
(5): 38
(6): 13,21,22,24,40
(7): 17

Fig. 1. EGFR (ErbB1) and ErbB2 after ultraviolet irradiation (UV, UVA, UVB, UVC). Wavelengths: UV (100–400 nm), UVA (320–400 nm), UVB (280–320 nm), UVC (100–280 nm).

Discussion

The EGFR signalling pathway in human skin is a major target in skin ageing and cancer. The discovery of EGF won Stanley Cohen a Nobel Prize in Physiology and Medicine in 1986, and EGF was patented for cosmetic and antiageing use by Greg Brown in 1989.

To exert its biological effects, UV photons must first be transmitted through skin layers and absorbed by a chromophore or photosensitizer. Then, a series of biological reactions are initiated (41–44). El-Abaseri and Hansen (2007) compiled nine papers on EGFR activation and UV-induced skin carcinogenesis, concluding that UV irradiation activates EGFR, increases cell cycle progression through diverse mechanisms and promotes skin tumorigenesis. In all cases, UV-induced EGFR activation increases keratinocyte proliferation, suppresses apoptosis and augments and accelerates epidermal hyperplasia in response to UV (45). Here, we aimed to specify these mechanisms at a molecular level.

p53, p21WAF1, MMP, Stat3 and telomerase activity seem to play key actions in UV-induced skin–EGFR pathway. p53 is a transcription factor that regulates the cell cycle and thus functions as a tumour suppressor that is involved in preventing cancer. As such, p53 has been described as 'the guardian of the genome', referring to its role in conserving stability by preventing genome mutation. p21WAF1 is a cyclin-dependent kinase inhibitor (CKI) that directly inhibits the activity of cyclin–CDK2 and cyclin–CDK4 complexes. It is considered that p21WAF1 functions as a regulator of cell cycle progression and its expression is controlled by the tumour suppressor protein p53. In some cases, it is expressed without being induced by p53. This kind of expression plays a significant part in p53-independent apoptosis by p21WAF1. MMPs are zinc-dependent endopeptidases capable of degrading all kinds of extracellular matrix proteins, but can also process a number of bioactive molecules. They are known to be involved in the cleavage of cell surface receptors, participating in cell migration and differentiation, angiogenesis, apoptosis and immunoregulation. Other signal events of EGFR activation involve the tyrosine phosphorylation of some Stat proteins, especially Stat3, as well as changes in telomerase activity, a reverse transcriptase related to cell immortalization, photoageing and carcinogenesis.

Psoralens and UVA treatment (PUVA) have been related to the inhibition of EGFR binding (10–12). However, UV irradiation rapidly activates EGFR in keratinocytes, fibroblast and skin cell lines, and such activation probably occurs in all cells containing receptors with a functional kinase domain (Fig. 1). Only in one study, laser-pulsed UV light inhibited EGFR activity *in vitro*, in

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malignant cells with EGFR overexpression (36). This contradictory and unexpected result needs to be confirmed.

UVA, UVB and UVC activate EGFR by two ligand-binding independent mechanisms: tyrosine photophosphorylation of the receptor (13, 16, 17), and probably, from oxidative inhibition of the RPTP-κ (32). It appears that the generation of ROS secondary to EGFR activation leads to the reversible inactivation of the crucial protein – tyrosine phosphatases – by oxidizing the catalytic cysteine in their active site. Notably, oxidative inhibition of PTP by ROS underlies EGFR activation by UV irradiation (7, 31). What appears to be well established that is UV illumination induces keratinocyte proliferation and epidermal hyperplasia through ligand-independent activation of the EGFR. The anti-apoptotic response triggered in keratinocytes after UVB seems totally driven by EGFR-activated phosphatidylinositol 3 kinase-Akt pathway (32), and represents the successful effort to overcome the variety of UV-induced proapoptotic signals (7). Indeed, rapid and sustained EGFR activation is a demonstrated event in response to UVB in keratinocytes, and plays a crucial role in UVB-induced hyperplasia and cancer. On the basis of this, El-Abaseri and Hansen propose a simple but interesting hypothesis to explain the processes through which the UV-induced activation of EGFR contributes to skin carcinogenesis. UV-radiation-induced receptor phosphorylation is increasingly recognized as a widely occurring phenomenon. UV irradiation rapidly activates EGFR and a number of other cell surface receptors through ROS-mediated inactivation of the cytoplasmic PTPs. Receptor ligand expression of EGF and EGF-like molecules, increased oxidative stress and UV irradiation are possibilities for EGFR activation. After EGFR activation, it is possible that the activation of p38, ERK1/2 and JNK, subsequently increases epidermal proliferation, hyperplasia and augments skin tumour growth. On the other hand, after EGFR activation it is possible that an activation of P13K/AKT and the subsequent suppression of apoptosis, epidermal hyperplasia and increased skin tumour growth occurs. In some cells, activation of p38, ERK1/2 and JNK increases the suppression of apoptosis (45). However, as suggested in Fig. 2, the mechanisms appear to be far more complex. ERK-dependent mechanisms may be particularly relevant to disease states in which upregulated activation of EGFR is commonly

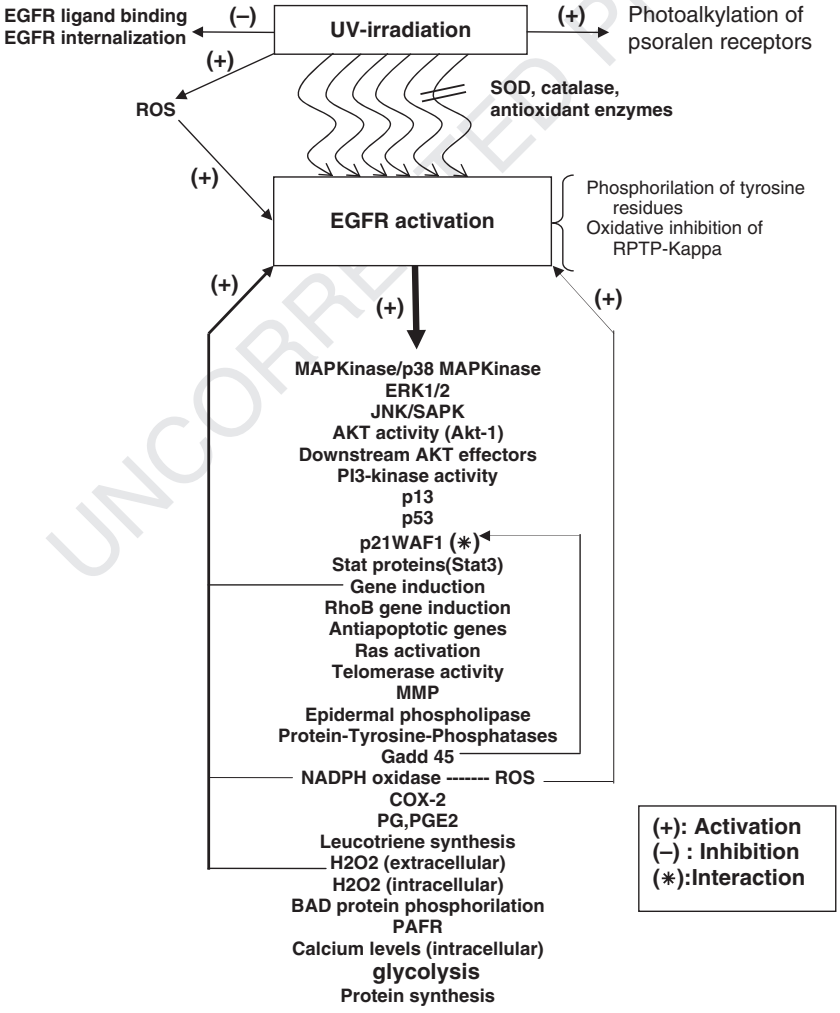

Fig. 2. Molecular mechanisms following UV-induced-EGFR signalling pathway. The chart lists the principle molecules investigated, which relate the effects of UV light to EGFR in the skin. Of note are the reactions of photoalkylation, photophosphorylation, oxidative inhibition, upregulation (positive feedback) through ROS, specific enzymatic changes and specific genetic induction (abbreviations and their meanings are explained in the text).

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observed, including wound healing, hyperproliferative skin diseases, photoageing and photo-oncogenesis. Pastore *et al.* (7) alert us to disparate mechanisms of EGFR activation. EGFR can be activated by several mechanisms under physiological or pathophysiological conditions. Apart from direct activation by specific ligands, heterologous ligand-dependent mechanisms are also at work, as demonstrated by the finding that the stimulation of a number of G-protein-coupled receptors result in EGFR activation via metalloproteinase-mediated cleavage of the mature form of EGFR ligands from membrane precursors. The tyrosine kinase activity initiates a signal transduction cascade that results in a variety of biochemical changes within the cell that ultimately lead to DNA synthesis and cell proliferation. Finally, a new article outlined in our study (July–August, 2009) demonstrates the requirement for metalloproteinase-dependent ERK and AKT activation in UVB-induced G1–S cell cycle progression of human keratinocytes. MMP enzymatic inhibitor GM6001 blocks UVB-induced ERK and AKT activation, cell cycle progression and decreases the EGFR phosphorylation, demonstrating that MMPs mediate the EGFR/ERK/AKT cyclin D1 pathways and cell cycle progression induced by UVB light (46).

Nowadays, we have an increasing number of effective small molecules of EGFR activators and inhibitors. Human recombinant epidermal growth factor (hrEGF) is effective in wound healing, and its therapeutic properties are very interesting for some skin and corneal diseases. Contrarily, EGFR inhibitors are clinically effective in enhancing the response to cytotoxic drugs of EGFR-dependent tumours, as well as in enhancing the response to PDT. The most selective compounds, which include gefitinib and erlotinib, possess a quinazoline nucleus. Broad-spectrum anti-Erb-B inhibitors, such as lapatinib or canertinib, may result in a greater efficacy and a broader spectrum of antitumour activity. Moreover, cetuximab and ABX-EGF show promise as chemotherapeutic agents (7). All these drugs, as well as other specific monoclonal anti-EGFR antibodies, represent invaluable tools for the investigation of EGFR-dependent cell events, particularly skin photo-oncogenesis and photoageing. It would be most interesting to establish an experimental model that might enable showing how commonly used solar photoprotection, which acts to filter UV irradiation, may be capable of modifying the biological response associated with EGFR. As yet, this has not been investigated either in live tissue or in sham-operated animals. In theory, one would expect a lack of EGFR activation, in spite of subjecting the tissue to UV irradiation. One may also speculate as to topical treatments with active ingredients capable of decelerating EGFR activity, that slow down cutaneous ageing in a way that is different, or synergic to that of current solar photoprotectors. The evidence analysed here would indicate that the topical use of hr-EGF for cosmetic or anti-ageing purposes may be inefficient and, moreover, contradictory and hazardous, because it would involve the continuous stimulation of the EGFR. However, the EFGR inhibitors, which are starting to be studied, may have highly effective clinical anti-ageing effects.

In conclusion, EGFR activation by UV irradiation implies a line of investigation that is of common interest to research in photodamage and photo-ageing (47). In this review, there is indication of several tens of molecules that participate in an orderly, concordant manner in EGFR signalling pathways. Based on what is known, this information provides numerous ideas with which to undertake important future research work on this subject. Without a doubt, the manipulation of the EGFR system promises huge breakthroughs in the next few years.

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