Modulation of the UVA activation of haem oxygenase, collagenase and cyclooxygenase gene expression by epigallocatechin in human skin cells

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Abstract We have investigated the modifying effects of epigallocatechin, a major polyphenolic constituent of green tea, on ultraviolet-A-activated gene expression in human fibroblasts and keratinocytes using the stress responsive enzymes: haem oxygenase-1, interstitial collagenase and cyclooxygenase-2. Although epigallocatechin strongly reduced ultraviolet-A-induced haem oxygenase-1 activation in skin-derived fibroblasts, the same compound activated collagenase and cyclooxygenase expression. In a keratinocyte cell line, ultraviolet-A-mediated haem oxygenase-1 over-expression was low and epigallocatechin failed to modulate it further. In contrast to the results with fibroblasts, ultraviolet-A activation of cyclooxygenase in keratinocytes was reduced by epigallocatechin. The results indicate that the effect of this green tea polyphenol on cellular stress responses is complex and may involve direct effects on signal transduction as well as changes that may be associated with its antioxidant activity.

Key words: Epigallocatechin; Ultraviolet-A; Hemoxygenase; Collagenase; Cyclooxygenase; Oxidative stress

1. Introduction

Polyphenols have been extensively studied as potential chemopreventive agents that could act against external inflammatory stimuli including tumour promoting agents and solar ultraviolet (UV) radiation [1,2]. Tea polyphenols also considerably decrease the mutagenicity of different types of carcinogens [3,4]. Moreover, the induction of ornithine decarboxylase and cyclooxygenase enzymes by skin tumour promoters was significantly inhibited by topical application of green tea polyphenols in SENCAR mice [5]. Green tea polyphenols, catechin, epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin gallate, are effective free radical scavengers [6], chain-breaking antioxidants [7] and scavengers of reactive nitrogen species [8]. The protective effects of green tea polyphenols have been attributed to both their antioxidant properties as scavengers of reactive oxygen species and the activation of phase II detoxifying enzymes [9,10]. Transcription factors such as those included in the AP-1 complex are also modulated by green tea polyphenols in human cell lines. In particular, it has been shown that treatment with green tea polyphenols increased mRNA levels of the immediate-early genes c-*jun* and c-*fos* in human hepatoma cells [10] and that epigallocatechin gallate down-regulated lipopolysaccharide-activated nuclear factor-κB transcription in rodent macrophages [11].

Epigallocatechin (EGC) and epigallocatechin gallate (EGCG) are the predominant catechins in green tea [12]. It has been shown previously that green tea polyphenols protected against UVB-induced skin carcinogenesis in mice [5,13,14]. It was proposed that reactive oxygen species generated by UVB play a fundamental role in the process of carcinogenesis and that green tea polyphenols acted by quenching such oxidant species [14]. The UVA component of solar radiation exerts its biological effects primarily by oxidative pathways [15] and antioxidants like the water-soluble ascorbic acid, and the lipophilic α-tocopherol and butylated hydroxytoluene are believed to act as photo-protective agents by their ability to scavenge reactive oxygen species generated during UVA irradiation [16–18]. In contrast, a recent study suggests that green tea polyphenols may have a pro-oxidant role since they lead to the generation of hydrogen peroxide in human cancer cell lines [19].

In this study, we have investigated the involvement of a major polyphenolic constituent of green tea in the regulation of UVA-activated stress response genes in human skin cells. The result show that pre-treatment with EGC can modulate the expression of haem oxygenase-1 (HO-1), cyclooxygenase-2 (Cox-2) and metalloproteinase-1 (MMP-1) in UVA-irradiated dermal fibroblasts and in UVA-irradiated transformed epidermal keratinocytes, but that the effects observed are critically dependent upon cell type and the specific stress protein examined.

2. Materials and methods

2.1. Reagents

Cell culture media and serum were purchased from Fakola (Basel, Switzerland). All chemicals and biochemicals were obtained from Sigma Chemical Company (St. Louis, MO, USA) unless otherwise indicated. Epigallocatechin was a gift from Dr Paul Quinlan, Unilever plc (Colworth Laboratories, Bedfordshire, UK).

2.2. Cell strains and culture

The human skin fibroblast cell line FEK4 was derived from a foreskin explant and cultured as described before [20]. The human oral carcinoma cell line KB [21] was kindly provided by Prof. Jean Krutmann (Heinrich-Heine-University, Dusseldorf, Germany).

2.3. Cell treatments

Cells which grew in monolayers were plated (0.5×10^5 cells/dish) in 10 cm diameter tissue culture dishes and grown to 70–80% confluency. A 3 mg/ml (10 mM) EGC stock solution was prepared in water and stored at −20°C. Where appropriate, cells were incubated overnight with 10 or 15 μg/ml (33 and 50 μM respectively) EGC prior to irradiation. For UVA treatment, medium was removed and cells were rinsed in isotonic PBS. During irradiation, cells were covered with a solution of PBS containing $CaCl_2$ and $MgCl_2$. UVA radiation was

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Abbreviations: EGC, epigallocatechin; HO-1, haem oxygenase-1; Cox-2, cyclooxygenase-2; MMP-1, metalloproteinase-1; UVA, ultraviolet-A

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provided by a broad-spectrum Uvasun 3000 lamp (Mutzhas, Munich, Germany) and the irradiance was monitored with an IL1700 radiometer. Cells were irradiated through the plastic cover of the culture dish. After irradiation, reserved medium was replaced and cell populations were incubated for various periods of time prior to RNA extraction.

2.4. Isolation and analysis of total RNA

Total RNA was isolated by the acid guanidinium thiocyanate/phenol/chloroform extraction method and subjected to Northern analysis. Twenty-five micrograms of total RNA were then loaded onto a MOPS/formaldehyde agarose gel (1.3%), electrophoresed and transferred to a sheet of Zeta-Probe Blotting (Bio-Rad, Hercules, CA, USA) membrane and hybridised to a ^{32}P-labeled cDNA probe. ^{32}P-Labeled cDNA probes for HO-1, Cox-2 and MMP-1 were prepared by random primed synthesis. Interstitial collagenase (MMP-1) cDNA was kindly provided by Dr M. Wlaschek (University of Cologne, Germany). Northern blots were also probed for glyceraldehyde phosphate dehydrogenase (GAPDH), as an internal control. RNA levels were quantified by Phosphorimager (Molecular Dynamics, Sunnyvale, CA, USA) densitometry analysis. Statistical analyses were conducted using Minitab version 11.12 (Minitab Inc., PA, USA) and statistical protocol was one-way analysis of variance (ANOVA), followed by paired Student's *t*-test.

3. Results

3.1. Protection against UVA-mediated HO-1 induction by EGC in FEK4

UVA radiation regulates several stress response enzymes in mammalian cell lines [22]. HO-1, the rate-limiting enzyme in haem catabolism, is the major gene induced by UVA radiation in human dermal fibroblasts [23]. Fig. 1A shows that overnight incubation of human dermal fibroblasts (FEK4) with 15 μg/ml EGC significantly inhibits the basal level of HO-1 gene expression ($P < 0.01$). As observed previously [23], UVA radiation strongly up-regulated HO-1 gene expression at doses of 250 and 400 kJ/m^2. Overnight pre-incubation with EGC significantly protected against UVA up-regulation. At UVA doses of both 250 kJ/m^2 and 400 kJ/m^2 we obtained a significant decrease of HO-1 gene expression at 3 and 4 h post irradiation with respect to EGC untreated cells ($P < 0.05$). UVA irradiation of epidermoid keratinocytes (KB) led to a small and variable increase in HO-1 gene expression (Fig. 1B). As shown in Fig. 1B, overnight incubation with EGC did not significantly alter UVA-induced HO-1 gene expression in KB.

Since neither EGC or its photo-degradation products absorb UVA significantly at a concentration of 15 μg/ml (50 μM) (Tyrrell, Vinicombe and Rice-Evans, unpublished results), we consider that the effect of direct UV absorption by intracellular EGC is likely to be negligible.

3.2. Increase of collagenase expression by EGC in FEK4

Another UV-activated stress response gene is interstitial collagenase (MMP-1) [24]. MMP-1 is an extracellular matrix degrading enzyme specifically involved in collagen I and III cleavage [25]. The enzyme is regulated by both UVB and UVA radiation [26,27]. In our system, a peak of interstitial collagenase expression was observed 24 h after irradiation of dermal fibroblasts with UVA, but no MMP-1 expression was manifested in KB for up to 8 h (data not shown). Pre-incubation of FEK4 with EGC produced a consistent and significant ($P < 0.05$) increase of MMP-1 over the basal level (Fig. 2). FEK4 irradiated with 250 or 400 kJ/m^2 of UVA showed no significant ($P > 0.05$) increase of MMP-1 at 3–6 h post irradiation with respect to sham-irradiated cells (Fig. 2). However, FEK4 incubated overnight with EGC and then UVA-irradiated showed an increase in MMP-1 expression similar to that obtained in sham-irradiated FEK4 pre-treated with EGC (Fig. 2).

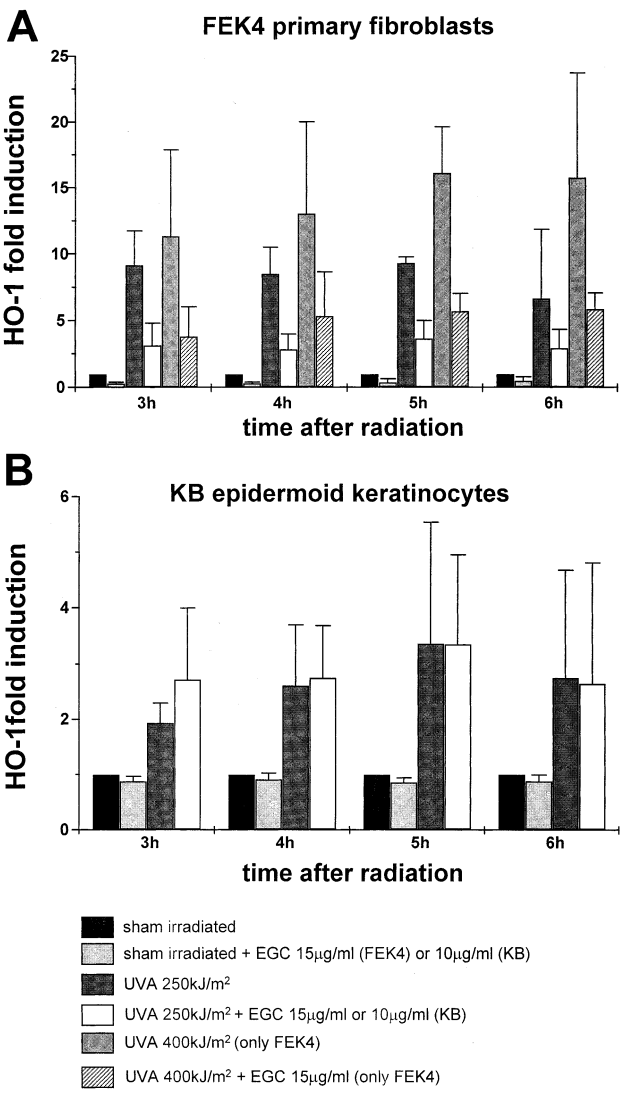

Fig. 1. Effect of EGC on UVA-mediated HO-1 mRNA accumulation in FEK4 (A) and KB (B). Cells were overnight incubated with 15 μg/ml (A) or 10 μg/ml (B) EGC and UVA-irradiated with doses of 250 (A and B) or 400 kJ/m^2 (A). The results are the mean ± S.D. of four independent experiments.

3.3. Modulation of UVA-mediated cyclooxygenase expression by EGC in FEK4 and KB

Cyclooxygenase (Cox) is a haem-containing enzyme that plays an important role in inflammation and cancer progression [28]. Cox is encoded by two related genes, Cox-1 and Cox-2 [29,30]. The Cox-1 gene is constitutively and ubiquitously expressed, while the Cox-2 gene is only expressed at high levels when cells are exposed to growth factors [31], cytokines [21,32,33] and extracellular stimuli, such as UVB radiation [21]. In both FEK4 and KB we observed an UVA-mediated induction of Cox-2 (Fig. 3). The induction was moderate (max. ~5-fold in KB) and showed a high variability due to a fluctuating basal level. Fig. 3A,B shows that

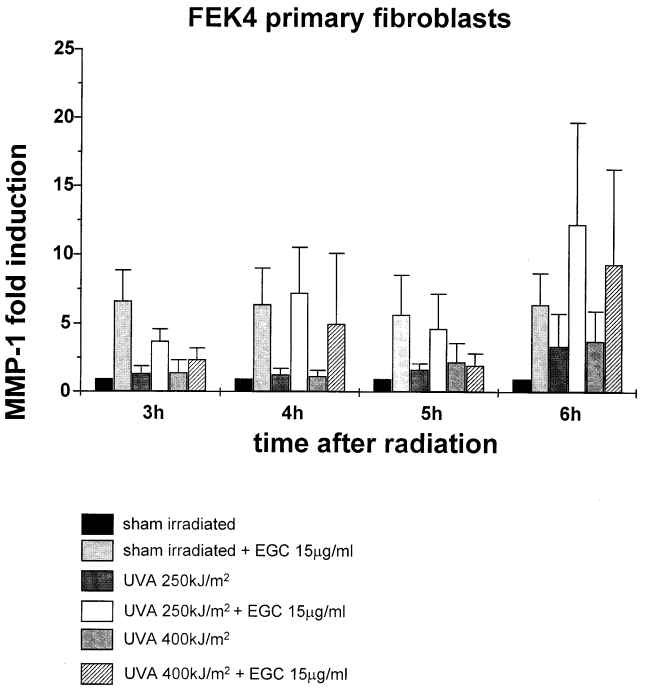

Fig. 2. Effect of EGC on UVA-mediated MMP-1 gene expression in FEK4. Cells were overnight incubated with or without 15 μg/ml EGC and UVA irradiated with doses of 250 and 400 kJ/m^2. The results are the mean ± S.D. of four independent experiments.

EGC significantly protects against UVA driven Cox-2 induction in KB. A maximal effect was observed between 4 and 6 h post irradiation at a UVA dose of 250 kJ/m^2. UVA-induced Cox-2 expression was decreased by approximately 40–50% by EGC (Fig. 3A). In fibroblasts, there was no protective effect of EGC on Cox-2 expression and, in contrast with KB cells, fibroblast populations pre-incubated with EGC showed 60–70% increases in UVA-mediated Cox-2 expression at 6 h post UVA irradiation (Fig. 3C,D).

4. Discussion

In vivo studies in rodents have shown that green tea polyphenols protect skin from both tumour-promoter [3] and UVB-induced carcinogenesis [5,14]. Several hypotheses have been proposed concerning the molecular mechanism underlying such chemoprevention. Many studies claim that green tea polyphenols exert their role through their antioxidant properties [34], while more recent papers showed that they can also act by modulating signal transduction pathways [10,35]. In the present study, we have compared the effect of epigallocatechin, a green tea polyphenol, on UVA-activated gene expression in two human skin cell lines: KB transformed keratinocytes and FEK4 primary dermal fibroblasts. Keratinocytes are the first barrier to external stimuli including solar UV radiation, and keratinocyte-derived cytokines are pivotal in mobilising leukocytes from blood and signaling other cutaneous cells [36,37]. Dermal fibroblasts are less exposed to short-wavelength solar UV (UVB) but are a target for UVA radiation which penetrates more deeply into the skin. As observed previously [38,39], regulation of gene expression by solar UV radiation in epidermal and dermal cells is very different. In particular, HO-1 gene expression, although strongly activated in dermal fibroblasts by UVA, is only weakly activated in epidermal keratinocytes if at all [40]. Also collagenase, an extracellular matrix-degrading enzyme involved in skin photo-aging and tumour cell metastasis [25], is regulated differently by UVA in different cell types. In dermal fibroblasts, UVA induces MMP-1 gene expression to high levels through a mechanism mediated by singlet oxygen [41], which in turn activates interrelated autocrine loops of interleukin-1 and interleukin-6 [42,43]. However, UVA is unable to induce collagenase production in human keratinocytes [44]. This is consistent with our results showing that in KB epidermoid keratinocytes there is neither basal or UVA-mediated expression of interstitial collagenase.

In dermal fibroblasts, HO-1 activation is mediated by the oxidative component of UVA [45] and, in particular, by UVA-mediated singlet oxygen generation [46]. It is likely that the EGC-mediated protective effect observed in UVA-irradiated fibroblasts reported here is due to its antioxidant properties [7]. Moreover, EGC, by protecting against UVA-mediated increases in HO-1 expression, may decrease both haem breakdown and the consequent enhancement in 'free' intracellular iron that participates in the generation of oxidative membrane damage [47]. The EGC-mediated decrease in basal levels of HO-1 mRNA accumulation observed in FEK4 cells (Fig. 1A) is an indication that EGC can lower the level of oxidising intermediates present in cells as a result of normal metabolism. In contrast we have observed (Fig. 1B) a lack of an effect of EGC on HO-1 levels in epidermal KB cells (for either basal or UVA-induced expression). This could be due in part to the fact that epidermis is less susceptible to oxidative stress than dermis because of its greater antioxidant capacity [48,49] that includes higher levels of intracellular glutathione [50]. This thiol has a critical role in protecting skin cells from photo-oxidative damage [50].

The dramatic increase in MMP-1 expression by EGC described in Fig. 2 adds to the complexity of understanding the role of EGC in protecting against skin damage. Skin collagenase levels regulate the integrity of the extracellular matrix and its up-regulation can cause severe damage to the connective tissue, processes that are implicated in skin aging and tumour cell metastasis. The observed increase in MMP-1 mRNA accumulation following EGC treatment of dermal fibroblasts is an indication that polyphenols can interfere with skin cell metabolism. This observation is entirely consistent with previous studies that demonstrated that c-*fos* and c-*jun* proteins are activated by green tea polyphenols in human cell lines [10]. The c-*fos* and c-*jun* heterodimeric complex binds to the AP-1 element of the promoter region of several eukaryotic genes, including human interstitial collagenase, and thereby regulates the basal level and the inducibility of collagenase by a variety of agents [51]. Green tea polyphenols also stimulate mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase 2 (ERK2) and c-Jun N-terminal kinase 1 (JNK1) in a human hepatoma cell line [10]. MAPK signaling cascades are activated by several extracellular stimuli and regulate steps of signal transduction that are involved in cellular proliferation and differentiation [52]. These findings support the hypothesis that EGC could modulate collagenase expression by activating specific signal-transduction pathways.

The effect of EGC on Cox-2 expression differed between UVA irradiated FEK4 and KB. UVA-induced Cox-2 expression was up-regulated in FEK4 that had been incubated over-

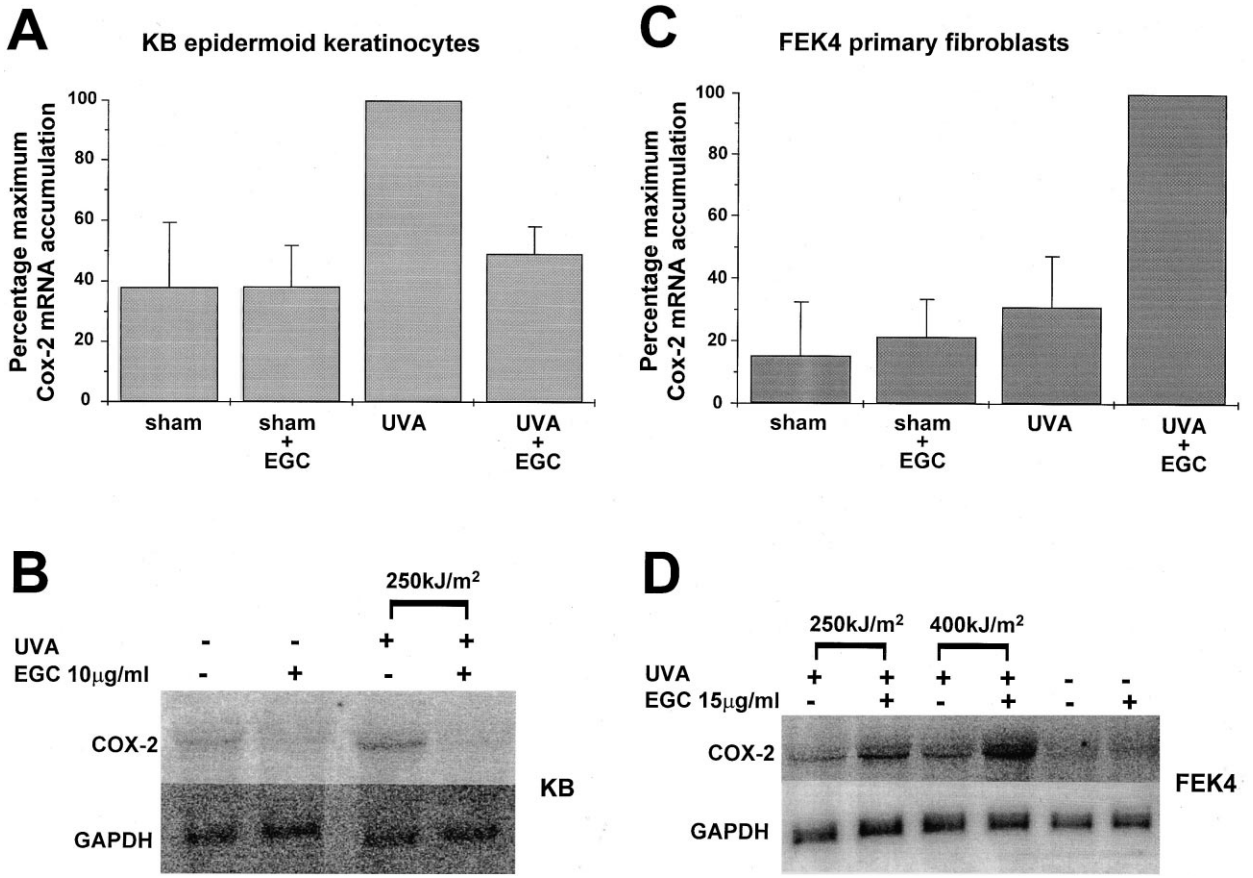

Fig. 3. Effect of EGC on UVA-mediated Cox-2 gene expression in KB (A and B) and FEK4 (C and D). Northern blots (B and D) show typical pattern of Cox-2 and GAPDH mRNA expression in the presence (+) or absence (−) of either UVA radiation or EGC. Treated cells were overnight incubated with 10 μg/ml (A and B) or 15 μg/ml (C and D) EGC and treated with 250 kJ/m^2 of UVA radiation. Total RNA was collected 4 h (A and B) or 6 h (C and D) postirradiation. Northern blots represent typical experiments. Data shown in the graphs are the mean ± S.D. of three independent experiments.

night with EGC (Fig. 3C,D), but decreased in EGC-treated KB cells (Fig. 3A,B). The protective effect observed in KB was consistent with the hypothesis proposed by Agarwal et al. [5] that green tea polyphenols prevent in vivo UV-induced cyclooxygenase activity by scavenging UV-generated free radicals. The EGC protection of UVA-mediated Cox-2 expression in keratinocytes is particularly relevant to cyclooxygenase involvement in cutaneous tumour promotion [53]. Indeed, oral administration of a cyclooxygenase inhibitor, indomethacin, to hairless mice has been shown to inhibit UV radiation-induced erythema and skin cancer [53]. Moreover, recent studies show that human squamous cell carcinoma biopsies contain higher levels of Cox-2 protein compared with normal control skin [54]. Although protection of UVA-mediated Cox-2 expression in KB is likely to be associated with an antioxidant effect of EGC, the mechanism by which EGC up-regulates Cox-2 expression in UVA irradiated FEK4 remains obscure (Fig. 3C,D).

Our results show that UVA induction of stress responses genes can be modified differentially by EGC according to cell type and have described the effect of polyphenols on gene expression in human skin cells. This in vitro model allows the investigation of a response to polyphenol treatments in cell types (skin fibroblasts and keratinocytes) that are a potential target of external stimuli such as solar UV radiation. We propose that the contrasting effects shown by EGC in altering the expression of stress response genes may reflect the ability of the compound to act both as antioxidant [7] and as a modifier of the intracellular signal transduction response [9,10,14].

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