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Review

Transcription factor Sp1 functions as an anchor protein in gene transcription of human 12(*S*)-lipoxygenase

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Abstract

The signal transduction of human 12(*S*)-lipoxygenase and the regulation of gene activation, induced by epidermal growth factor (EGF), are discussed in this review article. Treatment of human epidermoid carcinoma A431 cells with EGF induces the gene expression of human 12(*S*)-lipoxygenase, and two Sp1 binding sites residing at −158 to −150 bp and −123 to −114 bp are essential in the mediation of EGF induction of the 12(*S*)-lipoxygenase gene. EGF induces MAPK activation in cells, followed by the activation of AP1. Thus, the biosynthesis of c-Jun is enhanced, which subsequently interacts with Sp1. c-Jun on Sp1/c-Jun complex is then recruited to gene promoter through the binding of Sp1 to Sp1-binding sites on gene promoter. Subsequent transactivation of the promoter activation of the human 12(*S*)-lipoxygenase gene is induced. In addition to the functional role of Sp1 in gene regulation of 12(*S*)-lipoxygenase, recent studies have also demonstrated that Sp1 acting as an anchor protein to recruit transcription factor c-Jun is essential for growth factor and/or phorbol ester-induced expression of several genes.

Keywords: Sp1; c-Jun; Epidermal growth factor; 12(*S*)-Lipoxygenase

Arachidonate 12(*S*)-lipoxygenase (arachidonate:oxygen 12-oxidoreductase; EC 1.13.11.31) in the platelet is the first mammalian lipoxygenase discovered [1,2]. It catalyzes the transformation of arachidonic acid into 12(*S*)-hydroperoxyeicosatetraenoic acid (12*S*-HPETE), which is subsequently converted to 12(*S*)-hydroxyeicosatetraenoic acid (12*S*-HETE). There are three 12-lipoxygenase isoforms that are named after the cells that were originally discovered; i.e., platelet, leukocyte, and epidermis [3–5]. In humans, the platelet-type 12(*S*)-lipoxygenase is detected in platelets [1,2], erythroleukemia cells [6,7], skin epidermal cells [8], and epidermoid carcinoma A431 cells [9]. The biological activities of 12*S*-HETE are less studied than the metabolites formed by 5-lipoxygenase catalysis. However, 12*S*-HETE seems to play a significant role in the pathogenesis of some epidermal and epithelial inflammation. A markedly elevated 12*S*-HETE is observed in psoriatic plague, whereas the level of prostaglandins E_2 and $F_{2\alpha}$ is only minimally elevated [10]. In guinea pig skin, unequivocal growth promotion in addition to the inflammatory reaction is observed upon 12*S*-HETE activation [11]. As a result, high concentrations of 12*S*-HETE may contribute to the inflammatory changes and the abnormal epidermal hyperproliferation in the development of a psoriatic plaque. Indeed, the human 12(*S*)-lipoxygenase is overexpressed in human psoriatic lesions [12], which is accountable for the high level of 12*S*-HETE in these lesions. Both TGFα, which is the natural ligand for EGF receptors, and EGF receptors, present in keratinocytes, are also overexpressed in psoriatic skin [13,14]. The increased expression of both TGFα and EGF receptors might contribute

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to keratinocyte hyperplasia, since TGFα is a potent mitogen for keratinocytes [13]. Moreover, application of phorbol 12-myristate 13-acetate (PMA) to mouse skin also induces psoriaform hyperplasia [15]. In studying the regulation of 12(*S*)-lipoxygenase, we reported that EGF, TGFα and PMA induce expression of human 12(*S*)-lipoxygenase in A431 cells, and two Sp1-binding sequences on promoter are required for the gene activation of 12(*S*)-lipoxygenase induced by EGF, TGFα and PMA [16–18]. Although these two Sp1-binding sites residing at −158 to −150 bp and −123 to −114 bp are essential in the mediation of EGF induction of the 12(*S*)-lipoxygenase gene, the EGF response is caused neither by the increase in Sp1 biosynthesis nor by the dephosphorylation of Sp1, because no change of the binding between nuclear Sp1 proteins and promoter DNA is observed in control and EGF-treated cells [16]. We therefore speculated that Sp1 might interact with other transcription factor, which then leads to activation of the 12(*S*)-lipoxygenase gene promoter. In this review article, the signal transduction of human 12(*S*)-lipoxygenase and the regulation of gene activation, induced by EGF, are discussed.

Essential role of mitogen-activated protein kinase activation

The EGF response is mediated through the activation of mitogen-activated protein kinases [19]. The EGF increases the activation of extracellular signal-regulated kinase (ERK) and c-Jun amino terminal kinase (JNK) in a time-dependent manner. Activation of ERK and JNK could initially be observed in cells treated with EGF for 0.5 min, and the maximum response is observed in cells treated with EGF for 5 min. In order to determine whether EGF-induced expression of 12(*S*)-lipoxygenase is mediated by ERK activation, PD098059, an inhibitor of ERK signaling, is used. Pretreatment of the cells with 30 μM PD098059 significantly inhibits the EGF- and pSV-ras-induced expression of 12(*S*)-lipoxygenase mRNA. The effect of dominant negative mutants of Ras, ERK, Rac, and JNK on the EGF-induced promoter activation of 12(*S*)-lipoxygenase is then studied. Transfection of the cells with Ras, ERK2, Rac, and JNK dominant negative mutants pMMrasDN, K52R ERK2, RacN17, and mJNK all inhibit the EGF-induced promoter activation of the 12(*S*)-lipoxygenase gene in a dose-dependent manner. Transfection of the cells with a dominant negative mutant K52R ERK2 induces a more complete inhibition than that with either dominant negative mutant mJNK or RacN17. These results indicate that the Ras-ERK and Ras-Rac-JNK signaling pathways are essential for the EGF-induced expression of 12(*S*)-lipoxygenase, and the Ras-ERK pathway plays a more significant role than the Ras-Rac-JNK pathway in this EGF response.

Functional role of c-Jun induction in EGF response

The c-Jun expression induced by EGF treatment is found to play a functional role in the EGF-induced expression of the 12(*S*)-lipoxygenase gene [19]. The EGF induces the expression of both c-Jun mRNA and protein in a time-dependent manner. The maximum induction of mRNA and protein is observed in cells treated with EGF for 0.5 and 1 h, respectively, and the maximum induction of c-Jun protein persisted for at least up to 6 h after EGF treatment. The effect of transient transfection with an expression vector of c-Jun on the expression of 12(*S*)-lipoxygenase mRNA takes place in a dose-dependent manner. Overexpression of c-Jun also activates the promoter activity. Compared with the effect of the EGF response, the promoter region from −224 to −100 bp is required for the c-Jun overexpression response as well as the EGF response. Disruption of the Sp1 binding sites in this region blocked the response of c-Jun overexpression as well as the EGF response. These results indicate that both c-Jun overexpression and EGF activate the gene promoter of 12(*S*)-lipoxygenase in the same manner.

Coimmunoprecipitation of c-Jun and Sp1 in EGF-treated cells

Expression of Sp1 and c-Jun in nuclear extracts prepared cells treated with EGF for 1–9 h is studied by using immunoblot analysis [20]. No difference of Sp1 expression between control and EGF-treated cells is observed. Expression of c-Jun is observed in cells treated with EGF for 1 h and sustained at least up to 9 h after EGF treatment. Interaction between Sp1 and c-Jun is then studied by coimmunoprecipitation by using Sp1 antibodies. No change of the immunoprecipitated Sp1 between control and EGF-treated cells is observed. The coimmunoprecipitated c-Jun increases in a time-dependent manner in EGF-treated cells. A significant binding of c-Jun to Sp1 is observed in cells treated with EGF for 1 h. The binding is significantly increased in cells treated with EGF for up to 9 h. To verify further the interaction between Sp1 and c-Jun, coimmunoprecipitation is performed by using c-Jun antibodies. The immunoprecipitated c-Jun is observed significantly in cells treated with EGF for 1 h and increased significantly up to 9 h of EGF treatment. An increase in coimmunoprecipitated Sp1 is observed similar to that of the immu-

noprecipitated c-Jun, supporting the presumption that on EGF treatment, c-Jun interaction with Sp1 is enhanced.

c-Jun dominant negative mutant attenuates c-Jun/Sp1 interaction and 12(*S*)-lipoxygenase promoter activation in cells overexpressing c-Jun

The expression vector of the c-Jun dominant negative mutant TAM-67 [21] is used to study whether interaction between c-Jun and Sp1 mediates activation of the 12(*S*)-lipoxygenase gene promoter [20]. Dominant negative c-Jun expressed by vector TAM-67 is a 29-kDa protein, which is an N-terminal truncated protein of wild-type c-Jun. Its molecular mass is 10 kDa smaller than that of wild-type. c-Jun and its dominant negative mutant TAM-67 are therefore distinguishable by Western blot analysis. The polyclonal antibodies of c-Jun recognize the expression of c-Jun and its dominant negative mutant TAM-67. Expression of the dominant negative mutant TAM-67 takes place in a dose-dependent manner in cells transfected with the dominant negative vector. Coimmunoprecipitation of Sp1 and c-Jun is then performed by using Sp1 antibodies. Cotransfection of the c-Jun dominant negative vector with the expression vector of c-Jun in cells inhibits the coimmunoprecipitated c-Jun with Sp1 in a dose-dependent manner, and concurrently the dominant negative mutant protein coimmunoprecipitated with Sp1 is increased in a dose-dependent manner. Changes in c-Jun and in dominant mutant c-Jun coimmunoprecipitated with Sp1 correlate in a mirror-image fashion. These results indicate that the dominant negative mutant c-Jun induces inhibition of c-Jun/Sp1 interaction in cells overexpressing c-Jun by competing with c-Jun to interact with Sp1. The promoter activity of the 12(*S*)-lipoxygenase gene induced by c-Jun overexpression is also inhibited by the c-Jun dominant negative mutant in a dose-dependent manner.

EGF enhances the interaction between Sp1 oligonucleotide and c-Jun/Sp1

To study directly the binding of nuclear c-Jun/Sp1 with Sp1-binding sites in the 12(*S*)-lipoxygenase gene promoter, an immunoprecipitation method is developed [20]. An Sp1 oligonucleotide radiolabeled with [^{32}P]ATP is incubated with cell nuclear extract. A complex of Sp1 oligonucleotide and c-Jun/Sp1 is immunoprecipitated with agarose bearing c-Jun antibodies, and the immunoprecipitated radiolabeled Sp1 oligonucleotide is measured. Treatment of cells with EGF increased interaction between the Sp1 oligonucleotide and nuclear c-Jun/Sp1 in a time-dependent manner. A significant effect is observed in cells treated with EGF for 1 h, and a maximum increase is found in cells treated with EGF for 3 h and is sustained up to 9 h after EGF treatment.

Sp1 functions as an anchor protein to recruit c-Jun to gene promoter

Nuclear c-Jun/Sp1 binding to the Sp1 consensus sequence in the promoter seems to play a crucial role in transcriptional activation of 12(*S*)-lipoxygenase in EGF-treated cells, we thus studied the functional role of Sp1 in this process [20]. Sp1 may function as an anchor protein to recruit c-Jun to the gene promoter. To study this possibility, a chimeric promoter (pXLO-8G) consisting of 10 tandem GAL4-binding sites, which replaces the three Sp1-binding sites in the promoter of 12(*S*)-lipoxygenase, is constructed. It is then used to test promoter activation of pXLO-8G by a fusion protein consisting of GAL4 and the N terminus of c-Jun, which is overexpressed by vector pFA2-c-Jun, through the mediation of binding between the GAL4 protein and its binding sites in the chimeric promoter of pXLO-8G. A vector pFC2-dbd that overexpresses only GAL4 protein is used as a negative control in this assay system. Overexpression of the fusion protein GAL4-c-Jun induced a 1-fold increase in the promoter activity of pXLO-8G compared with control cells. EGF treatment of cells activates the effect of fusion protein GAL4-c-Jun on the promoter activity of pXLO-8G in a time-dependent manner. Treatment of cells with 50 ng/ml EGF for 6, 12, and 18 h results in 25%, 116%, and 283% increases in the stimulatory effect of GAL4-c-Jun on the promoter activity. To study the essential role of binding between GAL4 and GAL4-binding sites of promoter in transactivation of GAL4-c-Jun, pFC2-dbd overexpressing only GAL4 protein is cotransfected with the expression vector of GAL4-c-Jun for the competition of binding to GAL4-binding sites. The promoter activity of vector pXLO-8G induced by GAL4-c-Jun overexpression in EGF-treated cells is inhibited by cotransfection with pFC2-dbd overexpressing GAL4 protein. These results indicate clearly that, in EGF-treated A431 cells, c-Jun recruited to the gene promoter through mediation between GAL4 of fusion protein and its binding sites in the chimeric promoter is also able to transactivate the promoter activity of vector pXLO-8G and to support the notion that Sp1 is able to serve as an anchor protein to recruit c-Jun to the promoter to transactivate the transcriptional activity of the 12(*S*)-lipoxygenase gene.

Conclusions

Sp1 belongs to a zinc finger family of transcription factors that recognize GC-rich DNA sequence [22]. It

interacts with several transcription factors that bind to their response elements in gene promoter in the regulation of responsive genes. YY1 [23], the p65 subunit of NFκB [24], GATA1 [25], and HLTF [26] have been shown to interact functionally with the zinc domain of Sp1. In EGF-induced gene expression of human 12(*S*)-lipoxygenase, since no AP1-binding site is present in the responsive region of the gene promoter, the activation mechanism of c-Jun is, therefore, different from the other genes regulated by a transcription factor that binds to its responsive element, followed by interaction with Sp1 in the gene promoter.

AP1 is formed either by the homodimer of c-Jun or the heterodimer of c-Jun and c-Fos. We reported previously that, in the treatment of A431 cells with EGF, the expression of both c-Jun and c-Fos is induced, but the induction of c-Jun is more significant than that of c-Fos protein [19]. The maximum induction of c-Jun is observed in cells treated with EGF and then sustained for at least up to 9 h after EGF treatment. The kinetic changes in the formation of the nuclear c-Jun/Sp1 complex, and in the binding of the nuclear c-Jun/Sp1 complex to the Sp1-binding oligonucleotide are similar to the induction of c-Jun biosynthesis [20]. The maximum induction in these three parameters is observed in cells treated with EGF for 1 h and then sustained up to at least 9 h after EGF treatment. This evidence strongly supports the functional role of interaction between c-Jun and Sp1 in EGF-induced expression of the 12(*S*)-lipoxygenase gene promoter. The functional role of c-Fos in EGF-induced expression of 12(*S*)-lipoxygenase is not as evident as that of c-Jun. Although a slight induction of promoter activity of 12(*S*)-lipoxygenase is observed in cells overexpressing c-Fos, it is only one-eighth of the response of c-Jun overexpression [19,27]. In contrast to the long-term expression of c-Jun, the maximum expression of c-Fos is observed in cells treated with EGF for 1 h, but the induction then declines and almost disappears in cells treated with EGF for 6 h [14]. A plateau interaction between nuclear c-Jun and Sp1 is still present in cells treated with EGF for 6 and 9 h [20]. Therefore, the induction of c-Jun contributes more than that of c-Fos in EGF-induced expression of 12(*S*)-lipoxygenase and thus c-Fos may play a slight functional role in the interaction between nuclear c-Jun and Sp1 in the activation of the 12(*S*)-lipoxygenase gene promoter in A431 cells treated with EGF.

Our present results clearly indicate that the nuclear c-Jun biosynthetically induced by EGF in A431 cells interacts directly with Sp1 in the activation of 12(*S*)-lipoxygenase expression by EGF. Another important finding from this series of studies is the demonstration of an increase in the binding of nuclear c-Jun/Sp1 to the Sp1-binding oligonucleotide in cells on EGF treatment [20]. This evidence strongly supports our theory that recruitment of c-Jun through direct interaction with Sp1 to the gene promoter plays a pivotal role in the transactivation of 12(*S*)-lipoxygenase on EGF treatment.

Results from our continuing efforts provide an example of an intact cell system to study how c-Jun, induced by extracellular stimulators such as growth factors, cytokines, or stress signals, by cooperatively interacting with Sp1, which binds to the Sp1-binding sites of the gene promoter, directly regulates some gene expression. The signal transduction pathway of EGF-induced gene expression of the human 12(*S*)-lipoxygenase in A431 cells is given as indicated in Fig. 1. EGF induces MAPK activation, followed by the activation of AP1. Thus, the biosynthesis of c-Jun is enhanced, which subsequently interacts with Sp1. c-Jun on Sp1/c-Jun complex is then recruited to gene promoter through the binding of Sp1 to Sp1-binding sites on gene promoter. Subsequent transactivation of the promoter activation of the human 12(*S*)-lipoxygenase gene is induced. In addition to the functional role of Sp1 in gene regulation of 12(*S*)-lipoxygenase, recent studies have also demonstrated that Sp1 acting as an anchor protein to recruit transcription factor c-Jun is essential for growth factor and/or phorbol ester-induced expression of genes including nicotinic acetylcholine receptor β4 [28], cytosolic phospholipase A_2 [29], $p21^{WAF/CIP1}$ [30], human keratin 16 [31], and vimentin [32]. Functions of these Sp1-regulated genes have been well documented. Therefore, the gene activation mediated through the interaction between c-Jun

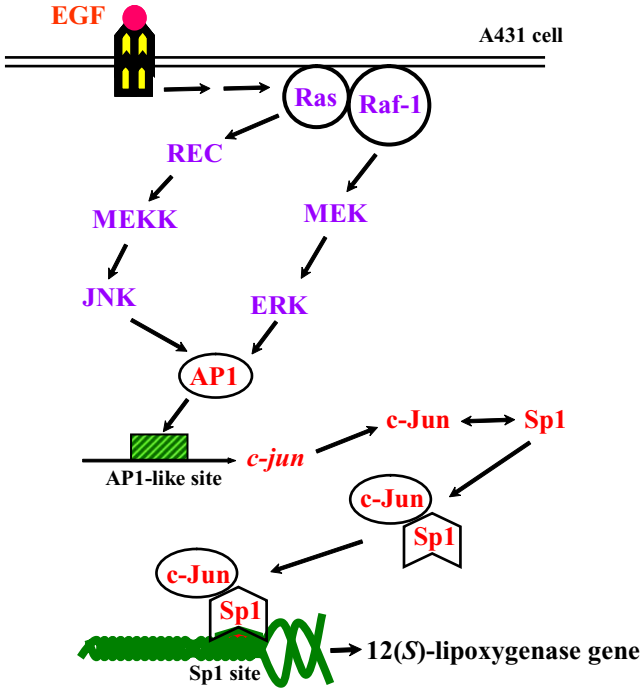

Fig. 1. Sp1 functions as an anchor protein to recruit c-Jun in gene activation of human 12(*S*)-lipoxygenase.

and Sp1 provides an important mechanism in the gene transcriptional regulation.

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