Introduction

We have previously shown that expression of platelet-derived growth factor β-receptor (PDGFRβ) is controlled during the cell cycle and the increase in c-Myc and p73α following mitogenic stimulation represses the PDGFRβ promoter (Hackzell et al., 2002; Izumi et al., 2001; Oster et al., 2000; Uramoto et al., 2004). c-Myc and p73α bind NF-Y, thereby interfering with the transcription activation independently of each other. NF-Y binds the CCAAT motif proximal to the initiation site of the PDGFRβ promoter and activates transcription (Ballagi et al., 1995; Ishisaki et al., 1997). NF-Y consists of three subunits A, B, and C (Kim et al., 1996); the B and C subunits dimerise through the conserved histone-fold motif (HFM) to interact with the A subunit (Sinha et al., 1995).

p73 belongs to the p53 tumour suppressor family existing as several C-terminal splicing isoforms with some isoforms also expressed as N-terminal deleted variants. Structurally p73 is a typical transcription factor and activates the common target genes of p53 by binding to the p53-responsive DNA sequence (Irwin and Kaelin, 2001). The N-terminal deleted variants are disrupted in the transactivation (TA) domains, acting as dominant negative molecules by competing with the full-length isoforms for DNA-binding and oligomerisation (Nakagawara et al., 2002; Zaika et al., 2002). In our previous report, the C-terminal SAM domain of p73α was shown to bind NF-YB and NF-YC, thereby interfering with the NF-Y-mediated transactivation of the PDGFRβ promoter (Hackzell et al., 2002). However, the mechanism for p73α repression of NF-Y activity has not been completely elucidated.

Several studies have demonstrated that NF-Y activation is dependent on the presence of co-activators such as p300 and P/CAF in the complex (Currie, 1998; Faniello et al., 1999). The structure of the HFM of NF-YB/YC is closely related to the α-helical structure important for the dimerisation of the histone proteins H2A and H2B (Baxevanis et al., 1995). The dimerisation domain of NF-Y forms a DNA-binding surface that associates with two related histone acetyltransferases (HAT), hGCN5 and P/CAF (Currie, 1998). p300 has been shown to interact with and acetylate NF-YB through the C-terminal region containing HAT- and bromo-domains (Li et al., 1998). Recently, Caretti et al. (Carette et al., 2003) demonstrated by using chromatin immunoprecipitation (ChIP) assays that NF-Y, HAT, histone deacetylase HDAC1/3/4 and E2F1/4/6 bind the promoters of several cell-cycle regulating molecules. These promoters typically contain CCAAT boxes.
Binding profiles of NF-Y, HAT, HDACs and E2Fs were different between these promoters, correlating with their distinct activities during the cell cycle. In the same study they also examined the PDGFβ-receptor promoter as a typical gene activated at G0. In agreement with the high expression of the PDGFβ-receptor, HDACs were not found bound at G0; however, acetylated histone 4 was observed.

In the search for the mechanism of the p73-mediated repression on PDGFRB promoter, we found that p73α competes with the binding of co-activators to NF-Y and also that p73α, but not ΔNp73α, binds HDAC1 directly. In order to determine the physiological relevance of these p73 molecules, we performed ChIP assays and compared the promoter binding status of p73 and ΔNp73 with that of p300, NF-YB and HDAC1. As expected, p73 and HDAC1 were found bound to the promoter at G0, when the expression of PDGFRB was at its lowest level. Conversely, the in vivo binding of ΔNp73 decreased at this time point, supporting our hypothesis that the co-activators are crucially involved in the p73α-mediated repression on the PDGFRB promoter.

Materials and Methods

Cell culture and drugs

NIH3T3 cells and COS-1 cells were maintained in DMEM containing 10% foetal bovine serum, 100 units/ml penicillin and 60 µg/ml streptomycin in 5% CO2 atmosphere at 37°C. Trichostatin A (TSA; Sigma) was added at a final concentration of 0.4 µg/ml at 12 hours before assay to the culture medium. The expression of PDGFβ-receptor decreases upon G0/G1 exit after serum stimulation in starved 3T3 cells (Uramoto et al., 2004). Thus, 3T3 cells were growth arrested for 48 hours after serum depletion and harvested at 0, 6, 12, 18 and 24 hours after addition of fresh medium containing 10% foetal calf serum (Carreti et al., 2003).

Plasmid constructs and antibodies

The PDGFβ-receptor promoter constructs in the pGL3 vector (Promega) are described elsewhere (Izumi et al., 2001). The P/CAF and p300 cDNA were provided by Drs Y. Nakatani (Dana-Farber Cancer Institute) and R. Janknecht (Mayo Clinic), respectively. They were used in the N-terminal haemagglutinin (HA)-tagged pcDNA3 expression vector. The Flag-NF-YA, Flag-NF-YB, Flag-NF-YC, HA-NF-YA, HA-p73α, Flag-p73α, Flag-p73αΔ424, Flag-p73αΔ269 and His-ΔNp73α are described elsewhere (Hackzell et al., 2002). The C-terminal HA-tagged HDAC1 in the pCMX expression vector was provided by Dr R. Evans (Ordentlich et al., 1999), from which GST-HDAC1 was made in the pGEX4T vector (Amersham). Antibodies used were peroxidase-coupled HA (3F10, Roche), HA (F-7, Santa Cruz), Flag (M2, Sigma), acetyl-lysine (Upstate Biotechnology), His (H-15, Santa Cruz), NF-YB (FL-207X, Santa Cruz), p300 (058X, Santa Cruz) and HDAC1 (Sigma, H3264). N-terminal p73 (H-79, Santa Cruz) was raised against the N-terminal 15 amino acids of human p73. The anti-ΔNp73 antiserum was developed by using the first 13 amino acid residues of human ΔNp73 (Sigma-Genosis). This antibody recognised only ΔNp73 without any cross-reactivity with TAp73. The TAp73-specific antibody used for immunofluorescence was raised against the N-terminal 15 amino acids (ab77, abcam).

Promoter reporter assay

The promoter reporter assay was performed as described (Hackzell et al., 2002). The total amount of DNA per well was adjusted to 1.0 µg by addition of mock DNA plasmid. Results shown were normalised to cotransfected β-galactosidase activity and were representative of at least three independent experiments.

Protein binding assay

COS1 cells were used for co-immunoprecipitation assays performed as previously described (Hackzell et al., 2002). 48 hours after transfection with various expression vectors, cells were lysed in lysis...
buffer. Lysate was centrifuged and a part of the supernatant was used for expression control of transfected plasmids. The remaining lysate was incubated with anti-HA antibody (F-7), anti-Flag M2 antibody, anti-ΔNp73 antibody, or mouse immunoglobulin (Ig), plus protein A/G agarose (Qiagen). The agarose beads were washed, separated by SDS-PAGE (10%), and blotted onto Hybond-P membrane (Amersham). The membranes were immunoblotted with anti-Flag M2 or anti-HA (3F10) antibody and developed by enhanced chemiluminescence kit (Amersham) and the signal was detected in LAS-1000 Plus.

**Immunofluorescence double staining**

Double labelling with rabbit anti-TAp73 antibody and anti-HDAC1 antibody was performed on 3T3 cells seeded at a density of 1×10^4 cells/well on eight-well chamber slides (Nalge Nunc). Cells were fixed with ice-cold methyl Carnoy’s fixative (60% methanol, 30% chloroform and 10% glacial acetic acid) for 15 minutes at 0, 6, 12 and 24 hours after serum stimulation following serum starvation for 48 hours. Cells were rinsed in ice-cold 70% ethanol and incubated in PBS containing 0.3% Triton X-100, 3% BSA, and 5% normal horse serum containing 0.3% Triton X-100, 3% BSA, and 5% normal horse serum containing 0.3% Triton X-100, 3% BSA, and 5% normal horse serum. Cells were rinsed in PBS/TS, and incubated overnight with a 1:500 dilution of sheep anti-TAp73 that recognises the N-terminal 15 amino acids of human TAp73. Biotinylated anti-sheep/goat Ig (RPN1025, Amersham Pharmacia Biotech) was used at a dilution of 1:500 as a secondary antibody and incubated for 2 hours, followed by incubation with streptavidin Texas-Red (1:1000, Jackson ImmunoResearch) for 2 hours. Following extensive washing in PBS/TS, the slides were incubated with a 1:1000 dilution of rabbit anti-HDAC1 in PBS/TS overnight and after rinsing, an Alexa488-conjugated anti-rabbit Ig (Molecular Probes) was used at a dilution of 1:1000 for 2 hours. The slides were rinsed and mounted in fluorescent mounting medium (DAKO). All incubations, except when otherwise stated, were made on ice overnight and after rinsing, an Alexa488-conjugated anti-rabbit Ig (Molecular Probes) was used at a dilution of 1:1000 for 2 hours. The slides were rinsed and mounted in fluorescent mounting medium (DAKO). All incubations, except when otherwise stated, were made on ice.
Trichostatin A (TSA) increases PDGFRB promoter activity through the CCAAT motif and attenuates its repression by p73α

In order to show that co-activators are involved in the activation of the PDGF β-receptor promoter, we used three reporter constructs: the HindIII/SacI reporter containing the CCAAT motif but lacking the upstream GC box; the SacI/SacI reporter containing both the CCAAT motif and GC box; and the SacI/SacI reporter with a mutation in the CCAAT motif. TSA treatment of NIH3T3 cells enhanced the PDGF β-receptor promoter activity regardless of the presence of the GC box. However, the reporter containing a mutation in the CCAAT motif was not activated by TSA (Fig. 1A). TSA treatment not only attenuated the repression mediated by p73α but also enhanced the PDGFRB promoter activity above control levels (Fig. 1B), confirming the presence of endogenous deacetylase activity. Transfection of p300 significantly increased the promoter activity in NIH3T3 cells only when the promoter contained the intact CCAAT motif, suggesting that NF-Y is the target of acetylation (Fig. 1C).

NF-Y binds P/CAF and p300, and p300 and p73α reciprocally regulate the PDGFB receptor promoter through the CCAAT motif in NIH3T3 cells

It has been reported that the NFYB/YC heterodimer associates with the human GCN5 and its homologue P/CAF (Currie, 1998; Li et al., 1998). Here, each of the HA-tagged expression plasmids, HA-P/CAF, HA-p300 and control HA-vector, was co-transfected with each one of the Flag-NF-YA, Flag-NF-YB and Flag-NF-YC vectors to COS-1 cells. Forty-eight hours after transfection, cells were lysed and immunoprecipitated with an anti-HA antibody and immunoblotted with an anti-Flag antibody. As shown in Fig. 2, NF-YB and NF-YC bind P/CAF, and NF-YB also binds p300. NF-YA did not bind to any of the co-activators.

Next, we investigated the relationship of p73 and p300, when they are simultaneously expressed, on the PDGF β-receptor promoter by reporter assays. Increasing the concentration of p300 resulted in a reduction of the p73α-mediated repression of the receptor promoter activity. Conversely, the coexpression of p73α decreased the promoter activity that had been enhanced by p300 in a concentration-dependent fashion (Fig. 3A). The activation by P/CAF was also completely attenuated by the additional expression of p73α. Similarly, the p73α-mediated repression was overridden by coexpression of P/CAF (Fig. 3B).

Interference of p73 on the p300-induced acetylation of NF-Y

In order to investigate the p300-induced acetylation of NF-Y, all NF-Y subunits, HA-NFYA, Flag-NFYB and Flag-YC were expressed in NIH3T3 cells together with p73α or ΔNp73α with or without HA-p300. We used HA-NFYA to distinguish from NF-YC since the sizes of NF-YA and -YC are similar, and NF-YA does not bind p73α. The immunoprecipitated NF-Y was blotted with an acetyl-lysine antibody. The acetylation of NF-Y was detected when p300 was coexpressed, and the acetylation of NF-YC was completely abolished by additional coexpression of p73α. In contrast, coexpression of ΔNp73α did not evidently alter the effect of
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p73 (Fig. 4A). Surprisingly, NF-YB was acetylated in all conditions examined, and the transfection of p300 only slightly increased the acetylation. Coexpression of p73α did not affect the acetylation of NF-YB. In order to determine whether there is a competition between p300 and p73α to bind NF-Y, we coexpressed them with increasing amounts of p73α and immunoprecipitated with a Flag-antibody that recognises NF-Y. By increasing the amount of p73α, the association of p300 with NF-YB decreased (Fig. 4B). We also examined whether p73α competes with P/CAF to bind NF-YB and -YC in the same manner (Fig. 4C,D). Again, competition was observed between p73α and P/CAF, which could be due to the proximity of their binding sites on NF-Y.

p73α binds and recruits HDAC1 to the PDGFRB-promoter, and p73α exists bound to the promoter in vivo

The potent repression exhibited by p73α on the promoter led us to question whether there are other mechanisms additional to the mere sequestration of co-activators. Coexpression and immunoprecipitation with an anti-HA antibody showed that HDAC1 binds p73α (Fig. 5A), which occurs directly as shown by bacterial fusion proteins GST-HDAC1 and HA-p73α (Fig. 5B). The C-terminal deleted p73αΔC24 and p73αΔC269, but not ΔNp73, bind HDAC1, indicating the N-terminus of p73α as the HDAC1 binding site (Fig. 5C,D). In order to observe whether p73α binds the PDGF β-receptor promoter in vivo, we ran a ChIP assay using NIH3T3 cells. PCR amplification of the proximal β-receptor promoter containing the CCAAT motif was carried out with DNA extracted from an immunocomplex with a p73α antibody. The antibody recognised the N-terminal 80 amino acids of TAp73 and had a stronger affinity with TAp73 than ΔNp73 as examined by immunoblotting (results not shown). No PDGF β-receptor promoter sequence was detected by pre-immune serum or by mouse IgG. In contrast, PCR product for the receptor promoter was enriched in the complex precipitated with the p73α antibody (Fig. 6A). However, when cells were treated with TSA the amount of PCR product was reduced in the complex precipitated with the p73α antibody. The PDGFRB promoter was activated under these conditions as shown by our luciferase assays.

p73 and ΔNp73 are recruited to the PDGFRB promoter in a cell cycle-dependent fashion

In order to determine whether the in vivo recruitment of p73 and ΔNp73 to the PDGFRB β-receptor promoter occurs in association with the activity of the promoter, we ran a ChIP assay after serum stimulation in 3T3 cells that had been arrested (Fig. 6B). In addition, the binding kinetics were compared with those of NF-Y, p300 and HDAC1, which were found to collaborate with or antagonise p73 and ΔNp73 in order to regulate the promoter activity. The expression of PDGFRB decreases upon G0/G1 exit after serum stimulation in starved 3T3 cells (Uramoto et al., 2004). In order to compare our results with those reported by Carreti et al. (Carreti et al., 2003), we chose the same time intervals that were used by these authors. The dynamics of the binding affinity of p300 resembled that of ΔNp73: weak at the start, undetectable at 6 hours, highest at 12 hours and only slightly weakened at 18 and 24 hours. NF-YB was bound to the promoter when cells were stimulated with serum, disappeared at 6 and 12 hours but reappeared at 18 and 24 hours. The amplified promoter DNA
band precipitated with a HDAC1 antibody was found to be strongest at 6 hours. The p73 antibody recognises TA,p73 more strongly, but it cross-reacts with ΔNp73, showing a distinct band at 6 hours, which was not visible with the anti-ΔNp73 antibody that efficiently recognises ΔNp73 isoforms. The amplified DNA precipitated by the anti-p73 antibody was most abundant at 12 hours, suggesting that an increased amount of ΔNp73 was precipitated together with TA,p73. The signals at 18 and 24 hours were almost at the same level or slightly stronger than that detected by the ΔNp73 antibody, indicating a decrease in the binding of TA,p73. None of these antibodies resulted in amplification of the distal promoter sequence that is located ~1.5 kb upstream. This sequence lacks CCAAT, Sp1 motifs and the initiation site. Neither mouse Ig nor pre-immune serum drawn from rabbits prior to the immunisation with the ΔNp73 peptide yielded DNA bands at any time point.

Immunolocalisation of TA,p73 and HDAC1
Double immunofluorescence staining with anti-TA,p73 and anti-HDAC1 antibodies showed an increase in TA,p73-positive cells 6 hours following serum stimulation that remained at all the following time points. TA,p73 immunostaining was seen in both the cytoplasm and nucleus. However, the nuclear staining was clearly stronger at the 6 hour time point (Fig. 7) and moved toward the cytoplasm or accumulated around the nucleus at 12 hours (result not shown). HDAC1 staining also increased after serum stimulation, which localised exclusively in the nuclei and remained during all time points. Thus, the number of cells expressing both molecules in the nucleus was at its highest at 6 hours. Closer observation of the nuclear staining of TA,p73 and HDAC1 by confocal microscopy
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Discussion

Here we examined the mechanism behind the p73-mediated transcriptional repression on PDGF β-receptor promoter. In our previous study NF-Y was found to be the target of p73α in the repression (Hackzell et al., 2002). In recent years, it has become evident that the activity of NF-Y is strongly regulated by its modification by HAT and HDAC. We have confirmed here the interaction of NF-Y with co-activators and we also propose a mechanism for the action of p73α on the activation of NF-Y. Firstly, p73α competes with p300 and P/CAF to bind NF-Y, and secondly, p73 inactivates NF-Y by recruitment of HDAC1. This competitive binding was demonstrated by co-immunoprecipitation assays, supporting the competition observed in our luciferase assays. The heteromerisation domains of NF-YB and -YC are necessary for the P/CAF interaction (Li et al., 1998) and YB binds the central to the C-terminus of p300 and is a target for acetylation (Faniello, 1999). As the C-terminus of the heteromerisation domains of NF-YB and -YC are the binding sites of p73α, it is likely that this competition could actually occur in vivo (Hackzell et al., 2002). P/CAF interacts directly with p300 (Currie, 1998), suggesting that both P/CAF and p300 can build a complex with NF-Y.

It has been reported that co-activators increase protein stability by acetylation (Grönroos et al., 2002; Zeng et al., 2001). However, we could not see such effects on NF-Y as judged by their expression kinetics following cyclohexamide treatment (data not shown). This is somewhat analogous to the situation where the N-terminus of p300 was shown to bind p73 in competition with MDM, which does not degrade p73 unlike p53 (Zeng et al., 2001). p300 can stimulate p73-mediated transcription without involving its intrinsic acetylase activity. Similarly, in the case of PDGFRB promoter repression, acetylation of p73α is dispensable as the acetylation-defective p73α mutant retained the activity (data not shown). It was also reported that acetylation of p73 is not a requirement for the transcriptional activity (i.e. necessary for

Fig. 6. p73α and acetylated proteins were found to be bound in vivo to the promoter. (A) Chromatin extracted from 3T3 cells treated with or without Trichostatin A (TSA) was immunoprecipitated with p73α antibody, acetyl-lysine antibody, or pre-immune serum. DNA was purified and analysed by PCR together with whole cell lysate (input), using primers specific for the proximal and distal areas of the PDGFRB promoter. (B) Chromatin was extracted from cells harvested at indicated time points following serum stimulation after being cultured in serum-free media for 48 hours. Samples were immunoprecipitated with antibodies against p73α, ΔNp73, NF-YB, p300 and HDAC1, respectively and DNA was detected as described above. Primers for the proximal promoter sequence were used as controls.

Fig. 7. Nuclear colocalisation of TAp73 and ΔNp73. (A-C) Double immunofluorescence labelling of 3T3 fibroblasts 6 hours after serum stimulation with anti-TAp73 antibody (A, red) and anti-HDAC1 antibody (B, green), and the merged image (C). The majority of cells in this field express both molecules in the nucleus. Bar, 5 μm.
p21 transcription) but is dispensable for transcription of the proapoptotic gene, p53AIP1 (Costanzo et al., 2002). In the case of PDGF receptor regulation, NF-Y seems to be a common target for p300 and p73α. In fact, we found a marked decrease of p73 bound to the promoter after the treatment of cells with TSA, a potent deacetylase inhibitor, implying that p73 is bound when acetylation of the promoter is weak.

Recently, it was shown using ChIP assays that NF-Y, HAT, HDAC1/3/4 and E2F1/4/6 bind the promoters of several cell-cycle regulating molecules (Caretti et al., 2003). These promoters typically contain CCAAT boxes. Binding profiles of NF-Y, HAT, HDACs and E2Fs were different for the examined promoters, correlating with their differential activities during the cell cycle. They also examined the PDGFRB promoter as a typical gene activated in G0 (Caretti et al., 2003). In concord with the high expression of the PDGF β-receptor, HDACs were not found bound at G0, but acetylated H4 was observed. Soon after serum stimulation following starvation, histones were deacetylated and HDAC1 and HDAC4 were found. Interestingly, NF-YB was found to bind at all time points examined except at 6 hours after serum stimulation. However, the mechanism behind the distinct binding profile has not yet been demonstrated.

p73α prevents the transcriptional activation induced by the co-activators by competing for the interaction with NF-Y. NF-YB seems to be constitutively acetylated and thus less sensitive to the effect of p73α compared to NF-YC (Fig. 4). NF-YB contains a very short stretch of TA, whereas NF-YC has the largest TA of the three subunits. Therefore, NF-YC may be the most important subunit controlling the activity of the transcription as proposed previously (Izumi et al., 2001). As all three subunits are needed for DNA binding, changes in the acetylation state of NF-YC would affect the binding affinity of the complex. The ability of p73 to inhibit NF-YC acetylation led us to question whether p73 might recruit HDAC. The coexpression and immunoprecipitation as well as the interaction using bacterial GST-proteins revealed that HDAC1 binds p73 but not ΔNp73. The binding of HDAC1 could be the reason why coexpression of p73 not only attenuates the p300-mediated activation but also further suppresses the promoter activity. The recruited HDAC1 may also deacetylate histones around the promoter. As ΔNp73α can bind NF-Y in competition with p73α without recruiting HDAC1 and can also sequester p73 by heterodimerisation, ΔNp73 may act as a dominant negative molecule.

Our ChIP assays with antibodies against NF-YB, p300 and HDAC1 essentially agreed with the results shown by others (Caretti et al., 2003), suggesting that HDAC1 might release the NF-Y complex from the promoter. Moreover, a dynamic correlation between the binding of p73/ΔNp73 and that of the above-mentioned molecules was demonstrated. Hence, at G0/G1 exit the promoter chromatin was precipitated by the anti-p73 antibody, but not by the ΔNp73-specific antibody, implying that p73 is a physiological regulator of the PDGF β-receptor promoter. Following G0/G1 exit, p73 is induced by c-Myc (Zaika et al., 2002) and recruits HDAC1 to the NF-Y complex, resulting in the inactivation and release of NF-Y from the promoter. The nuclear colocalisation of TAp73 and HDAC1 was confirmed by double immunofluorescence staining, supporting presence of an endogenous interaction. At the 12 hour time point, TAp73 moved out and accumulated around the nucleus, in agreement with the increase and interaction of ΔNp73 with the chromatin.

p73α, but not other isoforms lacking the SAM domain, interferes with NF-Y. However, p73α and p73β are the only isoforms expressed in normal tissues (Ikawa et al., 1999) and p63α, which is expressed in epithelial cells (Koster and Roop, 2004), also binds NF-Y to repress the PDGF β-receptor (results not shown), suggesting that this control mechanism is physiologically important. According to a report published recently (Liu et al., 2004), ΔNp73α has different and seemingly opposite functions to ΔNp73α in certain cellular conditions, such as induction of growth arrest and apoptosis, underlining the importance of the existence of the various C-terminal p73 isoforms. The ΔNp73 is induced by p73, acting as a negative feedback molecule (Grob et al., 2001; Kartasheva et al., 2002; Nakagawara et al., 2002) and antagonises p73. We report here that ΔNp73α competes with the binding of TAp73α to NF-Y, resulting in activation of an NF-Y complex by allowing the co-activators to rebind to NF-Y upon further progression of the cell cycle. Our results support the notion that p73α acts as a physiological repressor for the PDGF β-receptor promoter and that negative regulators may play important roles for this promoter.

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