PERGAMON

Vision Research 39 (1999) 2511–2518

Vision Research

# Differential DNA binding activities of the transcription factors AP-1 and Oct-1 during light-induced apoptosis of photoreceptors

Farhad Hafezi [a,*], Andreas Marti [b], Christian Grimm [a], Andreas Wenzel [a], Charlotte E. Remé [a]

[a] *Department of Ophthalmology, University Hospital, Frauenklinikstrasse 24, CH-8091 Zurich, Switzerland*
[b] *Laboratory for Clinical and Experimental Research, University of Bern, 3004 Bern, Switzerland*

Received 8 May 1998; received in revised form 17 November 1998

**Abstract**

The activity of transcription factors like AP-1 and Oct-1 is critical for the regulation of gene expression. Whereas Oct-1 mainly regulates the expression of housekeeping genes, AP-1 is often involved in cellular responses to external stimuli and plays an essential role in the regulation of light-induced apoptosis of mouse retinal photoreceptors. In this study, we investigated AP-1 and Oct-1 DNA binding activity and AP-1 complex composition in the mouse retina during light-induced photoreceptor apoptosis. AP-1 DNA binding activity was low in dark-adapted animals but was transiently elevated within 12 h after exposure of mice to apoptosis-inducing levels of white fluorescent light. Maximal AP-1 activity was found 6 h after light-exposure. Antibody interference analysis at 6 h after damaging light exposure and under normal light conditions revealed that the major fraction of AP-1 consists of c-Fos/JunD heterodimers in both situations. In contrast to AP-1, Oct-1 DNA binding activity was maximal in dark-adapted animals and was reduced during photoreceptor apoptosis. Transient induction of AP-1 (c-Fos/JunD) and inactivation of Oct-1 may be crucial events for light-mediated apoptosis of retinal photoreceptors. 

*Keywords:* AP-1; Oct-1; Apoptosis; Mouse retina; Transcription factor

## 1. Introduction

Cell death by apoptosis is involved in a wide range of physiological and pathological processes such as developmental morphogenesis as well as cancer, autoimmune and neurodegenerative diseases. Apoptosis is morphologically defined by membrane blebbing, chromatin and cytoplasm condensation and fragmentation of the cell body. In the retina, death by apoptosis is the common fate of retinal photoreceptors in many forms of human and animal dystrophies and degenerations (Chang, Hao & Wong, 1993; Portera-Cailliau, Sung, Nathans & Adler, 1994; Lolley, Rong & Craft, 1994; Li & Milam, 1995). To date, little is known about the molecular regulation and execution of apoptotic cell death in photoreceptors.

AP-1 is a dimeric transcription factor consisting of members of the Fos family (c-Fos, FosB, Fra-1, Fra-2) and the Jun family (c-Jun, JunB, JunD) of proteins (Hai & Curran, 1991). AP-1 binds to defined DNA sequences (called TRE and CRE) present in the regulatory regions of many viral and cellular genes (Curran & Franza, 1988; Hirai, Bourachot & Yaniv, 1990; Macgregor, Abate & Curran, 1990; DiPolo, Lerner & Farber, 1997). Fos and Jun protein expression is upregulated during diverse cellular processes such as induction of proliferation (Angel & Michael, 1991; Morgan & Curran, 1995), stress responses including exposure to UV (Schreiber, Baumann, Cotten, Angel & Wagner, 1995) and ionizing radiation (Haimovitz Friedman, Kan, Ehleiter, Persaud, McLoughlin, Fuks & Kolesnick, 1994) or during apoptosis in a number of different systems (Colotta, Polentarutti, Sironi & Mantovani, 1992; Smeyne, Vendrell, Hayward, Baker, Miao, Schilling, Robertson, Curran & Morgan, 1993; Estus, Zaks, Freeman, Gruda, Bravo & Johnson, 1994;

* Corresponding author. Tel.: +41-1-255-37-19; fax: +41-1-255-44-38.
*E-mail address:* hafezi@opht.unizh.ch (F. Hafezi)

0042-6989/99/$ - see front matter 
PII: S0042-6989(98)00313-7

Marti, Jehn, Costello, Keon, Ke, Martin & Jaggi, 1994; Agarwal, Patel, Brun & Nir, 1995; Bossy Wetzel, Bakiri & Yaniv, 1997; Hafezi, Steinbach, Marti, Munz, Wang, Wagner, Aguzzi & Reme, 1997).

The Oct-1 protein is a ubiquitous transcription factor of the POU-homeo family of proteins which is involved in the regulation of housekeeping genes such as the histone H2B and small nuclear RNA genes (Fletcher, Heintz & Roeder, 1987; Sturm, Dalton & Wells, 1988). The inactivation or degradation of the Oct-1 protein during apoptosis has been described for various cell culture systems and in vivo (Sikora, Grassilli, Radziszewska, Bellesia, Barbieri & Franceschi, 1993; Marti et al., 1994). However, whether the loss of Oct-1 activity represents a general and significant process in apoptosis remains an open issue.

Little is known about the role of transcription factors such as AP-1 and Oct-1 in retinal development, the maintenance of retinal function or the pathogenesis of retinal diseases. The AP-1 member c-Fos is expressed in a diurnal manner and can be evoked by light pulses (Nir & Agarwal, 1993; Yoshida, Kawamura & Imaki, 1993). Furthermore, we have shown recently that *c-fos* is essential for light-induced photoreceptor apoptosis in the mouse retina in vivo (Hafezi et al., 1997).

In this study, we have analyzed Oct-1 and AP-1 DNA binding activities and AP-1 complex composition during light-induced photoreceptor apoptosis and under normal light conditions in the mouse retina. We found that AP-1 was transiently activated after damaging light exposure, mainly as a c-Fos/JunD complex, and to a lesser extent as an AP-1 complex consisting of c-Jun, JunB and possibly other Fos members. Oct-1 was found to have high DNA binding activity in dark-adapted mice. After light exposure, Oct-1 DNA binding activity decreased remarkably over a 12 h time period.

## 2. Methods

### 2.1. Animals

All procedures concerning animals in this study adhered to the ARVO resolution for the care and use of animals in Vision Research. Experimental animals were bred on a C57BL/6x129Sv background and maintained in a 12:12 light–dark cycle (lights on at 06:00 h) with 10–20 lux within the cages.

### 2.2. Light exposure

Male mice 4–6 weeks old were dark-adapted for 36 h and the pupils of all experimental animals were dilated with cyclopentolate 0.5% (Alcon Pharmaceuticals, Cham, Switzerland). Animals were either immediately killed or exposed to 5000 lux of diffuse, cool, white fluorescent light for 2 h. During illumination, particular care was taken that the eyes were evenly illuminated. Other groups of mice were taken from the regular light–dark cycle and killed at the end of the light period at 18:00 h. Mice were anaesthetized with $CO_2$ and killed by cervical dislocation at the following times: immediately after light exposure or after a period of 6 or 12 h in darkness which followed the 2 h light exposure. Eyes were rapidly enucleated, fixed in 2.5% glutaraldehyde for 12 h, dehydrated and processed for light microscopic analysis or the retinas were isolated and immediately frozen in liquid nitrogen for preparation of nuclear extracts.

### 2.3. Preparation of nuclear extracts

Nuclear extracts were prepared as described previously (Marti et al., 1994). Briefly, one retina was homogenized in 200 μl of buffer A (10 mM Hepes–KCl, 1 mM β-mercapto-ethanol, 1 mM DTT) in the presence of protease inhibitors (5 μg $ml^{-1}$ leupeptin, aprotinin, antipain, chymostatin, and pepstatin, 5 mM benzamidin, 1 mM aminohexaenoic acid, 0.125 mM PMSF). After incubation on ice for 10 min the homogenate was vortexed for 10 s and centrifuged. The supernatant was discarded and the pellet was resuspended in 50 μl buffer C (20 mM Hepes–potassium hydroxide pH 7.9, 25% glycerol, 420 mM NaCl, 1.5 mM $MgCl_2$, 0.2 mM EDTA, 1 mM β-mercaptoethanol, 1 mM DTT) in the presence of protease inhibitors (see above), and incubated on ice for 10 min. Resuspension was enhanced by pipetting the pellet several times. Cellular debris was removed by centrifugation at $23\,000 \times g$ for 30 min at 4°C. Protein concentration was determined using the Bradford protein assay (Bio-Rad) with BSA as standard.

### 2.4. EMSA

Electrophoretic mobility shift assay (EMSA) was performed as described previously (Marti et al., 1994). Briefly, the oligonucleotides coding for an AP-1 specific (5′-AAG CAT GAG TCA GAC AC-3′) or an Oct-1 specific (5′-CGG GTT AA T TTG CAT AGG GAG T-3′) DNA binding sequence were labeled using polynucleotide kinase (Boehringer Mannheim, Germany) and $^{32}$P-γATP. For EMSA, 2 μg nuclear extract was incubated in 25 μl incubation buffer (5 mM $MgCl_2$, 0.1 mM EDTA, 0.75 mM DTT, 7.5% glycerol, 0.05% NP-40) containing 8 μg BSA and 2 μg poly d(I-C). After incubation on ice for 20 min radiolabeled oligonucleotide was added and incubation was continued for another 20 min. Protein/DNA complexes were

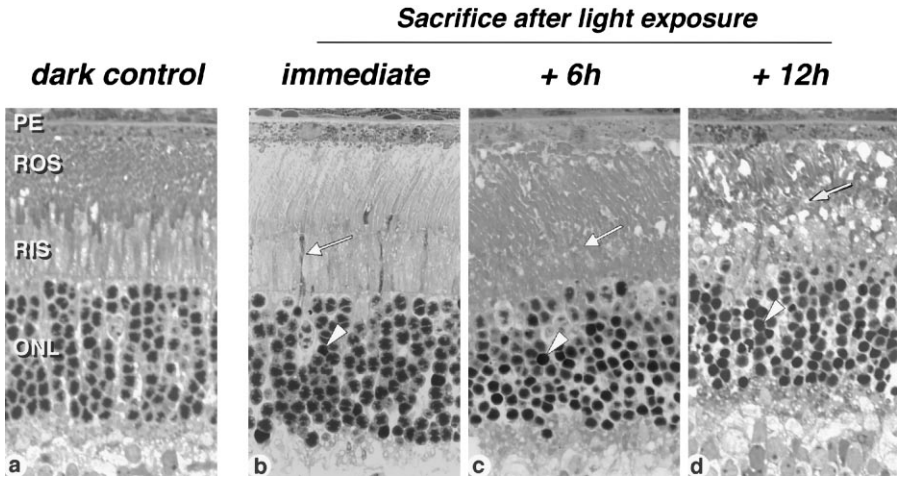


Fig. 1. Light-induced apoptosis in the mouse retina. Dark-adapted control mice show normal retinal morphology (a). After 2 h of light exposure and immediate sacrifice, some condensed RIS (arrow) and disseminated apoptotic nuclei (short arrowhead) are seen (b). Analysis at 6 h (c) and 12 h (d) after light exposure shows abundant apoptotic nuclei in the ONL (short arrowhead) and progressive ROS and RIS (arrow) deterioration.

resolved on a 0.75 or 1.5 mm 6% polyacrylamide gel using 0.25 × TBE buffer. For competition assays, an excess of cold oligonucleotide (Oct-1, AP-1 and SP-1) was used in combination with labeled oligonucleotide. The SP-1 specific sequence of the oligonucleotide was 5′-TCA CGG GGC GGG TCA A-3′.

For antibody interference analyses, 2 μl anti-serum was added 20 min prior to the addition of the oligonucleotide. Rabbit polyclonal antibodies directed against c-Fos, FosB, Fra-1, Fra-2, c-Jun, JunB and JunD (all from Santa Cruz, Biotechnology) and against Oct-1 (generated by A.M.) were used.

## 3. Results

### 3.1. Light-induced apoptosis in retinal photoreceptors

Light microscopic analysis of retinal damage induced by light was performed to assure the occurrence of photoreceptor apoptosis in the retinas of experimental animals.

Dark-adapted control mice showed regular retinal morphology (Fig. 1a). Immediately after the 2 h light exposure, the outer nuclear layer (ONL) displayed initial signs of apoptosis consisting of scattered condensed photoreceptor nuclei and few condensed rod inner segments (RIS). Rod outer segments (ROS) showed disruption and vesiculation of the disks (Fig. 1b). A total of 6 h after light exposure, photoreceptors showed distinct signs of apoptosis with deterioration of ROS and RIS and numerous condensed nuclei in the ONL (Fig. 1c). At 12 h after light exposure, the ONL showed dense and shrunken nuclei and most of the ROS and RIS had deteriorated (Fig. 1d).

### 3.2. AP-1 induction during light-induced apoptosis

To determine AP-1 DNA binding activity during light-induced photoreceptor apoptosis, we performed electrophoretic mobility shift assays (EMSAs) using retinal nuclear extracts.

As shown in Fig. 2(a), AP-1 DNA binding activity was transiently induced in retinas from mice exposed to light. DNA binding activity increased immediately after light exposure and reached a maximum at 6 h post light exposure. At 12 h after light exposure, AP-1 DNA binding activity was downregulated again to a level comparable to the activity in dark-adapted mice.

Fig. 2(b) shows a competition assay using an unlabeled AP-1 specific oligonucleotide and an unlabeled SP-1 specific oligonucleotide in combination with the labeled AP-1 specific probe. The AP-1/DNA complex (lane 2) was specifically competed by the unlabeled AP-1 specific oligonucleotide (lane 3) whereas unrelated oligonucleotides did not compete for complex formation (lane 4 and data not shown).

### 3.3. AP-1 complex composition during light-induced apoptosis and under normal light conditions

Fig. 3(a) shows an antibody interference experiment at 6 h after light exposure in which protein/DNA complexes formed in nuclear extracts were incubated with antibodies specific for c-Fos, FosB, fra-1, fra-2, c-Jun, JunB and JunD prior to electrophoretic separation. A strong interference with AP-1 DNA binding activity was found with the anti-c-Fos-antibody, the anti-JunD-antibody and the anti-c-Jun-antibody. Antibodies directed against fra-1, fra-2 and JunB showed only moderate inhibition whereas anti-FosB had no

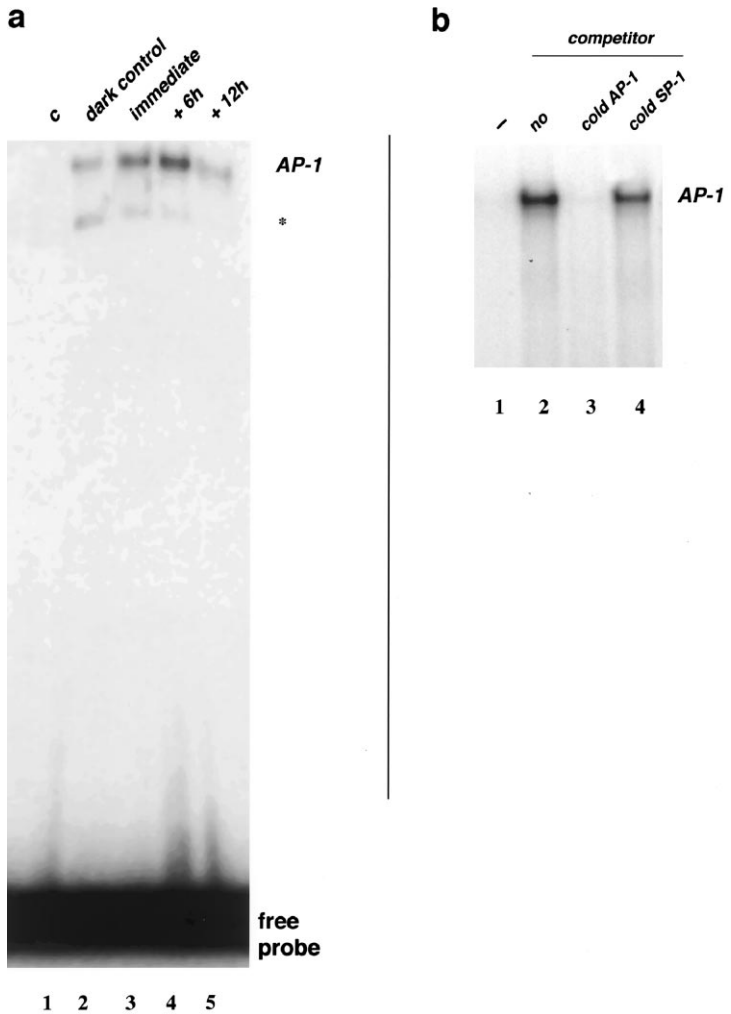


Fig. 2. (a) AP-1 induction in the mouse retina during light-induced photoreceptor apoptosis. Nuclear extract prepared from mouse retina was incubated with radiolabeled AP-1 specific oligonucleotide and AP-1 DNA binding was measured by EMSA. AP-1 DNA binding activity was analyzed in dark control mice (lane 2), immediately after light exposure (lane 3) and at 6 (lane 4) and 12 h (lane 5) in darkness following light exposure. Lane 1 (c) represents radiolabeled probe without nuclear extract. The asterisk (*) indicates a non-specific band. (b) Competition of AP-1/$^{32}$P complex formation by an excess of unlabeled AP-1 and SP-1 specific oligonucleotides. The area of the gel containing the protein/DNA complex is shown.

measurable effect. An additive and almost complete block of AP-1 DNA binding activity was found when anti-c-Jun, anti-JunB and anti-JunD antibodies were used in combination in one extract.

To determine whether the composition of the AP-1 complex under non-damaging light differs from the one observed after damaging light exposure, we performed EMSAs on retinal nuclear extracts from animals sacrificed at 18:00 h, the end of the regular light–dark cycle. Fig. 3(b) shows AP-1 DNA binding activity at 18:00 h which was strongly interfered by anti-c-Fos and anti-JunD-antibodies.

### *3.4. Oct-1 DNA binding activity during light-induced apoptosis*

In addition to AP-1, DNA binding activity of the transcription factor Oct-1 was measured during light-induced photoreceptor apoptosis. Fig. 4(a) shows high levels of Oct-1 DNA binding activity in retinas of dark-adapted mice. Oct-1 DNA binding activity was reduced in retinas analyzed immediately after light exposure and declined to a low level at 12 h after light exposure.

Specificity of the Oct-1 band was confirmed by a

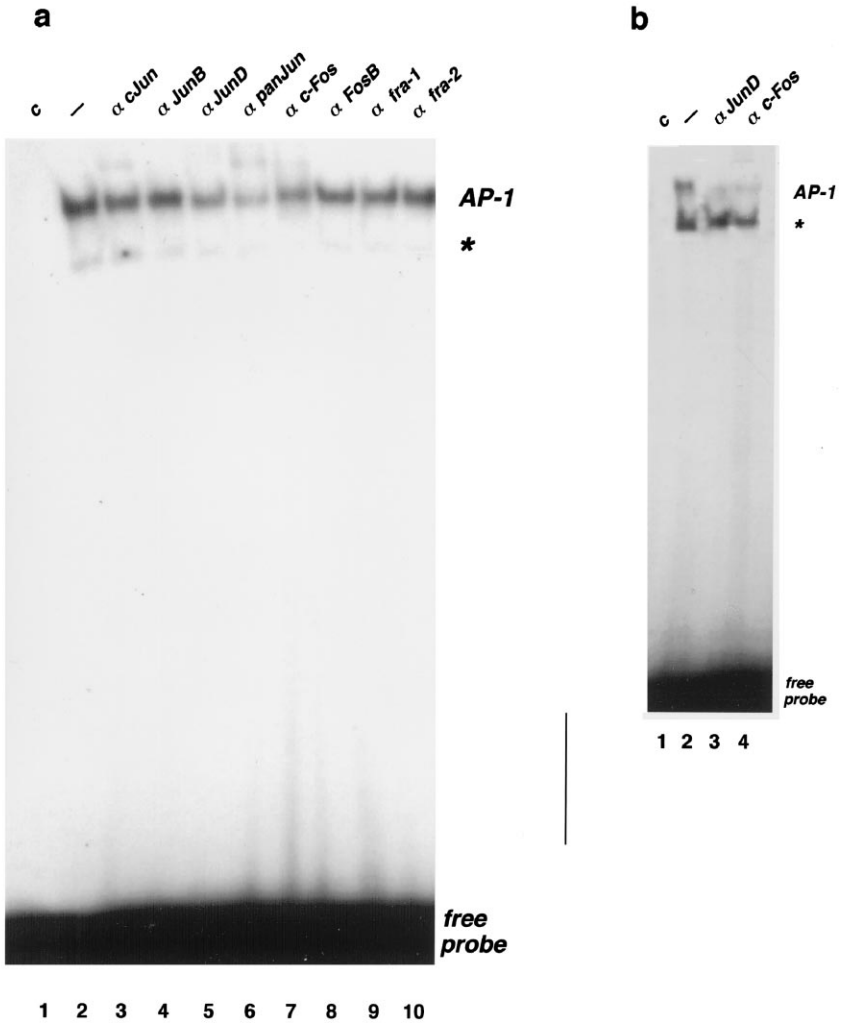


Fig. 3. (a) AP-1 complex composition after light exposure in the mouse retina. Nuclear extract from mouse retina was incubated with a radiolabeled AP-1 specific oligonucleotide and AP-1 DNA binding activity was assayed by EMSA. Lane 2 shows total AP-1 DNA binding activity 6 h after light exposure. The composition of the AP-1 complex was determined by antibody interference. Nuclear extract was incubated with antibodies specific for c-Jun, JunB, JunD (lanes 3–5), a combination of the three anti-Jun antibodies (pan Jun) (lane 6) and antibodies specific for c-Fos, FosB, Fra-1 and Fra-2 (lanes 7–10) before the addition of radiolabeled oligonucleotide probe. Lane 1 (c) represents radiolabeled probe without nuclear extract. The asterisk (*) indicates a non-specific band. (b) AP-1 DNA binding activity and complex composition under normal light conditions. Lane 2 shows total AP-1 DNA binding activity. Nuclear extract was incubated with an antibody specific for c-Fos (lane 3) and JunD (lane 4). Lane 1 (c) represents radiolabeled probe without nuclear extract.

competition assay using unlabeled Oct-1, AP-1 or SP-1 specific oligonucleotide in combination with the labeled Oct-1 specific probe (Fig. 4b). In addition, the specificity of the Oct-1/DNA complex also was verified using an Oct-1 specific antiserum (Fig. 4b, right panel).

## 4. Discussion

In this study we observed different DNA binding activities of the transcription factors AP1 and Oct-1 before and during light-induced apoptosis of photoreceptors in the mouse retina. Analysis of retinal nuclear extracts revealed that AP-1 DNA binding was transiently induced during apoptosis reaching maximal activity at 6 h after light exposure.

In contrast, the binding activity of the transcription factor Oct-1 was downregulated during the same period of cell death induction. Since both transcription factors modulate gene expression through binding to DNA consensus sequences in the enhancer/promoter region of specific target genes, the observed differences in binding activities may indicate different roles for AP-1 and Oct-1 in the regulation of apoptosis. Whereas there is strong evidence that AP-1 plays a major and active role in the control of apoptosis in a number of systems (Colotta et al., 1992; Smeyne et al., 1993; Estus et al., 1994; Agarwal et al., 1995;

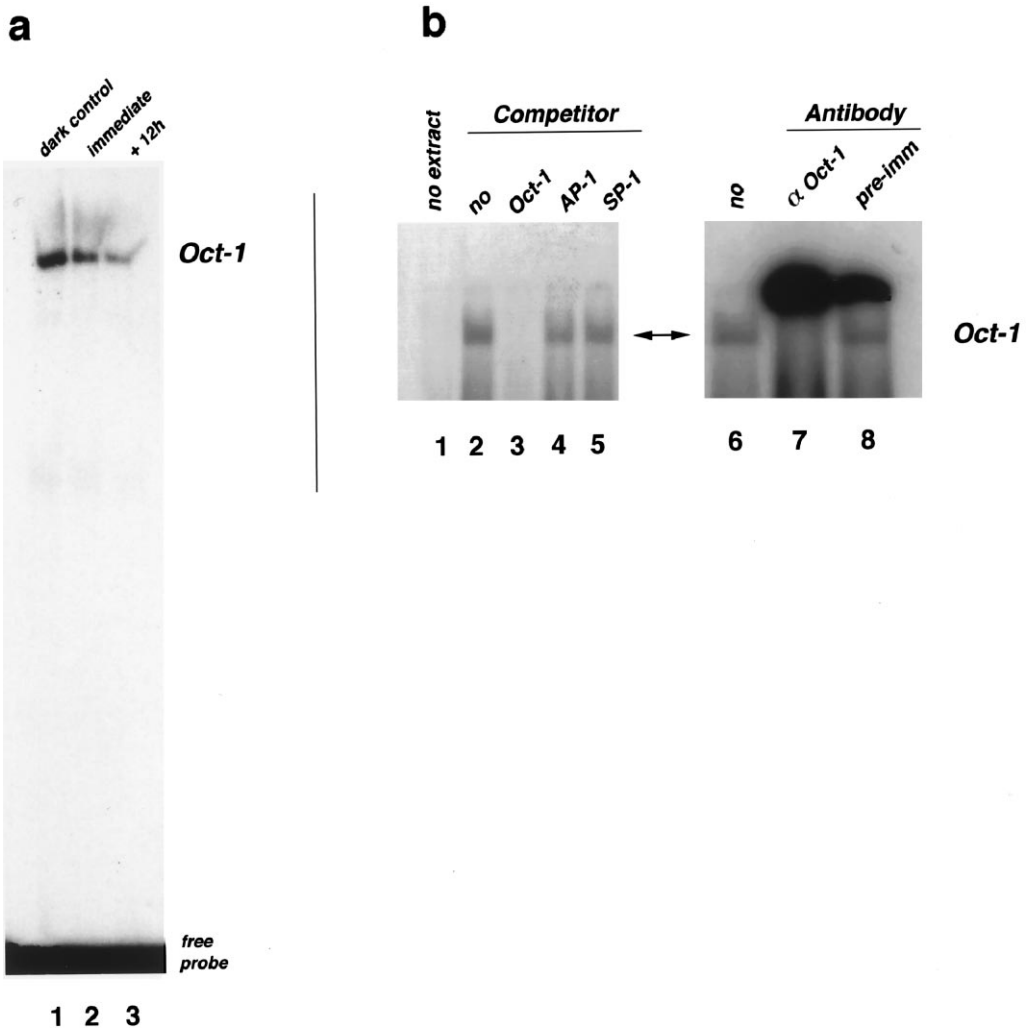


Fig. 4. (a) Oct-1 DNA binding declines during light-induced photoreceptor apoptosis. Nuclear extract prepared from mouse retina was incubated with radiolabeled Oct-1 specific oligonucleotide and Oct-1 DNA binding was assayed by EMSA. High Oct-1 DNA binding activity was observed in dark-adapted mice not exposed to our light regimen (lane 1). Immediately after light exposure, Oct-1 DNA binding declined to a lower level (lane 2) and was further reduced in the retinas of animals sacrificed 12 h after light exposure (lane 3). Free probe is indicated. (b) (left panel) Competition of Oct-1/$^{32}$P by an excess of unlabeled Oct-1 (lane 3), AP-1 (lane 4) and SP-1 (lane 5) specific oligonucleotides. Lane 2 shows complex formation without competitor oligonucleotides and lane 1 represents Oct-1/$^{32}$P incubated in buffer only. The area of the gel containing the protein/DNA complex is shown. (b) (right panel) Specificity of the Oct-1 band was verified by antibody interference experiments. Lane 1: Oct-1 band. Lane 2: supershift of Oct-1 by α-Oct-1 antibody. Lane 3: control with pre-immune serum.

Bossy Wetzel et al., 1997; Hafezi et al., 1997), little is known about the involvement of Oct-1 in apoptotic cell death.

However, since Oct-1 drives the expression of many housekeeping genes including histone and small nuclear RNA genes, it seems plausible that an inactivation of Oct-1 is beneficial to the death program. Therefore, it might be possible that the inactivation of Oct-1 is regulated and might even represent an initial stimulus for apoptosis. Alternatively, its inactivation might actively and irreversibly commit cells to the death pathway. Downregulation of Oct-1 DNA binding activity during apoptosis has also been observed in the ventral prostate following castration and in epithelial cells early during involution of the mammary gland (Marti et al., 1994).

These studies suggest that Oct-1 may be proteolytically degraded during apoptosis. However, it remains to be shown whether Oct-1 is merely inactivated nonspecifically or whether it represents a specific death signal in the involuting mammary gland and in apoptotic photoreceptors.

Although AP-1 is considered a key player in the regulation of apoptosis in many systems, little is known about potential target genes for AP-1 in the retina. Recently it has been shown that a DNA element resembling an AP-1 binding site can mediate transcriptional activation of the β-PDE (DiPolo et al., 1997), a gene encoding the cGMP phosphodiesterase which is a crucial element in phototransduction. Interestingly, disruption of the β-PDE gene is accompanied by elevated expression

of c-Fos and is responsible of excessive photoreceptor loss by apoptosis in the *rd* mouse, an animal model for inherited retinal degeneration (Rich, Zhan & Blanks, 1997).

Depending on their composition, the various AP-1 complexes may serve different biological functions by activating or repressing specific sets of target genes or regulating the same target genes at different transcription rates (Curran & Franza, 1988; Sonnenberg, MacGregor Leon, Curran & Morgan, 1989; Ryseck & Bravo, 1991; Kasof, Mandelzys, Maika, Hammer, Curran & Morgan, 1995). Therefore, it was of special interest to analyze the composition of AP-1 complexes under apoptotic and normal conditions in the retina. Antibody interference analysis at 6 h after exposure to damaging light showed that a major fraction of the dimeric AP-1 protein complex during apoptosis consists of c-Fos/c-Jun and c-Fos/JunD. Interestingly, under non-damaging light conditions, AP-1 complexes also consist mainly of c-Fos/JunD heterodimers (Fig. 3b). This shows that the qualitative composition of the AP-1 complexes was not altered substantially by the apoptotic stimulus. Induction of apoptosis may therefore depend on a quantitative increase of c-Fos/JunD and c-Fos/c-Jun AP-1 rather than on a drastic change in complex composition involving other members of the Fos and Jun families of proteins.

Increased c-Fos and c-Jun expression has been observed during apoptotic cell death mediated by nerve growth factor deprivation (Deckwerth & Johnson, 1993) and axotomy (Berkelaar, Clarke, Wang, Bray & Aguayo, 1994) in the nervous system. In the retina, the *c-fos* gene is upregulated concomitant with photoreceptor apoptosis in a mouse model of light-induced photoreceptor degeneration (Hafezi et al., 1997) and transgenic mice devoid of a functional *c-fos* gene were completely protected from light-induced photoreceptor apoptosis (Hafezi et al., 1997). Furthermore, transient induction of AP-1 consisting of c-Fos/JunD heterodimers has also been detected during apoptotic cell death in the involuting mouse mammary gland and in the involuting rat ventral prostate suggesting a role for c-Fos and Jun D in programmed cell death in these tissues (Marti et al., 1994). Furthermore, a recent study showed that involution of the rat ventral prostate does not occur in *c-fo*$^{-/-}$ mice indicating a similar role for c-fos in apoptosis in the prostate (Feng, Joos, Vallan, Mühlbauer, Altermatt & Jahhi (in press)).

In conclusion, this study shows that AP-1 is transiently induced and Oct-1 is inactivated during light-induced photoreceptor apoptosis in the mouse retina in vivo. AP-1 complexes found in the mouse retina during apoptosis may primarily consist of c-Fos/JunD and c-Fos/c-Jun heterodimers. However, further studies are needed to investigate the potential role of the various AP-1 complexes and the relevance of Oct-1 inactivation in the chain of events leading to photoreceptor degeneration in the retina.

## Acknowledgements

FH and AM contributed equally to this study. The authors thank B. Gloor for continuous support. Supported by the Swiss National Science Foundation, No. 31-40791.94, Helmut Horten Foundation, Switzerland, Sandoz Foundation, Basel, Switzerland, Bruppacher Foundation, Zurich, Switzerland and Ian and Caroline Leaf and family, Gland, Switzerland.

## References

Agarwal, N., Patel, H., Brun, A.-M., & Nir, I. (1995). Alteration of c-fos by light/dark in rds mouse retina: possible involvement in apoptosis of photoreceptors. *Investigative Ophthalmology and Visual Science*, *36*, 2921.

Angel, P., & Michael, K. (1991). The role of Jun, Fos and the AP-1 complex in cell proliferation and transformation. *Biochimica Biophysica Acta*, *1072*, 129–157.

Berkelaar, M., Clarke, D. B., Wang, Y. C., Bray, G. M., & Aguayo, A. J. (1994). Axotomy results in delayed death and apoptosis of retinal ganglion cells in adult rats. *Journal of Neuroscience*, *14*, 4368–4374.

Bossy Wetzel, E., Bakiri, L., & Yaniv, M. (1997). Induction of apoptosis by the transcription factor c-Jun. *European Molecular Biological Organisation Journal*, *16*, 1695–1709.

Chang, G. Q., Hao, Y., & Wong, F. (1993). Apoptosis: final common pathway of photoreceptor death in rd, rds, and rhodopsin mutant mice. *Neuron*, *11*, 595–605.

Colotta, F., Polentarutti, N., Sironi, M., & Mantovani, A. (1992). Expression and involvement of c-fos and c-jun protooncogenes in programmed cell death induced by growth factor deprivation in lymphoid cell lines. *Journal of Biological Chemistry*, *267*, 18278–18283.

Curran, T., & Franza, B. R. Jr. (1988). Fos and Jun: the AP-1 connection. *Cell*, *55*, 395–397.

Deckwerth, T. L., & Johnson, E. M. Jr. (1993). Temporal analysis of events associated with programmed cell death (apoptosis) of sympathetic neurons deprived of nerve growth factor. *Journal of Cell Biology*, *123*, 1207–1222.

DiPolo, A., Lerner, L. E., & Farber, D. B. (1997). Transcriptional activation of the human rod cGMP-phosphodiesterase beta-subunit gene is mediated by an upstream AP-1 element. *Nucleic Acids Research*, *25*, 3863–3867.

Estus, S., Zaks, W. J., Freeman, R. S., Gruda, M., Bravo, R., & Johnson, E. M. (1994). Altered gene expression in neurons during programmed cell death: identification of c-jun as necessary for neuronal apoptosis. *Journal of Cell Biology*, *127*, 1717–1727.

Feng Z., Joos H. J., Vallan C., Mühlbauer R., Altermatt H. J., & Jahhi R. (in press). Apoptosis during castration-induced regression of the prostate is Fos dependent. *Oncogene* 17.

Fletcher, C., Heintz, N., & Roeder, R. G. (1987). Purification and characterization of OTF-1, a transcription factor regulating cell cycle expression of a human histone H2b gene. *Cell*, *51*, 773–781.

Hafezi, F., Steinbach, J. P., Marti, A., Munz, K., Wang, Z. Q., Wagner, E. F., Aguzzi, A., & Reme, C. E. (1997). The absence of c-fos prevents light-induced apoptotic cell death of photoreceptors in retinal degeneration in vivo. *Nature Medicine*, *3*, 346–349.

Hai, T., & Curran, T. (1991). Cross-family dimerization of transcription factors Fos/Jun and ATF/CREB alters DNA binding specificity. *Proceedings of the National Academy of Sciences*, *88*, 3720–3724.

Haimovitz Friedman, A., Kan, C. C., Ehleiter, D., Persaud, R. S., McLoughlin, M., Fuks, Z., & Kolesnick, R. N. (1994). Ionizing radiation acts on cellular membranes to generate ceramide and initiate apoptosis. *Journal of Experimental Medicine*, *180*, 525–535.

Hirai, S., Bourachot, B., & Yaniv, M. (1990). Both Jun and Fos contribute to transcription activation by the heterodimer. *Oncogene*, *5*, 39–46.

Kasof, G. M., Mandelzys, A., Maika, S. D., Hammer, R. E., Curran, T., & Morgan, J. I. (1995). Kainic acid-induced neuronal death is associated with DNA damage and a unique immediate-early gene response in c-fos-lacZ transgenic rats. *Journal of Neuroscience*, *15*, 4238–4249.

Li, Z.- Y., & Milam, A. H. (1995). Apoptosis in retinitis pigmentosa. In R. E. Anderson, M. M. LaVail, J. G. Hollyfield, *Retinal degeneration* (pp. 1–8). New York: Plenum Press.

Lolley, R. N., Rong, H., & Craft, C. M. (1994). Linkage of photoreceptor degeneration by apoptosis with inherited defect in phototransduction. *Investigative Ophthalmology and Visual Science*, *35*, 358–362.

Macgregor, P. F., Abate, C., & Curran, T. (1990). Direct cloning of leucine zipper proteins: Jun binds cooperatively to the CRE with CRE-BP1. *Oncogene*, *5*, 451–458.

Marti, A., Jehn, B., Costello, E., Keon, N., Ke, G., Martin, F., & Jaggi, R. (1994). Protein kinase A and AP-1 (c-Fos/JunD) are induced during apoptosis of mouse mammary epithelial cells. *Oncogene*, *9*, 1213–1223.

Morgan, J. I., & Curran, T. (1995). Immediate-early genes: ten years on. *Trends in Neuroscience*, *18*, 66–67.

Nir, I., & Agarwal, N. (1993). Diurnal expression of c-fos in the mouse retina. *Brain Research and Molecular Brain Research*, *19*, 47–54.

Portera-Cailliau, C., Sung, C. H., Nathans, J., & Adler, R. (1994). Apoptotic photoreceptor cell death in mouse models of retinitis pigmentosa. *Proceedings of the National Academy of Sciences*, *91*, 974–978.

Rich, K. A., Zhan, Y., & Blanks, J. C. (1997). Aberrant expression of c-Fos accompanies photoreceptor cell death in the rd mouse. *Journal of Neurobiology*, *32*, 593–612.

Ryseck, R. P., & Bravo, R. (1991). c-Jun, Jun B and Jun D differ in their binding affinities to AP-1 and CRE consensus sequences: effect of Fos proteins. *Oncogene*, *6*, 533–542.

Schreiber, M., Baumann, B., Cotten, M., Angel, P., & Wagner, E. F. (1995). Fos is an essential component of the mammalian UV response. *European Molecular Biological Organisation Journal*, *14*, 5338–53349.

Sikora, E., Grassilli, E., Radziszewska, E., Bellesia, E., Barbieri, D., & Franceschi, C. (1993). Transcription factors DNA-binding activity in rat thymocytes undergoing apoptosis after heat-shock or dexamethasone treatment. *Biochemical and Biophysical Research Communications*, *197*, 709–715.

Smeyne, R. J., Vendrell, M., Hayward, M., Baker, S. J., Miao, G. G., Schilling, K., Robertson, L. M., Curran, T., & Morgan, J. I. (1993). Continuous c-fos expression precedes programmed cell death in vivo. *Nature*, *363*, 166–169.

Sonnenberg, J. L., MacGregor Leon, P. F., Curran, T., & Morgan, J. I. (1989). Dynamic alterations occur in the levels and composition of transcription factor AP-1 complexes after seizure. *Neuron*, *3*, 359–365.

Sturm, R. A., Dalton, S., & Wells, J. R. (1988). Conservation of histone H2A/H2B intergene regions: a role for the H2B specific element in divergent transcription. *Nucleic Acids Research*, *16*, 8571–8586.

Yoshida, K., Kawamura, K., & Imaki, J. (1993). Differential expression of c-fos mRNA in rat retinal cells: regulation by light/dark cycle. *Neuron*, *10*, 1049–1054.