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Nuclear Factor-κB, Cancer, and Apoptosis

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ABSTRACT. The role of nuclear factor (NF)-κB in the regulation of apoptosis in normal and cancer cells has been extensively studied in recent years. Constitutive NF-κB activity in B lymphocytes as well as in Hodgkin's disease and breast cancer cells protects these cells against apoptosis. It has also been reported that NF-κB activation by tumor necrosis factor (TNF)-α, chemotherapeutic drugs, or ionizing radiations can protect several cell types against apoptosis, suggesting that NF-κB could participate in resistance to cancer treatment. These observations were explained by the regulation of antiapoptotic gene expression by NF-κB. However, in our experience, inhibition of NF-κB activity in several cancer cell lines has a very variable effect on cell mortality, depending on the cell type, the stimulus, and the level of NF-κB inhibition. Moreover, in some experimental systems, NF-κB activation is required for the onset of apoptosis. Therefore, it is likely that the NF-κB antiapoptotic role in response to chemotherapy is cell type- and signal-dependent and that the level of NF-κB inhibition is important. These issues will have to be carefully investigated before considering NF-κB as a target for genetic or pharmacological anticancer therapies. BIOCHEM PHARMACOL **60**;8:1085–1090, 2000. © 2000 Elsevier Science Inc.

KEY WORDS. apoptosis; cancer; transcription factors; NF-κB

NF-κB† is an ubiquitously expressed transcription factor that regulates several vital functions [1]: it controls apoptosis, cell proliferation, and differentiation and is a major player in the control of immune response and inflammation. The NF-κB proteins bind DNA as dimers and are sequestered in the cytoplasm of most cell types by inhibitory proteins [1, 2]. These inhibitors, which belong to a family of proteins named IκB for inhibitory κB, mask the NF-κB nuclear localization domain and inhibit its DNA-binding activity. In response to a large variety of stimuli, the IκB inhibitor is rapidly phosphorylated and degraded, thus allowing NF-κB nuclear translocation, DNA binding to specific recognition sequences in promoters, and transcription of the target genes [3, 4]. The nature of NF-κB-activating stimuli reflects its main functions, as it can be activated in response to proinflammatory cytokines, infectious agents, and growth factors, among others. Similarly, NF-κB controls the expression of many mediators of inflammatory and immune reactions.

A number of experimental data indicate that the NF-κB transcription factor is involved in the development or progression of human cancers:

1. The v-*rel* oncogene of the reticuloendotheliosis virus T (Rev-T) was the first member of the Rel/NF-κB family to be discovered [5, 6]. It is a transforming gene and young chickens injected with the Rev-T virus develop aggressive lymphomas. However, v-*rel* remains the only NF-κB-related protein that can directly transform cells *in vitro* or *in vivo*.
2. Several members of the NF-κB and IκB families derive from genes that are amplified or translocated in human cancers [7]. All these genetic events lead to increased NF-κB transcriptional activity, thus indicating that NF-κB target genes might control important steps for cellular transformation or cancer progression. As described below, NF-κB may indeed control apoptosis and cell cycle progression, but also invasion and metastasis.
3. More recently, NF-κB constitutive activity, as observed in Hodgkin's disease cells, has been associated with a mutation in the gene encoding the IκB-α inhibitor [8–10]. Again, this genetic modification leads to an impaired control of NF-κB activity and thus to increased nuclear activity.

NF-KB TARGET GENES REGULATING APOPTOSIS

NF-κB is activated in response to several proapoptotic stimuli (Fig. 1). Indeed, cellular treatment with TNF-α very potently and rapidly induces NF-κB nuclear DNA binding in almost all cell types [11]. NF-κB can also be activated in response to the major cytotoxic drugs as well as to ionizing radiations [4, 12–15]. Finally, oxidative stress, another inducer of apoptosis, also activates NF-κB in several cell types [4, 16].

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† *Abbreviations:* NF-κB, nuclear factor-κB; IκB, inhibitor of κB; and TNF, tumor necrosis factor.

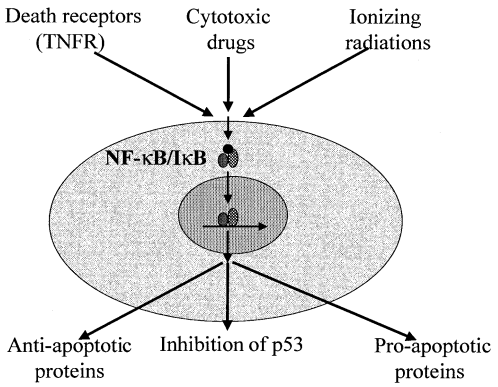

FIG. 1. The role of NF-κB in apoptosis. The NF-κB transcription factor is activated by many proapoptotic signals and regulates the expression of anti- and proapoptotic proteins. It also functionally antagonizes p53 transcriptional activity. TNFR: TNF-receptor type 1.

In response to these stimuli, the NF-κB transcription factor translocates to the nucleus and induces the expression of numerous target genes. Interestingly, several well-known antiapoptotic molecules are expressed as a consequence of NF-κB activation. These antiapoptotic target genes include those coding for TNF receptor-associated factor 1 (TRAF1) and TRAF2, cIAPs, manganese superoxide dismutase (MnSOD), A20, and IEX-1L [4, 17–21]. Moreover, NF-κB also controls the expression of Bfl-1/A1 and Bcl-xL, two antiapoptotic proteins from the Bcl-2 family [22–25]. It has also been reported that NF-κB activity influences Bcl-2 expression in some experimental systems [26, 27], but a direct regulation of the *bcl-2* gene by NF-κB has not been reported to date. NF-κB can also interfere with p53 transcriptional activity through the competition for cofactors [28–30], which constitutes a second potential mechanism for the NF-κB antiapoptotic effect.

Given these data, we explored the role of NF-κB in the regulation of several genes involved in the apoptotic pathways. As an NF-κB binding site had been identified in the human and murine p53 promoter [31], we investigated whether NF-κB influenced p53 expression in response to cytotoxic agents. Despite *in vitro* NF-κB binding to the p53 promoter and transactivation of this promoter by NF-κB in transient transfection experiments, there was no modification of p53 induction following cellular treatment with daunomycin in HCT116 or MCF7 cells stably transfected with an IκB-α repressor [15]. Interestingly, p53 and NF-κB could both transactivate the p53 promoter and there was no negative interaction between these two transcription factors on this particular gene promoter.* Similarly, expression of the p21 tumor suppressor in response to daunomycin was p53-dependent and NF-κB-independent.†

We also studied the expression of other pro- or antiapoptotic genes in cell lines transfected with the NF-κB inhipitor. In HCT116 and MCF7 cells, NF-κB inhibition led to decreased Bcl-2 and increased Bax expression.‡ In transient transfection experiments, NF-κB inhibited p53-dependent transactivation of the *bax* promoter, but this effect was not released by concomitant expression of several cofactors including CBP/p300. The mechanisms responsible for this NF-κB-induced inhibition of the *bax* promoter thus remain to be elucidated.

NF-KB AND THE CONTROL OF APOPTOSIS AND CELL CYCLE IN CANCER CELLS

The role of the NF-κB transcription factor in the control of pro- and antiapoptotic pathways in normal and cancer cells has recently been the subject of a very large number of studies. It was reported in 1996 that the activation of NF-κB in HeLa or Jurkat cells inhibits the apoptotic response to TNF-α, daunomycin, or ionizing radiations [32–35]. Later, a number of studies reported that NF-κB activation could prevent apoptosis in several untransformed and tumor cell types [36–38]. Moreover, constitutive NF-κB activity can be observed in B cells as well as in some cancer cells (including Hodgkin's disease Reed–Sternberg cells and breast cancer cells), and the inhibition of this spontaneous activity can be sufficient to induce apoptosis in these cells [39–41]. However, contradictory data were reported with other experimental systems. Indeed, in some cell types, the inhibition of NF-κB is not sufficient to allow apoptosis or to increase the cytotoxic response to TNF-α and anticancer drugs [42]. More surprisingly, NF-κB can even be required for the onset of apoptosis in a few experimental settings such as Sindbis-infected cells, Fas-induced cell death, or in response to oxidative stress, ischemia, or even to some cytotoxic drugs [36, 43–48].

In addition to its effect on apoptosis, NF-κB can activate cell cycling in cancer cells through the transactivation of the gene encoding cyclin D1 or c-Myc [49–51]. Taken together, these data suggest that, in cancer cells, NF-κB can both inhibit apoptosis and accelerate cell cycling through the increased expression of a variety of target genes.

We compared the effect of NF-κB inhibition on spontaneous or drug-induced apoptosis in several cancer cell lines. These experiments led to the following observations:

1. Level of NF-κB inhibition. We stably transfected cancer cell lines with an expression vector encoding a mutated IκB-α inhibitor that stably inhibits NF-κB activity. Under these conditions, we observed that a high expression of the transgene, correlated with an almost complete inhibition of constitutive and induced NF-κB activity, was required to observe an increased cytotoxicity in response to TNF-α. For instance, in OVCAR-3 ovarian carcinoma cells, only the clones expressing very high levels of the mutated IκB-α protein (OVCAR-

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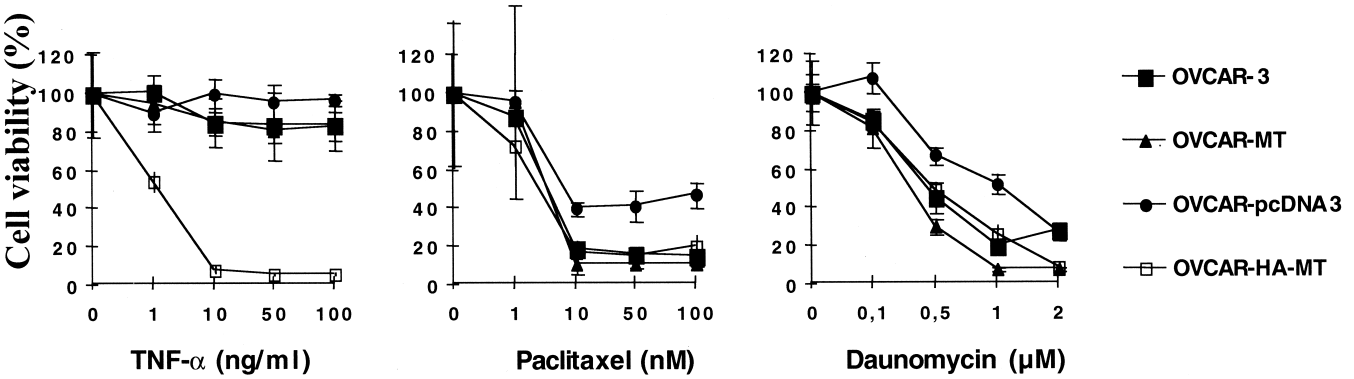

FIG. 2. NF-κB inhibition and cell death. Cellular viability was measured after treatment of OVCAR-3 cells with increasing concentrations of TNF-α, paclitaxel, or daunomycin for 48 hr. The following cell lines were compared: OVCAR-3 unmodified cells; OVCAR-pcDNA3 cells stably transfected with an empty pcDNA3 expression vector; OVCAR-MT cells expressing low levels of a mutated *IκB-α* transgene and OVCAR-HA-MT cells expressing high levels of mutated IκB-α transgene fused to an HA epitope. Cell viability was measured with the water-soluble tetrazolium (WST-1) test [42]. *Data points*: means of three different measures; *bars*: SD.

HA-MT cells) showed an increased cytotoxicity in response to TNF-α treatment (Fig. 2).

2. Specificity of the stimulus. TNF-α treatment of IκB-α-transfected OVCAR-3 led to an increased cytotoxic response as compared to unmodified OVCAR-3 cells, while anticancer drugs such as daunomycin or paclitaxel that could also activate NF-κB in these cells did not induce any difference in cell death between transfected and control cells (Fig. 2). Thus, in this cell type, the nature of the proapoptotic stimuli conditions the NF-κB antiapoptotic role.
3. Cell type specificity. By comparing cancer cells from various origins, we observed very different effects of NF-κB on apoptosis. In human and rat glioblastoma cell lines, constitutive NF-κB activity was high.* The inhibition of this activity, either by infecting the cells with an adenovirus carrying a mutated IκB-α gene or by NF-κB pharmacological inhibitors, led to cell cycle arrest and cell death. By contrast, inhibition of NF-κB activity sensitized OVCAR-3 cells to TNF-α, while it was shown not to have any effect on spontaneous or induced cell death in HCT116 (colon carcinoma), HPB (T cells), SKOV-3 (ovarian cancer), MCF7, or MCF7 A/Z (breast cancer) cells [42].

CONCLUSIONS

The NF-κB transcription factor is activated in response to the major proapoptotic signals, including TNF-α, anticancer drugs, and ionizing radiations. This NF-κB activity protects several cell types against cell death, although, in a few experimental settings, NF-κB itself is required for apoptosis or does not influence cell death. Moreover, spontaneous NF-κB activity in B lymphocytes and in some cancer cell types also inhibits apoptosis. These data thus indicate that in some cancer cell types, NF-κB could be an important factor for cell survival and resistance to therapy. However, before considering NF-κB as a therapeutic target for the treatment of cancers, a precise determination of its cell-specific anti- or proapoptotic function is required.

The NF-κB transcription factor is certainly a major regulator of the inflammatory reaction and thus could be targeted by anti-inflammatory agents [52–54]. Indeed, corticosteroids, aspirin, sulfasalazine, or cyclopentenones are well-characterized NF-κB inhibitors. However, none of these agents has any significant anticancer activity, with the exception of corticosteroids for the treatment of lymphoid tumors and Hodgkin's lymphomas.

Antiapoptotic NF-κB activity has been attributed to the regulation of antiapoptotic gene expression as well as to a functional antagonism with p53. Our work demonstrated that, in addition to the previously characterized genes, NF-κB also induces *bcl-2* and inhibits *bax* gene expression. Finally, under our experimental conditions, we observed that NF-κB induced the inhibition of p53 transactivation of the *bax* promoter but not of the p21 or p53 promoters, indicating that the functional antagonism between these two transcription factors is promoter-specific.

The role of NF-κB in carcinogenesis and cancer progression has recently received much support. However, more experimental studies are needed to determine whether NF-κB could constitute a therapeutic target in cancer. Moreover, given the limitations of *in vivo* gene therapy, specific NF-κB inhibitors will have to be developed. Ideally, these inhibitors should be able to interfere with the different transduction pathways that lead to constitutive or induced NF-κB activity.

* Robe P, Bentires-Alj M, Merville M-P and Bours V, unpublished data.

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