Time to harness the pro-apoptotic property of NFκB?

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We read with great interest the review article by Nakanishi and Toi[1], in which the authors highlight the usefulness of nuclear factor-κB (NFκB) inhibitors in anticancer therapy. This is in line with the central theme of NFκB biology, which portrays NFκB as oncogenic and anti-apoptotic. However, as the authors themselves briefly mention towards the end of the article, evidence is accumulating in support of a surprising pro-apoptotic role for NFκB. Arguably, the most striking demonstration of NFκB's involvement in cell death first came 5 years ago, when it was reported that NFκB is necessary for p53-mediated apoptosis[2]. So, in situations in which p53 activation in response to chemotherapy is the main mode of elimination of tumour cells, inhibition of NFκB might well be counterproductive. More recently, it was found that activation of NFκB is essential for doxorubicin and its analogues to mediate their cytotoxic effects, further underscoring the direct death-promoting role of NFκB[3]. These data do not, by any means, invalidate the earlier studies that characterized NFκB as anti-apoptotic. Rather, these observations emphasize that there is another side to NFκB that deserves equal attention.

It is now clear that several factors, including the cell-type and stimulus used, act together to confer a pro-apoptotic role for NFκB in certain situations[4]. There seems to be two major mechanisms through which NFκB induces apoptosis. The first is by transcriptional upregulation of pro-apoptotic target genes such as *TP53*, death receptor 4 (*DR4*), *DR5* and tumour-necrosis factor (TNF)-related apoptosis-inducing ligand (*TRAIL*)[5-8]. The second is by active repression of anti-apoptotic target genes such as $BCLX_L$ and *XIAP* (X-linked inhibitor of apoptosis)[9]. It should be pointed out that these two mechanisms are not mutually exclusive and can occur together[10].

Despite a considerable amount of work being undertaken in this area in recent years, it still remains to be elucidated why NFκB that is induced by the classic TNF-signalling pathway normally induces a cell survival pathway, whereas NF-κB activation that is induced by certain other stimuli leads to cell death. It has been suggested that differences in the post-translational modification of the NFκB subunits, especially p65/RELA, could cause a differential response[11]. Also, the subset of genes that are induced by NFκB could be influenced by the status of the chromatin in specific target genes (especially histone-acetylation status) and whether access to these genes is altered in response to particular stimuli. These factors could tilt the balance towards life or death[12].

We hope that a better understanding of the events that actually shape the NFκB response will help foster new ways for superior anticancer therapies to be developed. For example, instead of screening for inhibitors of NFκB, we might be able to come up with strategies that switch NFκB from being anti-apoptotic to pro-apoptotic.

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