MINIREVIEW

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c-Rel and its many roles in cancer: an old story with new twists

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When the genes encoding NF-κB subunits were first isolated, their homology to the previously identified c-Rel proto-oncogene and its viral homologue v-Rel was clear. This provided the first indication that these transcription factors also had a role in cancer. Because of its homology to v-Rel, which transforms chicken B cells together with the important role c-Rel can have as a regulator of B- and T-cell proliferation, most attention has focussed on its role in B-cell lymphomas, where the REL gene is frequently amplified. However, a growing number of reports now indicate that c-Rel has important functions in many solid tumours, although studies in mice suggest it may not always function as an oncogene. Moreover, c-Rel is a critical regulator of fibrosis, which provides an environment for tumour development in many settings. Overall, c-Rel is emerging as a complex regulator of tumorigenesis, and there is still much to learn about its functions in human malignancies and the response to cancer therapies.

The NF-κB subunits RelA/p65, RelB, c-Rel, p50/p105 (NF-κB1) and p52/p100 (NF-κB2) comprise a family of dimeric transcription factors with both common and distinct biological functions. NF-κB complexes are present in all cells but are generally held in an inactive form bound to a variety of inhibitory proteins, termed inhibitors of NF-κB (IκBs) (Perkins, 2012). IκBs possess a series of ankyrin repeat motifs that are also found in p100 and p105, the precursor forms of p52 and p50, which allows them to function as IκB-like NF-κB inhibitors. A wide range of NF-κB inducers, including inflammatory cytokines, cell stresses such as DNA damage, immune receptor engagement, bacterial products and viral proteins, can activate the IκB kinase (IKK) complex, resulting in IκB phosphorylation, degradation and the release of active NF-κB dimers (Perkins, 2012).

NF-κB activity is usually kept under tight control, with a variety of negative feedback loops, such as resynthesis of IκBα or expression of the ubiquitin editor A20, acting to limit the magnitude and duration of a typical NF-κB response (Perkins, 2012). However, in many human illnesses, NF-κB is aberrantly active and either causes or contributes to the pathology of the disease (Karin, 2009; Perkins, 2012; Bradford and Baldwin, 2014). This is particularly true with inflammatory diseases, where NF-κB-driven expression of genes encoding inflammatory cytokines such as tumour necrosis factor (TNF) α or interleukin 6 (IL-6), drives disease progression (Karin, 2009). Its critical role in the inflammatory phenotype allows NF-κB to act as a promoter of inflammation-associated cancers (Karin, 2009). However, NF-κB can also contribute to cancer in many others ways. Aberrant NF-κB activity in cancer only rarely results from direct mutation of the NF-κB subunits but arises either through mutation of upstream regulators (e.g., Ras, Myd88 or the B-cell receptor) leading to constitutive IKK activity or via effects of the tumour microenvironment (Bradford and Baldwin, 2014). Constitutive activation of NF-κB in tumour cells can activate many genes that regulate cancer-related cellular processes, including apoptosis, proliferation, angiogenesis and metastasis (Bradford and Baldwin, 2014). Thus NF-κB actively contributes to many of the 'hallmarks of cancer', resulting in more rapid disease progression, increased metastatic potential, a higher proportion of tumour recurrence and therapeutic resistance (Bradford and Baldwin, 2014).

THE NF-κB SUBUNIT c-REL

The NF-κB subunit c-Rel was first identified as the cellular homologue of the avian Rev-T retroviral oncoprotein v-Rel (Gilmore and Gerondakis, 2011). v-Rel causes lymphoma in birds and c-Rel is the only NF-κB family member that can also transform chicken lymphoid cells *in vitro* (Gilmore and Gerondakis, 2011).

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c-Rel, which is encoded by the *REL* gene in humans, has important roles in many aspects of lymphoid cell function (Gilmore and Gerondakis, 2011). c-Rel is expressed in mammalian B cells regardless of developmental stage, although c-Rel levels increase during B-cell development (Grumont and Gerondakis, 1994; Liou *et al*, 1994). *c-rel* knockout mice develop normally with no effects on haematopoietic cell development but do display several immunological defects, which include reduced mature B- and T-cell proliferation and activation in response to mitogenic stimuli, abnormal germinal centre formation and reduced numbers of marginal zone B cells (Gilmore and Gerondakis, 2011). In addition to cancer (see below), c-Rel has a key role in a number of human diseases, such as inflammatory bowel disease and rheumatoid arthritis together with cardiac and skin fibrosis (Wang *et al*, 2008; Gilmore and Gerondakis, 2011; Gaspar-Pereira *et al*, 2012; Fullard *et al*, 2013).

The most common isoform of human c-Rel is 587 amino acids. Overall, c-Rel has a similar structure to the RelA and RelB members of the NF-κB family, with an N-terminal DNA-binding and dimerisation domain termed the Rel homology domain and a C-terminal transcriptional activation domain (Figure 1A). c-Rel is most commonly found as a dimer with the p50 or RelA NF-κB subunits but other combinations can occur (Gilmore and Gerondakis, 2011). c-Rel has a slightly different DNA-binding specificity compared with other NF-κB subunits (Sanjabi *et al*, 2005), but ChIP-Seq analysis did not reveal any significant differences in DNA-binding site preference in EBV-transformed B cells (Zhao *et al*, 2014). Although posttranslational modifications can have profound regulatory effects on other NF-κB subunits, relatively little is known about how such modifications contribute to c-Rel activity and function (Gilmore and Gerondakis, 2011). c-Rel is generally described as an activator of transcription that can function to establish a permissive chromatin environment at NF-κB-regulated promoters (van Essen *et al*, 2010), but whether this varies in different cellular contexts has not been thoroughly explored. Similar to RelA, c-Rel is a regulator of antiapoptotic genes such as Bcl-xL (Gilmore and Gerondakis, 2011). However c-Rel also regulates other cellular functions. For example, it can induce the expression of CLSPN, a component of the checkpoint kinase Chk1 signalling pathway in the human U2OS osteosarcoma cell line (Kenneth *et al*, 2010). c-Rel can also regulate the expression of EZH2, a histone methyl transferase frequently upregulated in many cancers, in both primary murine B and T cells as well as human leukaemia and multiple myeloma cell lines (Neo *et al*, 2014).

THE ROLE OF c-REL IN B-CELL LYMPHOMA

NF-κB has a key role in several types of lymphoma, with many B-cell lymphomas dependent on mutations that activate the NF-κB pathway (Lim *et al*, 2012). Activation of NF-κB can arise in B-cell lymphoma owing to mutations in upstream regulatory genes such as *TNFAIP3*, *CARD11*, *MYD88*, *NFKBIA* and *CD79A/B*, chromosomal translocations such as t(11;18)(q21;q21)/*API-MALT1* or to signalling through cell surface receptors, such as CD40 and the EBV latent membrane protein 1 (Compagno *et al*, 2009; Hamoudi *et al*, 2010; Lim *et al*, 2012). Many diffuse large B-cell lymphomas (DLBCL), including almost all activated B-cell-like (ABC-DLBCL), primary mediastinal large B-cell lymphomas (PMBL) and a subset of germinal centre B-cell-like DLBCL (GCB-DLBCL), in addition to classical Hodgkin lymphoma (CHL) and MALT lymphomas, possess distinct NF-κB target gene signatures thought to promote lymphoma progression and survival (Compagno *et al*, 2009; Hamoudi *et al*, 2010; Lim *et al*, 2012).

Despite this, the contribution of individual NF-κB proteins to lymphomagenesis is poorly understood. However, evidence suggests an important role for c-Rel. Genomic and cytogenetic studies of human lymphomas have identified amplification of the

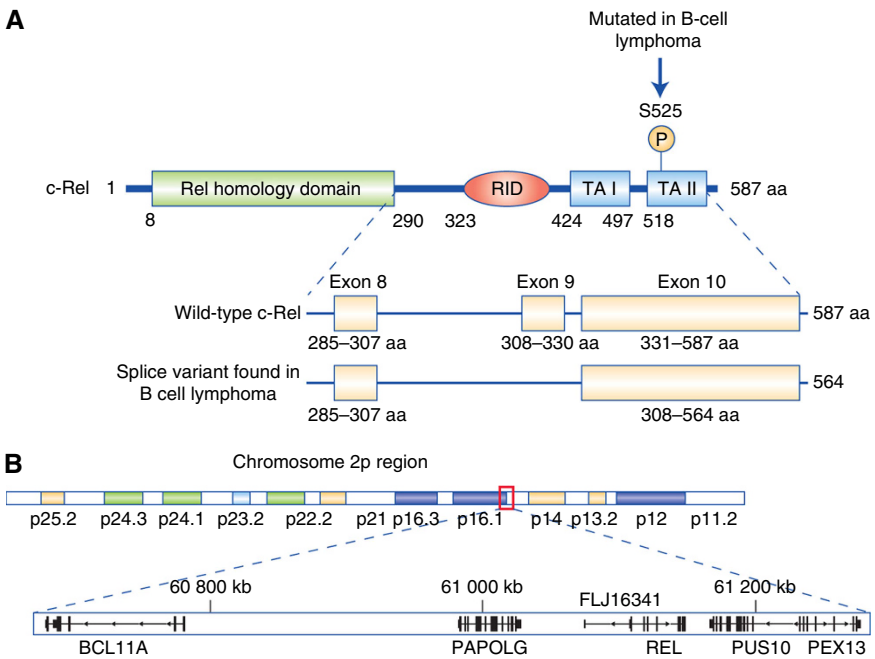

Figure 1. Structure and genomic location of human c-Rel. (**A**) Schematic diagram showing the structure of c-Rel and amino-acid positions of different regulatory motifs. A putative IKK phosphorylation site found mutated in some B-cell lymphoma patient samples together with a splice variant that removes 23 amino acids from the REL inhibitory domain (RID) also found in some B-cell lymphoma cell lines and patient samples are shown. TA I and TA II are c-Rel transcriptional activation domains. Adapted from (Leeman *et al*, 2008). (**B**) Diagram demonstrating the close proximity of the REL gene to the BCL11A proto-oncogene and the pseudouridine kinase *PUS10* on human chromosome 2. Both genes therefore have the potential to be co-amplified in human cancers. Figure compiled using the Integrated Genomics Viewer and the hg19 build of the human genome.

Table 1. List of different cancers where a role for c-Rel is known or implied

Disease	Alteration	Biological effect	References
c-Rel in lymphoid cancers			
Primary mediastinal B-cell lymphoma (PMBL)	Amplification of REL locus	Correlates with increased REL mRNA, nuclear c-Rel and NF-κB activity. Use of IKKβ inhibitor induced cell death in cell lines	Weniger *et al*, 2007
Classical Hodgkins lymphoma (CHL)	Gain of 2p	Correlates with nuclear c-Rel staining and constitutive NF-κB activity	Joos *et al*, 2002; Martin-Subero *et al*, 2002; Barth *et al*, 2003; Enciso-Mora *et al*, 2010
Germinal centre B-cell diffuse large B-cell lymphoma (GCB-DLBCL)	Amplification of REL locus and nuclear localised c-Rel	Not clear. Some studies indicate poor overall survival associated with c-Rel positivity but others do not	Lenz *et al*, 2008; Curry *et al*, 2009; Li *et al*, 2015
Activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL)	Distinct NF-κB gene signature and nuclear localised c-Rel	Lymphomas are dependent on this gene signature for proliferation and survival. c-Rel positivity associated with poor overall survival in some disease subtypes	Lenz *et al*, 2008; Campagno *et al*, 2009; Curry *et al*, 2009; Li *et al*, 2015
Marginal zone lymphoma	Increased REL mRNA expression	Shorter overall survival correlates with increased REL and other NF-κB gene expression	Barth *et al*, 2001
Adult T-cell leukaemia/lymphoma (ATLL)	Increased c-Rel expression	Increased expression confers resistance to therapy	Ramos *et al*, 2007
c-Rel in solid tumours			
Breast cancer	Increased REL mRNA, high nuclear c-Rel expression	c-Rel expression shown to induce mammary tumours in murine breast cancer models	Cogswell *et al*, 2000; Romieu-Mourez *et al*, 2003
Colitis-associated adenoma	Loss of c-Rel in mice	Increased disease susceptibility and tumour burden	Burkitt *et al*, 2015
Gastric cancer	Loss of c-Rel in mice	c-Rel$^{-/-}$ mice developed lesions similar to low-grade MALT lymphomas when exposed to pathogens	Burkitt *et al*, 2013
Pancreatic cancer	Increased c-Rel expression in cell lines	c-Rel acts to mediate TRAIL-induced apoptosis by controlling tumour-promoting genes, such as NFATc2	Geismann *et al*, 2014
Head and neck cancer	Amplification and nuclear localisation of c-Rel	Role for c-Rel in cancers expressing mutant p53 where it inactivates p73	Lu *et al*, 2011
Other c-Rel-regulated pathways affecting tumorigenesis			
Graft *versus* host disease (GVHD)	c-Rel expression drives T-cell response	Homing to GVHD organs reduced in c-Rel$^{-/-}$ T-cells. c-Rel inhibition reduced T-cell activation without compromising antitumour activity	Yu *et al*, 2013
Fibrosis	Loss of c-Rel in mice	Potentiates fibrosis in multiple organs via the regulation of gene expression	Gieling *et al*, 2010; Gaspar-Pereira *et al*, 2012; Fullard *et al*, 2013

Abbreviations: MALT = mucosa-associated lymphoid tissue; IKKβ = IκB kinase β; NFATc2 = nuclear factor of activated t-cells, cytoplasmic, calcineurin-dependent 2; NF-κB = nuclear factor κB; TRAIL = tumour necrosis factor-related apoptosis-inducing ligand. Please note that it was not possible to list all the primary literature here and a more comprehensive list of references, together with haematological malignancies associated with c-Rel, can be found in Gilmore and Gerondakis (2011) ($n = 112$) and Lim *et al*. (2012) ($n = 153$).

region of chromosome 2p13 where the *REL* gene is located (Table 1). Amplifications and gains of *REL*, often associated with elevated levels of nuclear c-Rel protein, have been detected in approximately 50% of CHL and at lower levels in other types of B-cell lymphoma, while c-Rel nuclear localisation is associated with both ABC- and GCB-DLBCL (Barth *et al*, 2001, 2003; Martin-Subero *et al*, 2002; Weniger *et al*, 2007; Lenz *et al*, 2008; Curry *et al*, 2009; Enciso-Mora *et al*, 2010; Gilmore and Gerondakis, 2011; Lim *et al*, 2012; Li *et al*, 2015). Interestingly, in a recent study of 460 DLBCL patients, the 26% scoring positive for nuclear c-Rel exhibited higher levels of clinical features, such as extra nodal disease (Li *et al*, 2015). In this study, nuclear c-Rel did not correlate with overall survival in the whole population of either ABC- or GCB-DLBCL patients but was a significant indicator of negative outcome in distinct subsets of patients. For example, in all patients with mutant p53 tumour suppressor or in ABC-DLBCL patients with low levels of the antiapoptotic protein Bcl-2, c-Rel positivity was associated with poor overall survival (Li *et al*, 2015).

Although the *REL* gene is frequently amplified in PBML and GCB-DLBCL, the association of this event with c-Rel activity and an NF-κB gene signature has been questioned (Feuerhake *et al*, 2005; Lenz *et al*, 2008; Li *et al*, 2015). For example, in 460 DLBCL patients, there was a poor correlation between c-Rel nuclear localisation and mRNA levels in both ABC and GCB forms of the disease (Li *et al*, 2015). Furthermore, a potential complication to our understanding of *REL* gene amplification is the close proximity of another myeloid and B-cell proto-oncogene, *BCL11A*, on human chromosome 2 (Figure 1B). Indeed, both the *REL* and *BCL11A* genes have been shown to be co-amplified in CHL (Martin-Subero *et al*, 2002), while the pseudouridine kinase *PUS10* that is also in close proximity to *REL* (Figure 1B) is the most significantly upregulated gene in this region in GCB-DLBCL (Lenz *et al*, 2008). However, whether BCL11A or PUS10 contribute to any of the pathological phenotypes associated with c-Rel is not known.

An additional potential complication in interpreting this data that has not generally been considered is the identification of an alternatively spliced hyperactive form of c-Rel (Leeman *et al*, 2008). This isoform lacks a central inhibitory domain and is preferentially expressed in a variety of lymphoma cell lines and DLBCL patient cells (Leeman *et al*, 2008; Figure 1A). Furthermore, a transactivation domain mutation (S525P) in c-Rel was identified in B-cell lymphomas from two patients, and this mutation enhances the ability of c-Rel to transform cells *in vitro* (Figure 1A; Starczynowski *et al*, 2007). However, the significance and frequency of these findings to disease progression and treatment has yet to be established.

c-REL IN SOLID TUMOURS

c-Rel is also associated with the malignant progression of solid tumours (Table 1). Unlike the situation with lymphoma or other haematological malignancies, these studies have used animal models to assess c-Rel's contribution to the disease. For example,

in the azoxymethane/dextran sulphate model of colitis-associated colon adenocarcinoma, c-Rel$^{-/-}$ mice show greater susceptibility to disease (Burkitt *et al*, 2015). The number of polyps formed in c-Rel$^{-/-}$ animals was not only significantly greater but were larger with higher proliferation indices, suggesting that loss of c-Rel drives a more aggressive form of the disease. Similarly, in a *Helicobacter felis* (*H. felis*)-induced model of gastric cancer, unlike NF-κB1$^{-/-}$ mice, c-Rel$^{-/-}$ animals did not develop spontaneous gastric atrophy after either acute or chronic exposure. However, after 1 year, half of the c-Rel$^{-/-}$ mice exposed to *H. felis* developed lesions similar to low-grade MALT lymphomas (Burkitt *et al*, 2013). These inflammatory gastric lesions were characterised as being highly proliferative and comprised of predominately B cells, while also partially affecting the mucosa and surrounding gastric glands. These studies suggest that, in contrast to its more commonly characterised tumour-promoting activities, c-Rel can also act to suppress tumorigenesis.

An interaction between the p53 family member ΔNp63α and c-Rel has been reported following TNF-α stimulation in a subset of head and neck carcinoma cell lines with mutant p53 (Lu *et al*, 2011). This interaction decreases the interaction of ΔNp63α with the tumour-suppressor TAp73 and alters the latter's effects on gene expression. For example, in cell lines with mutant p53, depletion of c-Rel by siRNA treatment was shown to increase the expression of the CDK inhibitor p21^{WAF1} gene and the two pro-apoptotic genes PUMA and NOXA, indicating that c-Rel mediates cell survival in head and neck cancer by inactivating TAp73. Another correlation between c-Rel and p63 emerged from the DLBCL study discussed above (Li *et al*, 2015). Here, in ABC-DLBCL, c-Rel nuclear positivity was associated with poor overall survival in patients with low p63 expression (Li *et al*, 2015).

It has also been suggested that c-Rel has a role in breast cancer. Expression of mRNA for c-Rel, as well as for other NF-κB family members, was shown to be upregulated in 35 primary inflammatory breast cancers (Cogswell *et al*, 2000). Moreover, in a study using transgenic mice in which c-Rel was expressed in breast tissue under the control of the mouse mammary tumour virus, approximately one-third of these mice developed tumours, albeit with a long latency of approximately 20 months (Romieu-Mourez *et al*, 2003).

Recently, a novel role for c-Rel in highly aggressive pancreatic ductal adenocarcinoma (PDAC) cell lines has been reported. In this case, c-Rel was found to be a key mediator of TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in PDAC and that the tumour promoter, NFATc2, was under the control of c-Rel and TRAIL, resulting in a resistance to TRAIL-mediated apoptosis (Geismann *et al*, 2014).

THE INFLAMMATION, FIBROSIS AND CANCER AXIS

c-Rel can potentially promote cancer by driving organ fibrosis (see Figure 2). Organ fibrosis is a pathological condition characterised by non-physiological wound healing leading to the excess deposition of extracellular matrix. The progression of chronic diseases in parenchymal organs such as the liver, kidney and lung are associated with fibrosis and extensive tissue remodelling. This fibrosis eventually leads to loss of organ function, and it can also act as a precancerous state in which the development of solid tumours is favoured (Elsharkawy and Mann, 2007). A key component of fibrosis is the recruitment and trans-differentiation of precursor cells to activated myofibroblasts. Activated myofibroblasts secrete a plethora of proinflammatory cytokines and chemokines, such as IL-6, IL-8, the growth factor VEGFA and the matrix metalloproteinase MMP9. These molecules are important for normal wound healing but can also drive tumour cell growth and metastasis (Coulouarn and Clement, 2014).

Importantly, c-Rel activity has recently been identified as a common potentiator of fibrosis in multiple organs. A role for c-Rel in myofibroblast activation is implied by analysis of c-Rel$^{-/-}$ mouse hepatic stellate cells, which display reduced levels of classical profibrogenic genes such as collagen I and alpha smooth muscle actin (Gieling *et al*, 2010). c-Rel has also been shown to be an important regulator of epidermal homeostasis and skin fibrosis in a mouse model of bleomycin-induced skin fibrosis. Here c-Rel$^{-/-}$ mice display reduced keratinocyte proliferation as well as reduced levels of fibrosis (Fullard *et al*, 2013). Similarly c-Rel is important for the development of stress-induced cardiac hypertrophy and fibrosis, with c-Rel$^{-/-}$ mice showing reduced levels of fibrosis in the heart and reduced cardiac growth (Gaspar-Pereira *et al*, 2012). The reduction of cardiac fibrosis and growth was attributed to the downregulation of two key regulators of cardiac hypertrophy, myocyte enhancer factor 2A and GATA4 (Gaspar-Pereira *et al*, 2012).

Hepatocellular carcinoma (HCC) is one of the most common forms of liver cancer, and 80% of these tumours arise in a setting of established fibrosis and/or cirrhosis (Coulouarn and Clement, 2014). In the liver, c-Rel has been implicated in modulating both fibrosis and regeneration. The livers of c-Rel$^{-/-}$ mice, following chronic treatment with hepatotoxic carbon tetrachloride or bile duct ligation, show impaired wound healing and reduced fibrosis, characterised by reduced levels of both collagen and hepatic myofibroblasts (Gieling *et al*, 2010).

Taken together, these reports indicate that by targeting the pathways regulating c-Rel, c-Rel itself or the gene products that c-Rel activates to induce fibrosis development may provide new strategies for the treatment of HCC and other cancers driven by a fibrotic microenvironment.

EFFECTS OF c-REL ON CANCER THERAPY

NF-κB is known to affect the cellular response to many common cancer therapies and c-Rel can also affect the treatment of haematological malignancies. For example, adult T-cell leukaemia/lymphoma (ATLL) is caused by the human T-cell leukaemia virus type 1 and is treated with antiviral therapy, zidovudine (AZT) in combination with interferon alpha, resulting in good rates of remission. However, resistance to AZT in cells from ATLL patients has been associated with high expression of c-Rel and IRF-4 (Ramos *et al*, 2007).

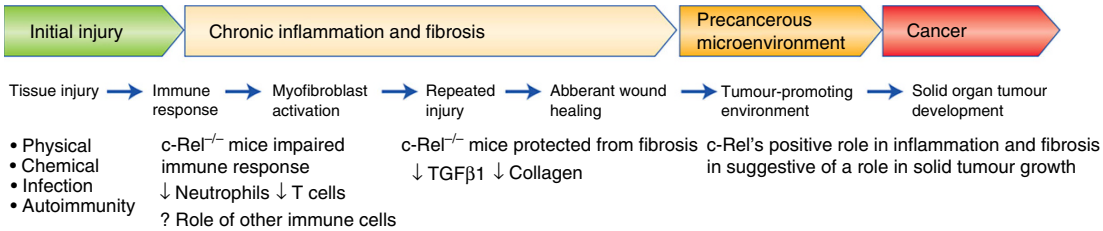

Figure 2. Schematic diagram showing how fibrosis can lead to cancer development and the role of c-Rel in this process.

c-Rel also regulates graft *vs* host disease (GVHD), a problem affecting patients following allogeneic haematopoietic stem cell transplantation (allo-HSCT) for the treatment of a variety of haematological malignancies, such as acute myeloid leukaemia. In mice, bone marrow transfer of c-Rel-deficient donor T cells significantly reduces GVHD compared with normal T cells (Yu *et al*, 2013). Moreover, these c-Rel$^{-/-}$ T cells also exhibit reduced homing to GVHD organs, such as the lung, liver and spleen. It has therefore been proposed that targeting c-Rel would provide a therapeutic strategy for preventing GVHD in patients undergoing allo-HSCT. Indeed, a small-molecule inhibitor of c-Rel, IT-603, which reportedly acts by directly binding to c-Rel and inhibiting its DNA-binding activity, was shown to reduce the c-Rel-induced activation of T cells without affecting the antitumour activity of allo-HSCT in mice (Shono *et al*, 2014).

CONCLUSIONS

Descriptions of the NF-κB pathway, in common with other highly investigated research areas, often contain many assumptions and simplifications regarding the role of pathway components. This is especially true of the NF-κB subunits and c-Rel in particular (Perkins, 2012). NF-κB subunits are subject to extensive regulation, that can involve their level of expression, interactions with heterologous transcriptional regulators and posttranslational modifications. This can determine their ability to regulate specific gene targets and thereby affect their functions in different physiological or pathological contexts. This review has highlighted not only the well-established association of c-Rel with B-cell lymphoma but also discussed evidence of a role for c-Rel in solid tumours. It is apparent from reports in these areas that c-Rel function is complex, can vary in different cell types or contexts and potentially contributes to tumorigenesis in tissues where it is not mutated through, for example, regulating the fibrosis–cancer axis. However, in mouse models of colitis-associated adenoma and gastric cancer (Burkitt *et al*, 2013; Burkitt *et al*, 2015), deletion of c-Rel had the opposite effect and resulted in increased susceptibility to disease. This underlines the importance of a thorough understanding of NF-κB subunit function in different cancer types if therapeutic intervention is to avoid unanticipated, negative consequences.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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