translation adds to our understanding of cancer cellular metabolism. While Skrtic et al. describe a dependency for ribosomal translation and oxidative phosphorylation in leukemia cells, the Warburg hypothesis, a cornerstone of cancer cellular metabolism, postulates that cancer cells, unlike normal cells, favor glycolysis for energy production, even under aerobic conditions (Warburg, 1956). This reprogramming of energy metabolism in cancer cells is now considered to be a distinct hallmark of cancer cells (Hanahan and Weinberg, 2011; Hsu and Sabatini, 2008; Luo et al., 2009). The shift in cancer cell metabolism termed "aerobic glycolysis" may be partially an adaptation to lower oxygen levels in tumors, but may also be a direct consequence of activation of certain oncogenes such as *MYC* and *RAS* (Hsu and Sabatini, 2008). In leukemia, inhibition of fatty acid oxidation was recently shown to sensitize leukemia cells to apoptosis induction, but whether this finding is linked to pathways affected by tigecycline remains to be elucidated (Samudio et al., 2010). The full relationship between dependencies on mitochondrial metabolism and glycolytic flux in leukemia cells remains to be determined, but both represent attractive therapeutic targets for the treatment of cancer.

Tigecycline is an FDA-approved drug with known pharmacokinetics and toxicity, facilitating preclinical studies. The authors administered the drug to mice engrafted with primary AML cells and found a reduction in the leukemic burden relative to controls, which demonstrates that AML cells are therapeutically accessible in vivo. Interestingly, combining tigecycline with daunarubicin, a cytotoxic drug in clinical use for AML, had an additive or synergistic antileukemic effect, suggesting that combining the two should be considered for future clinical trials. Similar results were obtained for the combination of tigecycline with Ara-C, another cytotoxic chemotherapeutic agent in routine use for the treatment of AML. Since tigecycline is already used in patients as an antimicrobial, and the toxicity profile is known, clinical trials in AML could be initiated expeditiously to determine the efficacy of tigecycline for the treatment of this challenging disease.

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The Two Faces of NF-κB Signaling in Cancer Development and Therapy

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Constitutive activation of NF-κB signaling can promote oncogenesis, providing a rationale for anticancer strategies that inhibit NF-κB signaling. Two recent publications in *Genes & Development* provide evidence that, in contexts where prosurvival signals derive from other oncogenes, NF-κB activity instead enhances sensitivity to cytotoxic chemotherapy, thereby exerting a tumor-suppressor function.

The nuclear factor-κB (NF-κB) signaling cascade is a major transducer of external signals, controlling the expression of a broad range of genes involved in cell survival, growth, stress response, and inflammation (Hayden and Ghosh, 2008). NF-κB signaling is tightly regulated and aberrant activation of this pathway has been associated with the pathogenesis of solid tumors (Ben-Neriah and Karin, 2011). Recent studies have shown that B cell lymphomas frequently harbor genetic

mutations in NF-κB pathway components resulting in constitutive, and presumably oncogenic, NF-κB signaling by establishing a prosurvival phenotype (Staudt, 2010). Taken together, these findings have identified NF-κB as a critical player in cancer development, creating a solid rationale for the development of antitumor therapies that inhibit NF-κB signaling. However, two recent studies provide compelling evidence that functional NF-κB signaling is required for inducing cytotoxic drug-mediated senescence in tumors with a particular genetic makeup (Chien et al., 2011; Jing et al., 2011) and thus suggest a more complex role for NF-κB in oncogenesis. The implication of these findings is that inhibition of NF-κB signaling would reduce chemosensitivity instead of promoting cell death in such tumors. These studies underscore the importance of determining the context dependency of NF-κB-mediated functions when using NF-κB inhibitors.

The common starting point of these two studies was the phenomenon that cytotoxic chemotherapy can induce tumor cell senescence as a mechanism to halt tumor growth (Schmitt et al., 2002; Kuilman et al., 2010). Therapy-induced senescence exhibits a senescence-associated secretory phenotype (SASP) characterized by a strong cytokine response that acts in an autocrine feedback loop to achieve growth arrest and attracts immune cells that eliminate senescent cells (Coppé et al., 2008; Kuilman and Peeper, 2009). The different experimental strategies followed by these studies both led to the identification of NF-κB signaling as the major mediator of the SASP. Intriguingly, the results suggest that NF-κB pathway inhibition is contraindicated in genetically defined cancer subtypes in which NF-κB activation has no primary role in prosurvival, but that instead require a functional NF-κB pathway for enhancing chemosensitivity.

Chien et al. identified the NF-κB subunit p65 (RelA) bound abundantly to senescent chromatin in a global proteomics analysis and confirmed its transcriptional activity. Whole genome gene expression profiling (GEP) studies revealed that an array of known NF-κB target genes, including SASP components, failed to be induced in p65 knockdown cells that were activated to senesce. These results suggested that NF-κB controls the transcriptional program mediating cellular senescence. Chien et al. then developed a mouse lymphoma model in which p65 can be knocked-down inducibly. Murine lymphomas constitutively expressing *Myc* and *Bcl2* oncogenes undergo senescence in response to cytotoxic chemotherapy. A cytotoxic drug treatment activated NF-κB and induced a senescence response in p65-proficient, but not p65-deficient lymphomas, demonstrating that silencing NF-κB activity impairs the senescence response to chemotherapy in this in vivo model. Consistently, p65-proficient tumors regressed in response to cytotoxic drugs, while p65 knock-down rendered tumors unresponsive. Thus, in this particular context in which apoptosis is suppressed by constitutive BCL2 expression, inhibition of NF-κB activity has the unwanted effect of promoting cytotoxic drug resistance.

Jing et al. pursued a different approach by first performing a GEP analysis on tumors arising in the Eμ-*myc* non-Hodgkin lymphoma mouse model that were retrovirally transduced with BCL2 to block apoptosis and subsequently exposed to cytotoxic agents. They found, in accordance with markedly elevated NF-κB activity upon treatment, that the expression of NF-κB-controlled cytokines characteristic of the SASP was strongly upregulated in the lymphomas. By functionally ablating the NF-κB pathway, Jing et al. then demonstrated in vitro and in vivo, that the observed therapy-induced senescence in the lymphoma cells indeed depended on NF-κB activity. To determine the extent to which activated NF-κB contributed to therapy-induced senescence, the panel of Eμ-*myc* mouse lymphomas was separated into those with high and low NF-κB activity. Since strong NF-κB activity is thought to be oncogenic by upregulating a prosurvival program, they expectedly observed that tumors with high NF-κB activity were resistant to chemotherapy, while those with low NF-κB activity were sensitive. Indeed, the NF-κB high group showed much stronger expression of BCL2 compared to NF-κB low tumors. When they then ectopically expressed BCL2 in tumors of both groups, all tumors were chemoresistant, independent of NF-κB activity. Taken together, it appears that when the antiapoptotic function of NF-κB is replaced by other prosurvival oncogenes, the role of NF-κB in therapy-induced senescence can be unleashed (Figure 1).

Finally, Jing et al. convincingly argue that the observed results may have direct implications for therapy strategies aimed at genetically distinct subtypes of the most common type of human non-Hodgkin lymphomas, diffuse large B cell lymphoma (DLBCL). The major DLBCL subtypes are activated B cell-type (ABC) DLBCL and germinal center B cell-type (GCB) DLBCL that differ in their spectrum of genetic alterations (Rui et al., 2011). While many ABC-DLBCL have mutations in various genes encoding NF-κB pathway components leading to deregulated NFκB signaling, such mutations are rare in GCB-DLBCL (Staudt, 2010). Conversely, a sizable fraction of GCB-DLBCL is associated with recurrent chromosomal translocations that result in deregulated *BCL2* expression; ABC-DLBCL also expresses high amounts of BCL2 likely due to constitutive NF-κB activation. Importantly, GCB-DLBCL has a markedly better clinical outcome following immunochemotherapy compared with ABC-DLBCL. This striking resemblance of the genetic and clinical characteristics of these DLBCL subtypes to the situation encountered in their lymphoma mouse model led Jing et al. to interrogate a GEP data set of human DLBCL that were treated with standard immunochemotherapy. By correlating an established NF-κB "signature" in the GEP data with progression-free survival, they observed that *BCL2*-overexpressing GCB-DLBCL tumors with high NF-κB activity showed a more favorable prognosis after chemotherapy compared to tumors with low NF-κB activity. As predicted, NF-κB activity did not correlate with survival in patients with ABC-DLBCL. While it remains to be proved experimentally whether the more favorable clinical course of GCB-DLBCL compared with ABC-DLCBL in humans is mechanistically linked to an NF-κB-mediated, therapy-induced senescence in tumor cells, the elegant studies by Chien et al. (2011) and Jing et al. (2011) provide new light on the context-dependent roles of NF-κB in oncogenesis and therapy.

The opposing roles of NF-κB in oncogenesis, promoting tumorigenesis on one hand and mediating therapy-induced senescence on the other (see Figure 1),

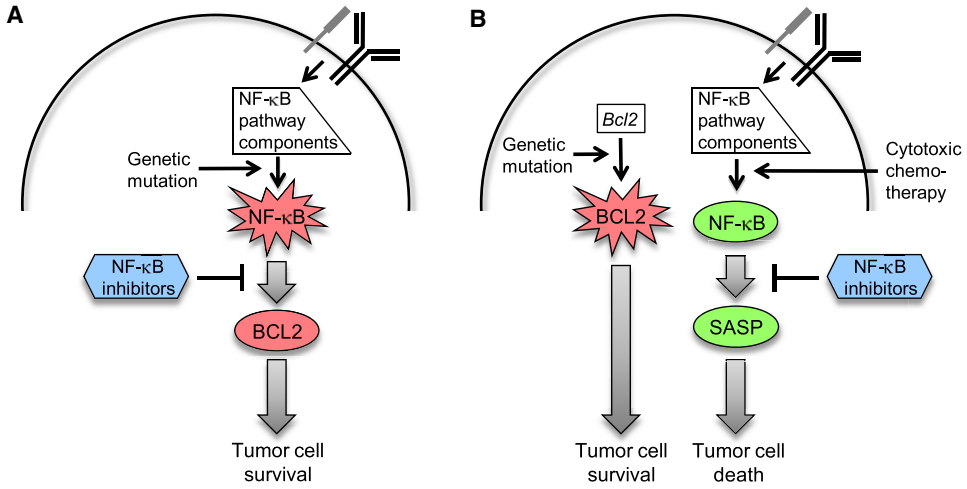

Figure 1. Model for the Context-Dependent Opposing Roles of NF-κB Signaling in Cancer Development and Therapy
(A) In tumors with genetic mutations in NF-κB pathway components leading to constitutive NF-κB signaling, the prosurvival *BCL2* oncogene is upregulated. In these tumors, such as ABC-DLBCL, NF-κB inhibitors are beneficial as they counteract the oncogenic function of NF-κB and would promote tumor cell death. (B) In tumors where the prosurvival signal derives from NF-κB-independent *BCL2* overexpression, a functional NF-κB pathway is required to mediate the therapy-induced senescence response by activating the transcription of genes of SASP. In this scenario, such as in GCB-DLBCL, NF-κB inhibitors are detrimental as they interfere with the senescence response that would normally promote tumor cell death.

have significant therapeutic implications. First, the findings imply that the use of NF-κB inhibitors in the clinic requires thorough assessment, since NF-κB inhibition could interfere with the cytotoxicity of standard chemotherapy in combination therapies. Second, Jing et al. (2011) observed that ectopic activation of NF-κB in mouse lymphomas with low NF-κB activity enhances therapy-induced senescence; these results provide a rationale for the development of therapeutic strategies that enhance chemosensitivity by activating NF-κB concomitantly with cytotoxic chemotherapy. Third, elucidating the precise mechanisms of NF-κB in oncogenesis versus therapy-induced senescence could lead to the identification of crucial downstream components of NF-κB that mediate chemosensitivity, with the eventual goal of developing strategies to boost senescence in tumors where NF-κB's oncogenic function dominates. The findings by Chien et al. (2011) and Jing et al. (2011) provide important new insights into the complexity of NF-κB signaling in cancer cells. In future studies, this knowledge will likely be exploited for the development of specific, more effective anticancer therapies.

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