Clinically relevant findings.

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Editorial

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The fully malignant cell has usually accumulated mutations that affect a variety of processes. For example, it is clear that many tumor cells contain mutations that sustain cell growth, that block growth inhibition and apoptosis, that affect DNA repair, and that allow the tumor to escape immune surveillance. The identification of the cellular processes that are altered in specific cancers forms the basis of much current research into molecular diagnosis and treatment. Rel/NF-κB transcription factors control myriad cellular processes in eukaryotes (for an extensive series of reviews see reference 1). In vertebrates, this family includes five distinct members (c-Rel, RelB, p50/p105, p52/p100, and RelA [p65]). Rel proteins can form a combinatorially diverse array of hetero- and homodimers that regulate the expression of a large number of cellular and viral genes. Classical NF-κB is a heterodimer of p50 and RelA, and is the Rel complex about which most is known. In most cells, NF-κB is sequestered as a latent inactive complex in the cytoplasm, due to interaction with an inhibitor protein, IκB. There are three predominant IκB proteins (IκB-α, IκB-β, and IκB-ϵ), the levels of which vary in different cell types. The regulation of NF-κB activity by IκB-α is known in some detail. A variety of extracellular signals induce site-specific phosphorylation of IκB-α, which leads to ubiquitination and proteasome-mediated degradation of this inhibitor and thus frees the NF-κB complex to enter the nucleus and alter gene transcription. Therefore, key regulatory steps in signal-induced control of NF-κB activation include the rate of phosphorylation, ubiquitination, and degradation of IκB-α. However, IκB-α also undergoes a basal turnover in cells by a process that is distinct from signal-induced degradation. Certain cells, such as mature B cells, display substantial amounts of constitutively nuclear NF-κB activity, which appears to be the result of increased basal degradation of IκB-α (2). The retroviral oncoprotein v-Rel, the first identified member of the Rel/NF-κB family, induces rapidly fatal lymphomas in young birds and transforms and immortalizes a number of cell types in culture (for review see reference 1). As such, v-Rel has provided much of the incentive for looking at changes associated with Rel factors in human cancers. It is now clear that several human cancers contain rearrangements, amplifications, or mutations that alter the expression or function of cellular Rel family transcription factors. However, it has not been possible to induce cancer in any animal model system with a mammalian Rel protein, suggesting that Rel transcription factors may provide an accessory function for mammalian cancer development, rather than serving a direct effector function. Consistent with this hypothesis, several studies have demonstrated that specific Rel proteins can act as survival factors (e.g., blockers of apoptosis) in a number of cell types (for review see reference 1). It is within this framework that two studies in this issue of *The Journal* describe tumor cell types that express constitutively nuclear and active Rel complexes that contribute to the viability of these tumor cells. In one report, Bargou et al. (3) confirm previous studies showing that several Hodgkin's lymphoma cell lines contain constitutively nuclear RelA-containing DNA-binding complexes, and proceed to show that inhibition of active NF-κB in one Hodgkin's cell line by overexpression of a noninducible superrepressing IκB-α molecule also inhibits proliferation and tumorigenicity of these cells. In a second report, Sovak et al. (4) show that many breast cancer cells also contain high levels of nuclear NF-κB DNA-binding activity, which is essential for the survival of these cells in culture. Perhaps more importantly, Sovak et al. show that chemically induced breast cancers in rats and many primary human breast cancer samples have high levels of nuclear Rel proteins or Rel DNA-binding activity. Similarly, a recent report has demonstrated that human thyroid carcinoma cells require nuclear RelA activity for proliferation and malignant transformation in vitro (5). It should be noted that although a subset of tumor cells in these three reports does not show increased nuclear NF-κB DNA-binding activity, Finco et al. (6) have found recently that some transformed cells have elevated RelA-mediated transactivation activity in the absence of apparent increases in nuclear κB site DNA-binding activity. The discovery of high levels of nuclear Rel/NF-κB activity in a variety of tumor cell types is likely only the preface to a larger story. Little is known about how constitutive nuclear NF-κB activity contributes to the malignancy of these cells. Based on several lines of evidence, it is almost certain that NF-κB directly causes increased expression of genes which contribute to the survival of these tumor cells, perhaps by blocking apoptosis. Along these lines, one can speculate that the diffuse and small nature of the tumors caused by Hodgkin's cells engineered to express a superrepressor form of IκB-α (3) signifies the increased sensitivity of these cells to in vivo induced apoptosis, i.e., that large solid tumors cannot form because internal tumor cells, lacking nuclear NF-κB activity, are sensitive to hypoxia-induced apoptosis. Relevant target genes for the constitutive NF-κB activity in tumor cells may include c-*myc* (1), those encoding antiapoptotic proteins, such as IAP proteins (7, 8), superoxide dismutase, and A20 (1), or genes which contribute to proliferation, a cellular state that may be incompatible with apoptosis. Although the two papers in this issue of *The Journal* show that some tumor cells have constitutive nuclear NF-κB DNA-binding activity, they do not unveil the molecular basis for this nuclear activity. For example, is it simply due to elevated levels of expression of Rel transcription factors which overwhelm the inhibitory IκB activity in these cells? Do these tumors synthesize an autocrine factor that constitutively induces nuclear translocation of NF-κB? Or, does NF-κB show an increased rate of nuclear translocation due to alterations (perhaps subtle) in the IκB regulatory system in these cells? If nuclear NF-κB activity is essential for the survival of these tumor cells, one might expect to find alterations at different levels of IκB control in different tumors. Consistent with this hypothesis, Wood et al. (9) have shown recently that some Hodgkin cell lines, which also have constitutively nuclear NF-κB activity,

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synthesize aberrant IκB-α proteins. Bargou et al. and Sovak et al. have not determined what percentage of total Rel/NF-κB protein is nuclear in the tumor cells they have studied. Based on other cell types containing nuclear NF-κB activity, it is likely to be fairly low (e.g., 10%; see reference 2). That is, while partial induction of nuclear NF-κB activity may be protective, full induction of NF-κB activity may itself be toxic or may induce apoptosis; many tumor cells are likely to have achieved a critical balance of nuclear versus cytoplasmic NF-κB. In short, chronic overinduction of nuclear NF-κB activity may be as lethal to a tumor cell as inhibition of this activity. There are several obvious clinical implications of these findings. First, they suggest that it may be possible to use drugs that target induction or maintenance of nuclear NF-κB activity (e.g., reference 10) as a means to selectively kill certain cancer cells or to render these cells more sensitive to chemotherapeutic agents. Second, because changes in nuclear NF-κB activity may be a late effect in certain cancers, it may serve as a diagnostic marker for the staging of certain cancers. Lastly, these findings suggest that mice with gene knockouts that eliminate the expression of specific Rel/NF-κB proteins or of specific target genes for these factors may provide important animal model systems for studying the development of particular human cancers.

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