diverse cancer model systems to examine the safety and effectiveness of NF-κB therapeutics. In that regard, computational modeling may prove useful in integrating the complexity of cell-intrinsic and intercellular molecular mechanisms, tonic and responsive signaling, and pharmacokinetics and drug metabolism to predict or evaluate the effectiveness of therapeutic agents.

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A Radical Role for p38 MAPK in Tumor Initiation

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It is established that p38 MAPK can negatively regulate tumorigenesis, but the mechanism is incompletely understood. A new study in this issue of *Cancer Cell* shows that p38 MAP kinase plays a selective role in tumor initiation mediated by oxidative stress.

Cells sense changes in their environment by activating signal transduction pathways that direct biochemical programs to mediate proliferation, differentiation, and survival. The mitogen-activated protein kinase (MAPK) family represents an important group of signaling proteins that can regulate these fundamental cellular processes. The extracellular signal-regulated kinase (ERK) MAPK pathway primarily directs a program of proliferation and survival, while the cJun NH_2-terminal kinase (JNK) pathway can promote either proliferation or apoptosis (Kennedy and Davis, 2003). Conversely, the p38 MAPK pathway is activated upon cellular stress and often engages pathways that can block proliferation or promote apoptosis (Bulavin and Fornace, 2004).

The importance of MAPK pathways to cell proliferation and death is highlighted by the observation that dysregulation of these kinase cascades can result in cell transformation and cancer. Activated ERK and JNK pathways can lead to increased proliferation and survival, although loss of JNK in some instances may also promote tumorigenesis (Kennedy and Davis, 2003). In contrast, the p38 MAPK pathway is implicated in suppression of tumorigenesis because it can inhibit cell growth by decreasing the expression of cyclin D (Lavoie et al., 1996), inhibit the activity of Cdc25 phosphatases (Manke et al., 2005), and engage the p16/Rb and $p19^{ARF}$/p53 tumor suppressor pathways (Bulavin et al., 2002, 2004). The p38 MAPK pathway can also cause apoptosis by a mechanism that is incompletely understood but may involve the phosphorylation of members of the Bcl2 family and activation of the mitochondrial apoptotic pathway (Figure 1). The selectivity of the p38 MAPK signaling pathway in tumor suppression is unclear. However, a new study by Dolado et al. (2007) reported in this issue of *Cancer Cell* now demonstrates that p38 MAPK selectively functions as a sensor of oxidative stress during the initiation of tumorigenesis.

Dolado et al. examined the properties of fibroblasts isolated from *p38*$\alpha^{-/-}$ mice when transformed by an activated HRasV12 oncogene. They report that p38α deficiency caused increased proliferation, an increased number of foci, an increased ability to form colonies in soft agar, and decreased apoptosis. The p38α-deficient cells also

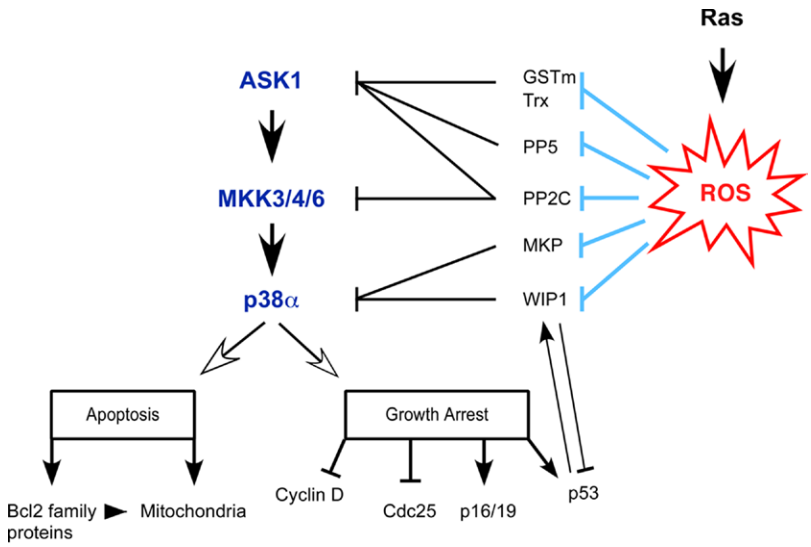

Figure 1. Schematic Illustration of the Effects of Reactive Oxygen Species on the p38 MAP Kinase Signal Transduction Pathway
ROS, reactive oxygen species.

formed subcutaneous tumors more rapidly than wild-type cells. Importantly, these effects of p38α deficiency were rescued by ectopic expression of p38 MAPK. Together, these data suggest that p38 MAPK acts to suppress tumor formation by HRas and lend strong support to the conclusions derived from previous studies that the p38 MAPK pathway contributes to tumor suppression (Brancho et al., 2003; Bulavin et al., 2002; Chen et al., 2000).

Dolado et al. show that the effects of p38α deficiency on HRas-stimulated transformation are mediated by reactive oxygen species (ROS). HRas is known to cause an increase in ROS production (Irani et al., 1997). Interestingly, transformed p38α-deficient cells accumulate much larger amounts of ROS than wild-type cells. Dolado et al. report that ROS-stimulated p38 MAPK activity acts to induce apoptosis in wild-type cells and that p38α-deficient cells are resistant to ROS-induced apoptosis. Pharmacological studies indicated that the source of ROS was from NADPH oxidases rather than mitochondria. Indeed, increased expression of NOX1 and NOX4 was detected in p38α-deficient cells. Dolado et al. propose that the increased accumulation of ROS in p38α-deficient cells contributes to the transformed phenotype because of the ability of ROS to induce genetic instability. The observation that the addition of an antioxidant to p38α-deficient cells can suppress their transformed phenotype is consistent with this conclusion.

How do ROS lead to the activation of the p38 MAPK pathway? Dolado et al. suggest that the activation of p38 MAPK is mediated by the MAPK kinase kinase ASK1. This protein kinase is activated by oligomerization and phosphorylation. However, in nonstressed cells, these processes are inhibited by the interaction of ASK1 with Thioredoxin (Trx) and Glutathione S-transferase μ (GSTm) proteins. Following ROS-mediated stress, the Trx and GSTm proteins dissociate from ASK1 in a manner that may involve oxidation of cysteine residues critical for these interactions. ASK1 can then activate the p38 MAPK pathway by phosphorylating and activating the MAPK kinases MKK3, MKK4, and MKK6 (Brancho et al., 2003). Therefore, Trx and GSTm proteins may act as ROS sentinels that are triggered by oxidation to activate stress MAPK pathways in response to oncogenic transformation (Figure 1).

ROS can also employ another tactic to activate MAPK pathways—the inactivation of phosphatases. The best-characterized example of ROS-mediated inactivation of a phosphatase is provided by structural analysis of PTP1B, which is inhibited by the reversible ROS-mediated oxidation of an active site cysteine residue. ROS may similarly modify a number of other phosphatases that inhibit the p38 MAPK pathway, including PP2Cε and PP5, which inactivate ASK1; PP2Cα, which inactivates MAPK kinases; and MAPK phosphatases (MKP) and WIP1/PPM1D, which inactivate p38 MAPK (Figure 1). Thus, the effect of ROS to activate the ASK1/p38 pathway is potentiated by the effect of ROS to inhibit phosphatases that inactivate the p38 MAPK pathway. A direct demonstration that ROS-mediated phosphatase inhibition contributes to p38 MAPK activation is required. Nevertheless, genetic analysis has confirmed that loss of p38 MAPK phosphatase function can modulate tumorigenesis. Thus, deficiency of the p38 MAPK phosphatase WIP1/PPM1D suppresses transformation caused by HRas (Bulavin et al., 2002). Moreover, WIP1-deficient mice display a delay in mammary tumorigenesis that was dependent on increased p38 MAPK activity (Bulavin et al., 2004). Interestingly, WIP1-deficient cells are unable to form tumors because of increased p38 MAPK activity and subsequently increased expression of the *Cdkn2a* tumor suppressor locus that encodes p19 ^{ARF}/p16^{Ink4a}, but the tumorigenic potential of WIP1-deficient cells is restored by *Cdkn2a* deletion (Bulavin et al., 2004).

Is ROS-stimulated p38 MAPK activation relevant to human cancer? p38 MAPK appears to protect against oncogenes that produce high levels of ROS. In this regard, Dolado et al. demonstrate that high levels of ROS were induced by some oncogenes (e.g., *HRas*, *NRas*, and *Neu*), and this result correlated with increased transformation of p38α-deficient fibroblasts. The suggestion that p38 MAPK may protect against ROS-stimulated transformation may therefore have clinical significance. The importance of the p38 MAPK pathway to cancer is further reflected by the observation that mutation or overexpression of genes that regulate p38 MAPK activity are found in human tumors. For example, *WIP1/PPM1D* is an oncogene that is overexpressed in mammary tumors (Bulavin

et al., 2002). No mutations in p38α have been reported in primary tumors; the presence of three other p38 MAPK genes could compensate for any partial loss of function of p38α.

The successful creation of a tumor requires that the apoptotic and antiproliferative effects of p38 MAPK must be suppressed. Dolado et al. propose that one mechanism employed by tumor cells to overcome the tumor-suppressive function of p38 MAPK is to uncouple the production of ROS from p38 MAPK activation. The increased expression of GSTm proteins (Gstm1 and GSTm2) observed in tumor cells may serve this function. Dolado et al. show that reduced expression of GSTm2 in MCF7 breast cancer cells increased p38 MAPK activity and apoptosis, whereas forced overexpression of GSTm2 further potentiated the transformed phenotype. Since GSTm proteins can inhibit the ASK1/p38 pathway, these data are compelling. However, it is unclear if the overexpression of GSTm proteins in these cancer cells is a cause of or a result of transformation or if the increased levels reflect responses to tumor treatment or passage in tissue culture. Nevertheless, proteins that serve as sensors for ROS levels (e.g., GSTm1/2) and other proteins that attenuate the p38 MAPK pathway (e.g., WIP1) represent candidate drug targets for the design of new therapies for cancer.

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Ten Genes for Inherited Breast Cancer

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Inherited breast cancer is associated with germline mutations in ten different genes in pathways critical to genomic integrity. *BRCA1* and *BRCA2* mutations confer very high risks of breast and ovarian cancer. *p53* and *PTEN* mutations lead to very high breast cancer risks associated with rare cancer syndromes. Mutations in *CHEK2*, *ATM*, *NBS1*, *RAD50*, *BRIP1*, and *PALB2* are associated with doubling of breast cancer risks. In addition, biallelic mutations in *BRCA2*, *BRIP1*, and *PALB2* cause Fanconi anemia. The convergence of these genes in a shared role reveals underlying biology of these illnesses and suggests still other breast cancer genes.

Fanconi anemia (FA) is a recessive syndrome characterized by chromosomal instability, congenital malformations, progressive bone marrow failure, and hypersensitivity to DNA crosslinking agents (Taniguchi and D'Andrea, 2006). The genes responsible for 11 of the 12 FA complementation groups (A, B, C, D1, D2, E, F, G, I, J, L, and M) have been identified. Eight FA proteins form a complex that activates FANCD2 via monoubiquitination (Figure 1). Monoubiquitinated FANCD2 then translocates to damage-induced nuclear foci containing BRCA1, BRCA2, and RAD51, allowing recognition and repair of DNA interstrand crosslinks. Biallelic mutations in *BRCA2* cause a rare and highly cancer-prone form of FA (FA-D1) (Howlett et al., 2002), and biallelic mutations in the DNA helicase *BRIP1* cause FA-J (Litman et al., 2005). BRCA2 and BRIP1 function downstream of the FANCD2 activation step.

Biallelic mutations in *PALB2*, the "partner and localizer of BRCA2," are responsible for a new FA complementation group, FA-N (Xia et al., 2006a; Reid et al., 2006). PALB2 was originally identified in a screen for proteins present in complexes containing BRCA2 (Xia et al., 2006b). PALB2 binds to the extreme N terminus of BRCA2 and stabilizes BRCA2 in key nuclear structures, allowing it to function in DNA repair and at the S phase checkpoint. Decrease of