New insights into oncogenic stress

Kevin M Haigis & Alejandro Sweet-Cordero

Expression of oncogenes in otherwise normal cells often leads to the activation of anti-oncogenic pathways through a poorly understood process described as 'oncogenic stress'. A new study implicates the Jnk pathway signaling in the activation of p53 in response to both K-Ras and Neu oncogene expression.

For more than a decade, it has been understood that activation of an individual oncogene is typically insufficient to induce cellular transformation and can instead induce permanent cell cycle arrest. This observation, first made by Serrano, Lowe and colleagues[1], gave rise to the concept of 'oncogenic stress' as a means of tumor suppression. Now designated oncogene-induced senescence (OIS), the importance of growth arrest induced by oncogenic stress was controversial for some time, as it was unclear if OIS was an artifact of overexpressing oncogenes in cells already under culture stress. Nevertheless, multiple reports of *in vivo* OIS (for example, the induction of senescent nevi in human and mouse melanocytes expressing endogenously activated B-Raf[2,3]) have established OIS as a *bona fide* negative regulator of tumorigenesis. What has remained unclear is how a cell senses oncogenic stress and ultimately commits to cell cycle arrest. On page 212 of this issue[4], Josef Penninger and colleagues perform a genetic tour de force to identify the c-Jun N-terminal kinase (Jnk) signaling pathway as a previously unknown sensor of oncogenic stress that plays an important role in tumor suppression. While answering important questions relevant to Jnk pathway function and the molecular mechanisms underlying oncogene-induced cell cycle arrest, this study suggests new avenues for future investigation.

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Jnk negatively regulates tumorigenesis

Genetic knockout studies in mice indicate that the three Jnk family members perform both overlapping and distinct functions in development and tumorigenesis[5]. However, conflicting results regarding the pro- or anti-oncogenic functions of Jnk-family kinases have arisen from *in vitro* experiments[5]. Rather than study the family members in isolation, Schramek *et al.* studied Jnk function as a whole by conditionally deleting Mkk7, a dual-specificity Map2k that is required for Jnk activation. Conditional Mkk7 mice were then crossed with mouse models of lung and mammary oncogenesis driven by the K-Ras and Neu oncogenes, respectively. The authors show that loss of Mkk7 potentiates tumor development by abrogating the stress-induced stabilization of p53 provoked by these

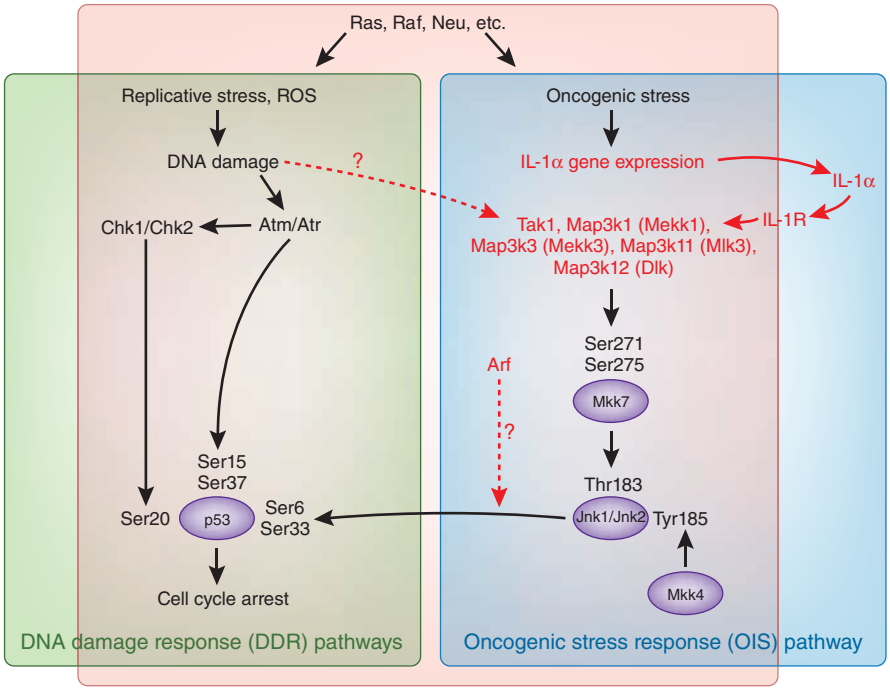

Figure 1 Pathways leading to cell cycle arrest due to oncogenic stress. The induction of DDR by activated oncogenes can feed into p53 through the DNA damage kinases Chk1/Chk2 and Atm/Atr, which phosphorylate p53 on distinct residues. DDR may also activate Jnk signaling directly. An alternate mechanism for activation of Mkk7-Jnk includes the stress-induced transcriptional upregulation of inflammatory cytokines, for example, IL-1α. Secreted IL-1α could activate Mkk7-Jnk in an autocrine or paracrine fashion through the IL-1 receptor and any of a number of Map3ks. Signaling from Mkk7 to p53 could be modulated by Mkk4, an alternate Map2k for Jnk, and/or Arf, a positive regulator of p53 stability. Annotated residues are phosphorylated in response to stress. The components in red are speculative. ROS, reactive oxygen species.

oncogenes. These data, in combination with additional genetic studies, strongly suggest that Jnk1 and Jnk2 perform redundant functions downstream of Mkk7 in phosphorylating p53 in response to oncogenic stress (**Fig. 1**). An interesting question that emerges from these studies is whether a specific isoform of Mkk7 is responsible for the transmission of the oncogenic stress signal to Jnk and p53. *Map2k7*, which encodes Mkk7, is alternatively spliced to produce six distinct kinase isoforms, each with differing kinase activity and affinity for Jnk[6]. Moreover, Mkk7 is activated through phosphorylation of its activation loop by any of a number of Map3ks (**Fig. 1**). The upstream kinases that are responsive to oncogenic stress remain unknown.

Pathways to oncogenic stress

The normal cellular response to oncogenic stress requires the tumor suppressor protein p53. Nevertheless, the mechanisms linking oncogene activation to p53 induction have remained controversial. Evidence from studies of early-stage human tumors and animal models suggests that oncogene-induced replication stress activates a DNA damage response (DDR), which in turn activates p53 (**Fig. 1**)[7–9]. The implication of these studies is that p53-dependent tumor suppression in response to oncogenic stress acts through the DDR. An alternative view, also supported by compelling evidence, suggests that the acute response to DNA damage is not the critical tumor suppressive function of p53. Elegant studies performed by Christoporou *et al.* have shown that only delayed activation of p53 (several days after acute DNA damage) can protect mice from later development of radiation-induced cancer[10]. Although the tumor suppressor function of p53 is dependent on the upstream factor Arf, the stabilization of p53 downstream of the DDR is Arf independent[11,12]. How do the findings by Schramek *et al.* fit into this picture? Their study shows that Mkk7 is required for activation of p53 in response to oncogenic stress and also in response to DNA damage[4]. It is possible, however, that oncogenic stress and DNA damage feed into p53 independently (**Fig. 1**). Indeed, the authors observed that acute K-Ras activation *in vitro* was not sufficient to activate the DDR, whereas it did result in upregulation of p53 target genes. It would be of interest to determine whether or not Arf functions to regulate the stabilization of p53 downstream of Mkk7 and Jnk in response to oncogenic stress.

OIS-induced activation of Mkk7

How does a cell sense oncogenic stress and subsequently activate Mkk7? One possibility, as suggested by Schramek *et al.* is that Mkk7, or an upstream Map3k, is directly activated by DNA damage, similar to other kinases that phosphorylate p53 to enhance its stability (**Fig. 1**). Alternately, Mkk7 could be activated in an indirect way, for example, through a feedback pathway. Indeed, Mkk7-Jnk signaling is highly activated by cytokines, such as IL-1α and Tnfα (ref. 13). Moreover, cells experiencing oncogenic stress establish a cytokine milieu by transcriptionally upregulating an inflammatory gene expression program[14,15]. IL-1α is among the cytokines that are dramatically induced by oncogenic stress[15]. As a result, Mkk7 could operate downstream in an autocrine-paracrine cytokine signaling pathway that promotes OIS (**Fig. 1**). Although further studies are required to determine precisely how oncogenic stress leads to p53 stabilization and subsequent cell cycle arrest, it is clear that the Jnk signaling pathway is a key player in this phenomenon.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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A twist on admixture mapping

Stephen J Chanock

A new study uses genome-wide SNP genotypes to identify a subset of children undergoing therapy for acute lymphoblastic leukemia that are at increased risk for relapse. Borrowing from the classical approach of admixture mapping, the work shows how genome-wide assessment of genetic ancestry can be used as a biomarker for disease outcome.

Over the last 40 years, there has been a steady improvement in survival rates for children with acute lymphoblastic leukemia (ALL), the most common form of pediatric cancer. Though it is viewed as a 'curable' cancer by some, this is not true for all children, as about 20% of affected children will suffer relapse and eventually die from this condition. For several decades, pediatric oncologists have recognized that children designated as Hispanic have a higher risk for relapse of ALL[1]. On page 237 of this issue[2], Mary Relling and colleagues use genome-wide SNP genotypes and principal component analysis[3] to explore the effects of genetic ancestry on the risk of ALL relapse (**Fig. 1**). They report that children estimated to have 10% or more Native American ancestry have a higher rate of relapse than children from other backgrounds, with an estimated effect roughly similar to that of self-reported Hispanic ancestry.

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Admixture mapping and beyond

Today, pediatric oncologists must balance efficacy and toxicity in deciding whether to treat a child with more or less intensive therapy based on clinical parameters. The determinants for risk categorization have expanded from clinical observations, such as leukocyte count at diagnosis, age at diagnosis and ethnic background, to molecular analyses, such as DNA index, T lymphocyte lineage, the presence of specific chromosomal translocations in leukemic blasts and evidence of minimal residual disease early in therapy. The studies used by Yang *et al.*[2] to investigate the role of genetic ancestry on treatment outcome were designed to evaluate response to late intensification of therapy. Notably, Yang *et al.*[2] found that one additional round of therapy