survey in the northern part of the basin has provided direct evidence of active strike-slip faulting (*12*) at several north-south active faults. These faults have a present-day left-lateral movement and are reactivated fracture zones of a fossil spreading center. According to the seismicity farther north and south, the faults must be at least 1000 km long, reaching the Sumatra trench to the north.

The large magnitude of the 18 June 2000 Wharton Basin earthquake and the availability of high-quality digital data with good station coverage allowed Robinson *et al.* (*5*) to model the details of the source. The earthquake turns out to have an unusual mechanism: Two subevents simultaneously ruptured a nearly north-south plane and a plane nearly conjugate to the first. Rupture along the north-south plane was similar to the movement along the surveyed strike-slip faults 800 km farther northwest. Therefore, all the fracture zones in the northern Wharton Basin are probably reactivated by strike-slip faulting between the Nynety East ridge and the Investigator ridge (see the figure). The northern Wharton Basin thus appears to be cut into north-south slivers that subduct more and more easily the further east one goes (*12*). Rupture along the east-west plane introduces some northwest-southeast compressional deformation (*5*).

The east-west plane is consistent with the orientation of the abyssal hills of the oceanic lithosphere. The lithosphere thus deforms along preexisting weakness directions: the north-south fracture zones and the east-west abyssal hill fabric, both of which originate at the mid-ocean spreading centers. Note that in the Central Indian Basin, most of the reverse faults result from the reactivation of the abyssal hill fabric (*8*). In both basins, the lithosphere may deform at large scale by buckling and folding perpendicular to the compression axis, but brittle failure of its upper part occurs along preexisting weakness directions (see the figure).

Some questions are still open. Is rupture along north-south and east-west directions specific to this earthquake or not? The June 18, 2000 earthquake is located in a broad area covered by numerous ridges and seamounts. Is there an influence of volcanism in the deformation process in this area? And how can southwest-northeast folding of the Wharton Basin lithosphere be compatible with brittle failure along north-south and east-west directions? To resolve these questions, we need to better understand the role of preexisting features in the mechanical response of an oceanic lithosphere when it is subjected to high compressive stress.

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14. I thank Hélène Hébert and Michel Diament for their contributions.

PERSPECTIVES: MOLECULAR BIOLOGY

Getting p53 Out of the Nucleus

Vanesa Gottifredi and Carol Prives

A cell becomes cancerous because it has sustained a number of genetic changes. To avoid accruing such changes, cells need a protective surveillance system. The tumor suppressor protein p53 is a transcription factor that switches on a series of protective genes when the cell is exposed to stressful events. Many solid tumors contain defective forms of p53 that are unable to stop cells from proliferating when, for example, their DNA has been damaged. The current picture of p53, however, requires that we view this transcription factor as working in partnership with its negative regulator MDM2 (see the figure). The p53–MDM2 partnership appears to operate rather simply: Activated p53 switches on the *MDM2* gene, and the MDM2 protein (an E3 ubiquitin ligase with a RING finger motif) then represses p53 activity by inducing its degradation in proteasomes (*1*).

Both p53 and MDM2 move between the nucleus and cytoplasm in the cell. They possess nuclear localization signals (NLSs) and so are found predominantly in the nucleus. But they must also be able to leave the nucleus and enter the cytoplasm under certain conditions. To exit the nucleus through the nuclear pores, proteins bigger than 40 kilodaltons must bind to nuclear export receptors; and to bind to these receptors, proteins must possess a nuclear export signal (NES). Both MDM2 (*2*) and p53 (*3*) contain an NES—the p53 NES resides in its carboxyl terminus between amino acids 320 and 355 (*3*). It comes as something of a surprise, then, to hear from Zhang and Xiong on page 1910 of this issue that p53 possesses another NES in its amino terminus, between amino acids 11 and 27 (*4*). This amino-terminal region becomes phosphorylated at several residues in response to different types of cellular stress such as DNA damage (*5*), and phosphorylation of at least one of these residues correlates with reduced nuclear export of p53.

The identification of a second NES in the amino terminus of p53 is intriguing because it is not clear what the different NES signals in p53 and MDM2 do. Also unclear is precisely how phosphorylation regulates the nuclear export of p53. Finally, there is plenty of room to speculate about why p53 needs to be exported from the nucleus at all.

A few years ago, Roth and colleagues set out to identify the tasks of the p53 and MDM2 NES (*2*). They carried out heterokaryon assays in which two different cell types (one with and one without MDM2) were fused together, resulting in two nuclei within a mutual cytoplasm. After incubating the heterokaryons with a protein synthesis inhibitor, they found that the MDM2-deficient nucleus had acquired MDM2, demonstrating that MDM2 was able to move from one nucleus into the other. Importantly, their data also revealed that shuttling of MDM2 from the nucleus into the cytoplasm was required for degradation of p53 (*2*). Moreover, MDM2 with either a defective NLS or NES could not degrade p53 (*6*), implicating MDM2 itself in the movement of p53 to the cytoplasm. This hypothesis came under challenge when an NES was discovered in the carboxyl-terminal domain of p53 (*3*), which is the region responsible for the assembly of p53 monomers into the active tetramer. The p53 NES is presumed to be masked and inactive when p53 forms a tetramer, but functional when p53 is either a monomer or a dimer. Although attractive, this model is difficult to prove because it is nearly impossible to determine the oligomeric state of the scant amount of p53 in unstressed cells. Then, two groups (*7*, *8*) put forward a unifying hypothesis, prompted by the somewhat unexpected observation that the NES of MDM2 is dispensable for nuclear export of p53, whereas the RING finger motif of MDM2 is not. This suggests that as MDM2 adds ubiquitin molecules (ubiquitination) onto p53 in the nucleus, the NES of p53 becomes unmasked, enabling ubiquitinated p53 to move into the cytoplasm and to be degraded by proteasomes.

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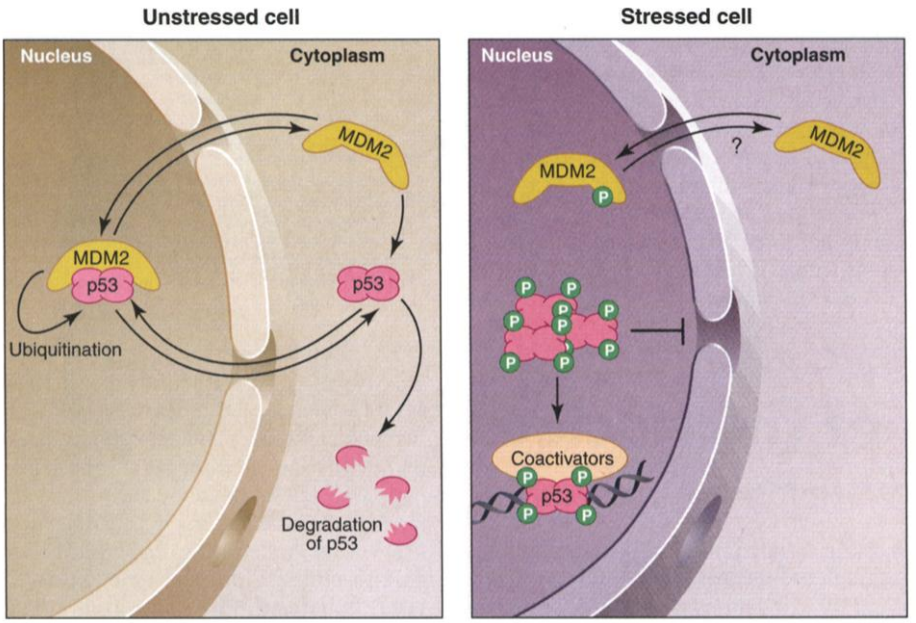
Now that a second p53 NES has been identified, the question to ask is, why two? The most straightforward explanation is that two are better than one. This could be the case as chimeric proteins composed of a green fluorescent protein (GFP) marker fused with either the amino- or carboxyl-terminal NES of p53 leave the nucleus relatively inefficiently, whereas a chimera in which both p53 NESs are attached to one GFP molecule accumulates more rapidly in the cytoplasm. Nevertheless, this simple interpretation is complicated by the fact that both p53 NESs overlap with regions that have other activities. The carboxyl-terminal NES is buried within the domain where p53 assembles with other p53 molecules into tetramers. The amino-terminal NES falls within a region that is required for p53 to bind to either MDM2 or to transcription factors such as the TAFs and histone acetylases (*9*). These interactions are likely to occlude the amino-terminal NES. It is possible, however, that there may exist time windows or circumstances during which the p53 amino-terminal NES is exposed. For example, p53 is preferentially bound to MDM2 during the G_2 phase of the cell cycle (*10*). Additionally, murine MDM2 becomes phosphorylated in early S phase at threonine-216, and such phosphorylation weakens its interaction with p53 in vitro (*11*). Therefore, it is possible that the two p53 NESs may in some cases collaborate to ensure that p53 is efficiently exported from the nucleus, and under other circumstances may operate independently.

Two separate pieces of evidence support the conclusion that phosphorylated p53 cannot leave the nucleus. Under conditions where some of the total cellular p53 is exported, p53 that is phosphorylated at serine-15 in response to ultraviolet irradiation appears to be completely retained in the nucleus. Furthermore, a mutant p53 that mimics phosphorylation of p53 at serine-15 and serine-20 does not shuttle into the cytoplasm. The most clear-cut explanation for this is that phosphorylation directly interferes with the interaction between the p53 amino-terminal NES and the nuclear export machinery. But other explanations exist too—for example, phosphorylation of p53 could increase recruitment of transcriptional cofactors (*12*), resulting in the export machinery having to compete for binding sites on p53.

Both the amino- and carboxyl-terminal NESs of p53 are likely to be affected by many forms of stress—for example, ultraviolet irradiation causes phosphorylation of the *same* p53 molecule at serine-15 and serine-392 (*13*). Indeed, phosphorylation of serine-392 was shown to result in more efficient formation of carboxyl-terminal tetramers (*14*). Given that ultraviolet irradiation simultaneously inhibits both NESs of p53, it may be difficult to determine which NES is essential for nuclear export. It is noteworthy that phosphorylation of p53 and also of MDM2 in response to DNA damage correlates with nuclear retention of p53 (*15*). Thus, stress-induced phosphorylation has multiple effects that may be coordinated to ensure efficient retention of p53 in the nucleus, where it is able to carry out its job as a master transcription factor.

Why should p53 ever have to leave the nucleus? A number of suggestions have been put forth to answer this question (*6*). Possibly there is a direct link between nuclear pores and proteasomes such that p53 shuttles out of the nucleus directly into proteasomes, where it is rapidly degraded. Alternatively, there could be a protein complex in the nucleus that binds to p53 (or to p53 and MDM2) and is required by the proteasomes for p53 degradation. We propose yet another reason for p53 nuclear export: Perhaps p53 is mono-ubiquitinated in the nucleus and then has to move to the cytoplasm to be polyubiquitinated before being degraded. Whatever the explanation, the nucleus should not harbor p53 unless it absolutely needs to because even a small amount of this potent protein might trigger unnecessary and even harmful events that would be detrimental to a stress-free cell.

Clearly, many questions remain to be answered before a fuller understanding of p53 nuclear export and degradation can be reached. In fact, blocking nuclear export of p53 may prove to be a valuable therapeutic strategy for magnifying the antitumor potential of this transcription factor (*16*). Undoubtedly, the challenge now is to tease apart the intricate circuitry that controls the cellular locations of p53 and MDM2.



Location is key. **(Left)** In unstressed cells, both p53 and MDM2 shuttle between the nucleus and the cytoplasm. When they form a complex in the nucleus, the RING finger of MDM2 ubiquitinates p53, causing p53 (and perhaps also MDM2) to exit the nucleus. Once in the cytoplasm, p53 degradation mediated by MDM2 is completed. **(Right)** Stress signals (such as damage to DNA) activate a subset of cellular kinases that add phosphate groups to different p53 amino acids. Modifying p53 by phosphorylation regulates many related processes that contribute to p53 stability and activity. Phosphorylation of p53 and MDM2 at key residues reduces the interaction between them, interfering with both MDM2-dependent p53 nuclear export and ubiquitination of p53. In addition, phosphorylation of p53 promotes the interaction between p53 and transcriptional coactivators such as p300; it also results in masking of p53's two nuclear export signals.

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