The finding of a role for nucleoplasmic Nups in transcription provides an important advance in our knowledge of the basic role of nucleoporins in gene regulation. Contrary to their proposed function in the "gene-gating" model, nucleoplasmic Nups directly participate in the activation of transcription away from the NPCs on the nuclear envelope. Some Nups are highly dynamic and rapidly shuttle between NPCs and the nucleoplasm. If these Nups are involved in both transcription inside the nucleoplasm and trafficking at the NPCs, it would be tempting to speculate that they may bridge two fundamental cellular processes taking place in the inside of the nucleus and at the periphery. This finding challenges the conventional views of how the constituents of NPCs regulate gene expression at the nuclear periphery and also potentially excludes the necessity of bringing chromatin to the NPCs in order to affect transcription.

Half a century after first unveiling the existence of the NPCs (Watson, 1959), the work of Capelson et al. and Kalverda et al. places a new cornerstone in nuclear biology upon which to build a better understanding of the role of nuclear transport components in transcription regulation. Like all key discoveries, these studies raise many additional questions. Most of the Nups lack structural motifs suggestive of a DNA-binding function. Therefore, it will be of interest to elucidate how nucleoplasmic Nups associate with chromatin and how they selectively bind to distinct subsets of genes involved in different biological processes. Due to the strict requirement of NPCs for directional transport between the cytoplasm and the nucleoplasm, it will be important to understand whether this additional function of the Nups will affect NPC activity under physiological conditions that require active transport of proteins and mRNAs. Elucidation of the molecular mechanisms by which the Nups participate in gene regulation may give new insights into the interplay among different nuclear compartments in the activation of eukaryotic genes.

REFERENCES

Blobel, G. (1985). Proc. Natl. Acad. Sci. USA *82*, 8527–8529.

Brown, C.R., Kennedy, C.J., Delmar, V.A., Forbes, D.J., and Silver, P.A. (2008). Genes Dev. *22*, 627–639.

Capelson, M., Liang, Y., Schulte, R., Mair, W., Wagner, U., and Hetzer, M.W. (2010). Cell, this issue.

Casolari, J.M., Brown, C.R., Komili, S., West, J., Hieronymus, H., and Silver, P.A. (2004). Cell *117*, 427–439.

Hirose, K., Abramovich, C., Argiropoulos, B., and Humphries, R.K. (2008). Oncogene *27*, 6056–6067.

Kalverda, B., Pickersgill, H., Shloma, V.V., and Fornerod, M. (2010). Cell, this issue.

Mendjan, S., Taipale, M., Kind, J., Holz, H., Gebhardt, P., Schelder, M., Vermeulen, M., Buscaino, A., Duncan, K., Mueller, J., et al. (2006). Mol. Cell *21*, 811–823.

Rabut, G., Doye, V., and Ellenberg, J. (2004). Nat. Cell Biol. *6*, 1114–1121.

Wang, G.G., Cai, L., Pasillas, M.P., and Kamps, M.P. (2007). Nat. Cell Biol. *9*, 804–812.

Watson, M.L. (1959). J. Biophys. Biochem. Cytol. *6*, 147–156.

USP10: Friend and Foe

Aart G. Jochemsen[1,*] and Yosef Shiloh[2]
[1]Department of Molecular Cell Biology, Leiden University Medical Center, 2300RC Leiden, The Netherlands
[2]The David and Inez Myers Laboratory for Cancer Genetics, Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel
*Correspondence: a.g.jochemsen@lumc.nl
DOI 10.1016/j.cell.2010.01.034

The tumor suppressor protein p53, a crucial player in the DNA damage response, is regulated in many ways, most notably through ubiquitination. In this issue, Yuan et al. (2010) identify the deubiquitinating protease USP10 as a new regulator of p53 in the DNA damage response and tumor development.

Many oncogenic alterations in cellular genomes may never result in tumors: rather than boosting cell proliferation, these mutations lead to replication stress, DNA damage, and a DNA damage response. The DNA damage response is a network of pathways that rapidly modulates many aspects of cellular metabolism, particularly following the induction of cytotoxic lesions such as DNA double-strand breaks. A central part of the DNA damage response is the activation of p53, which results in cell-cycle arrest, apoptosis, or senescence. These responses are important barriers to tumor progression and malignancy. Indeed, p53's tumor suppressor activity is believed to be attenuated in human tumor cells, either by inactivating mutations in the *TP53* gene encoding p53 or by altered expression of p53 modulators and effectors. In unstressed cells, p53 is kept at low levels through its continuous degradation via the ubiquitin-proteasome pathway, whereas upon DNA damage p53 degradation is attenuated (Figure 1). The primary regulator of DNA damage-induced p53 stabilization is the nuclear protein kinase ATM (ataxia-telangiectasia mutated),
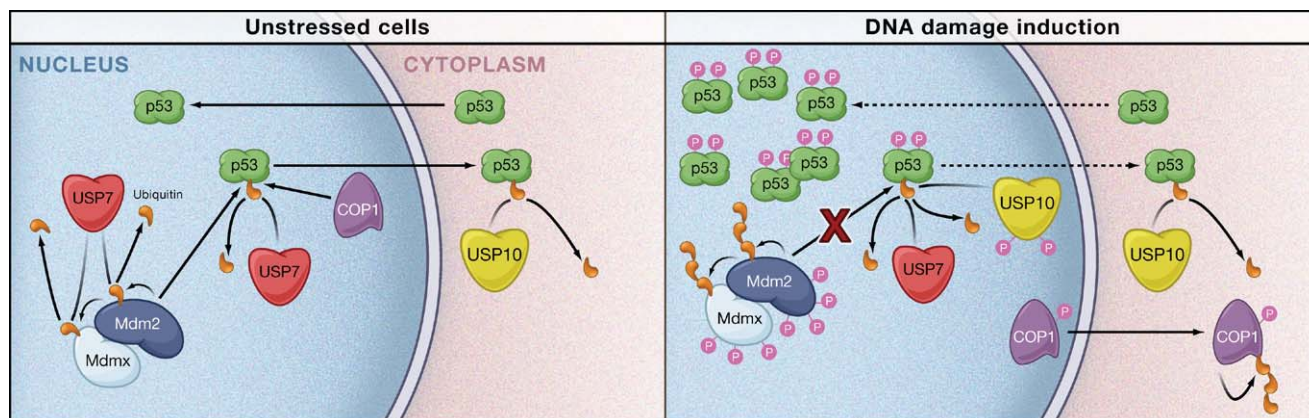
Figure 1. Regulation of p53 by USP10
(Left) In unstressed cells, the tumor suppressor protein p53 is kept at low levels in both the cytoplasm and the nucleus by the concerted action of the ubiquitin ligases Mdm2, Mdmx, and COP1. In addition, p53, Mdm2, and Mdmx are maintained at steady-state levels by the deubiquitinating enzyme USP7.
(Right) Following DNA damage, Mdm2 and Mdmx are phosphorylated by ATM and are downregulated as they can no longer interact with USP7. Phosphorylated COP1 is autodegraded outside the nucleus, and the deubiquitinating enzyme USP10 accumulates in the nucleus where it assists USP7 in the deubiquitination of p53, leading to its stabilization. USP10 can act as a tumor suppressor and an oncoprotein because it stabilizes both wild-type p53 and mutant p53, respectively (Yuan et al., 2010).

which is activated following the induction of DNA double-strand breaks. ATM phosphorylates a multitude of proteins, including p53 and its negative regulators: the ubiquitin ligases Mdm2 and COP1 that drive p53 ubiquitination and its strong inhibitor, Mdmx (Dornan et al., 2006; Meulmeester et al., 2005). Phosphorylation of these proteins by ATM accelerates their proteasome-mediated degradation, thereby stabilizing p53. The phosphorylation of Mdm2 and Mdmx enhances their degradation by reducing their interaction with the deubiquitinating protease USP7/HAUSP in the nucleus. USP7 regulates p53 in a dual fashion: it stabilizes p53 directly by deubiquitinating it and simultaneously deubiquitinates and stabilizes Mdm2 and Mdmx, thereby helping to keep the amount of p53 in check (Kruse and Gu, 2009; Meulmeester et al., 2005).

In this issue of *Cell*, Yuan et al. (2010) show that the current picture of p53 activation and stabilization by ATM is incomplete, and they add another player to the loop, a deubiquitinating enzyme called USP10. USP10 turns out to directly deubiquitinate p53 and to be an essential regulator of the stability of this tumor suppressor protein. In unstressed cells, USP10 is localized mainly in the cytoplasm where it deubiquitinates p53, enabling re-entry of p53 into the nucleus (Figure 1, left panel). Indeed, reducing the amount of USP10 results in increased

p53 degradation. Upon DNA damage and ATM activation, USP10 is phosphorylated and accumulates in the nucleus, where it joins forces with USP7 to stabilize p53 via p53 deubiquitination (Figure 1, right panel). Indeed, USP10 depletion attenuates DNA damage-induced stabilization of p53, an effect that was rescued by overexpression of wild-type USP10 but not by mutant USP10 lacking ATM phosphorylation sites. It will be interesting to discover whether overexpression of USP7 could also rescue the diminished DNA damage-induced p53 response caused by USP10 depletion. This could address questions about the specificity of these two p53-deubiquitinating enzymes and reveal whether the combined action of USP7 and USP10 is required to determine p53 stability.

In view of the critical role of p53's tumor suppressor activity in preventing tumor formation, each of its regulators can be thought of as either an oncoprotein or a tumor suppressor, depending on its effect on p53. Indeed, Yuan and colleagues find that USP10 levels are altered in renal cell carcinomas and cell lines derived from them. Most renal cell carcinomas do not contain mutant p53, and their USP10 levels are greatly diminished. However, a subset of renal cell carcinomas that do contain p53 mutations have elevated USP10 levels and increased levels of mutant p53. Yuan and coworkers go on to show that in

such cases the high levels of mutant p53 exert an oncogenic effect on the cultured tumor cells. USP10 thus appears to be a Janus-like player in tumorigenesis—it stabilizes both wild-type and mutant p53 and so functions as both a tumor suppressor and an oncoprotein.

The new findings point to USP10 as a potential therapeutic target for the roughly 50% of human cancers that contain p53 mutations. However, further work is needed to address the generality of the correlation between USP10 and p53 levels. USP10 overexpression has been associated with poor prognosis in patients with glioblastoma multiforme, which could fit with Yuan et al.'s data on the enhancement of the malignant phenotype by high levels of mutant p53. Notably, in the renal cell carcinoma samples investigated by Yuan et al., the status of wild-type p53 does not correlate with an increase in Mdm2 and Mdmx, as has been reported in other tumor types, like retinoblastoma. It would be of interest to examine the expression of USP10 in tumors with wild-type p53 and high Mdm2/Mdmx levels. It will also be important to discover whether USP10 activity is involved in regulating the ubiquitination status of the mitochondrial fraction of p53, as has been reported for USP7; the deubiquitination of p53 by mitochondrial USP7 generates apoptotically active nonubiquitinated p53 (Marchenko et al., 2007).

Both the yeast ortholog of USP10, Ubp3, and human USP10 have been implicated in vesicular transport and trafficking of membrane proteins (Bomberger et al., 2009; Cohen et al., 2003). In yeast, the deubiquitination of Ubp3 target proteins involved in this process depends on association of Ubp3 with another protein, Bre5 (Cohen et al., 2003). Interestingly, human USP10 interacts with the human Bre5 ortholog, G3BP1. However, this association may block the deubiquitinase activity of USP10. Notably, G3BP proteins interact with p53 and stimulate its localization in the cytoplasm (Kim et al., 2007). It would be interesting to know whether regulation of p53 by USP10 is modulated by G3BP proteins, as the expression of G3BP proteins is modulated in various tumors. Intriguingly, mutant p53 can stimulate the invasive capabilities of cancer cells by enhancing the endocytic recycling of membrane proteins such as epidermal growth factor receptor EGFR and α5β1 integrin (Muller et al., 2009). USP10 is important for endocytic trafficking (Bomberger et al., 2009) and also, as Yuan et al. report, for stabilizing mutant p53. Future work will reveal whether this versatile deubiquitinase has even more talents up its sleeve.

REFERENCES

Bomberger, J.M., Barnaby, R.L., and Stanton, B.A. (2009). J. Biol. Chem. *284*, 18778–18789.

Cohen, M., Stutz, F., Belgareh, N., Haguenauer-Tsapis, R., and Dargemont, C. (2003). Nat. Cell Biol. *5*, 661–667.

Dornan, D., Shimizu, H., Mah, A., Dudhela, T., Eby, M., O'Rourke, K., Seshagiri, S., and Dixit, V.M. (2006). Science *313*, 1122–1126.

Kim, M.M., Wiederschain, D., Kennedy, D., Hansen, E., and Yuan, Z.M. (2007). Oncogene *26*, 4209–4215.

Kruse, J.P., and Gu, W. (2009). Cell *137*, 609–622.

Marchenko, N.D., Wolff, S., Erster, S., Becker, K., and Moll, U.M. (2007). EMBO J. *26*, 923–934.

Meulmeester, E., Pereg, Y., Shiloh, Y., and Jochemsen, A.G. (2005). Cell Cycle *4*, 1166–1170.

Muller, P.A.J., Caswell, P.T., Doyle, B., Iwanicki, M.P., Tan, E.H., Karim, S., Lukashchuk, N., Gillespie, D.A., Ludwig, R.L., Gosselin, P., et al. (2009). Cell *139*, 1327–1341.

Yuan, J., Kuntian, L., Zhang, L., Cheville, J.C., and Lou, Z. (2010). Cell, this issue.

Shedding Light on Sperm pHertility

Harvey M. Florman,[1],* Melissa K. Jungnickel,[1] and Keith A. Sutton[1]
[1]Department of Cell Biology, University of Massachusetts Medical School, Worcester, MA 01655, USA
*Correspondence: harvey.florman@umassmed.edu
DOI 10.1016/j.cell.2010.01.035

The acquisition of fertilization capacity by sperm is regulated by intracellular pH (pH$_i$), but the transport pathways that regulate pH$_i$ are not well understood. Lishko et al. (2010) now report that Hv1, the voltage-sensitive proton channel, is present in human sperm and is an important regulator of the functional maturation of sperm.

Males of all mammalian species store sperm in the caudal portion of the ductus epididymis. These sperm have completed morphological differentiation and are generally believed to have terminated gene expression, and yet they are not capable of fertilization. The capacity to fertilize eggs is only expressed after sperm have been "educated" by the female reproductive tract. This final phase of maturation is known as capacitation and results in the development of new patterns of flagellar motility, in the expression of chemotactic responsiveness, and in the acquisition of the ability to interact with eggs. An understanding of capacitation is central to assisted reproductive approaches for treating infertility, to the design of contraceptive agents, to our models of fertilization, and to deciphering the evolutionary processes of sperm competition and sexual selection (Florman and Ducibella, 2006; Sutton et al., 2008). In this issue of *Cell*, Lishko et al. (2010), with their identification of a voltage-gated proton channel (Hv1) in sperm, suggest an exciting new model that may account for the regulation of sperm intracellular pH (pH$_i$) and for key events that control the onset of capacitation.

One factor that regulates capacitation is the intracellular pH of sperm. The pH$_i$ is maintained at a slightly acidic level during sperm storage within the cauda epididymis and rises during capacitation. Both the acid load during sperm storage and the subsequent alkaline shift after release are required for fertility (Florman and Ducibella, 2006; Blomqvist et al., 2006). Yet, the metabolic and ion transport activities that control the pH$_i$ set point in sperm and modulate the capacitation-associated changes required for fertility are poorly understood.

Lishko et al. (2010) now show that a voltage-sensitive proton channel, Hv1, is present in human sperm. Hv1 contains the voltage sensor domain that was first identified in voltage-sensitive cation channels, but it lacks the ion permeation pore of those channels. Instead, voltage-driven conformational movements in the sensor activate an intrinsic transmem-