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Connecting the Dots between Septins and the DNA Damage Checkpoint

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DOI 10.1016/j.cell.2007.08.022

In budding yeast, septins are involved in the morphogenesis checkpoint and the DNA damage checkpoint, both of which regulate cell-cycle progression. In this issue of *Cell*, Kremer et al. (2007) link septins to DNA damage in mammalian cells by identifying a new signaling pathway that includes the adaptors SOCS7 and NCK. As NCK controls actin dynamics, this pathway may connect DNA damage responses and cellular morphology in metazoans.

Cells ensure the fidelity of DNA replication, chromosome segregation, and cytokinesis through various checkpoint mechanisms that sense specific anomalies during the cell cycle and halt progression to the next phase (Hartwell and Weinert, 1989). Proper organization of the cytoskeleton, including that of septin filaments, is required for cell-cycle progression. Septins are GTP/GDP-binding proteins that assemble into filamentous cytoskeletal polymers (Sirajuddin et al., 2007). The budding yeast *Saccharomyces cerevisiae* builds the septin ring at the site of cell division as a versatile platform that serves as a scaffold and a diffusion barrier for various molecules, a positional cue for orientation of the mitotic spindle, and a sensing unit of the morphogenesis checkpoint machinery (Versele and Thorner, 2005). The morphogenesis checkpoint senses and transmits the status of cytoskeletal organization to cell-cycle regulators in the nucleus: Swe1p kinase (homologous to *S. pombe* Wee1) shuttles between the nucleus and the cytoplasm and also binds to the septin ring. The interaction with septins triggers the degradation of Swe1p and its depletion from the nucleus, thereby releasing the cyclin-dependent kinase Cdc28p (*S. pombe* Cdc2) from its Swe1p-mediated inhibition (Lew, 2003). Thus, the organization of septins is directly involved in driving or halting the cell-cycle engine. When compared with microtubules and actin filaments, septins appear to have diversified more through evolution both in appearance and in function. Metazoan versions of septin polymers are involved in the organization of several structures, including the contractile ring, actin stress fibers, the mitotic spindle, and sperm flagella (Kinoshita, 2006), but their molecular function has been elusive.

In this issue, Kremer et al. (2007) report an unexpected role for septins in mammalian cells during interphase. They show that septin heteropolymers dispersed throughout the cytoplasm serve as a cytoplasmic sink for the signaling protein SOCS7. This protein exhibits dynamic shuttling between the nucleus and cytoplasm via its nuclear import and export signals and a septin-interacting region. SOCS7 is responsible for the nuclear localization of NCK, another multifunctional adaptor protein involved in actin organization. Depletion of septins using RNA interference causes SOCS7 to accu-

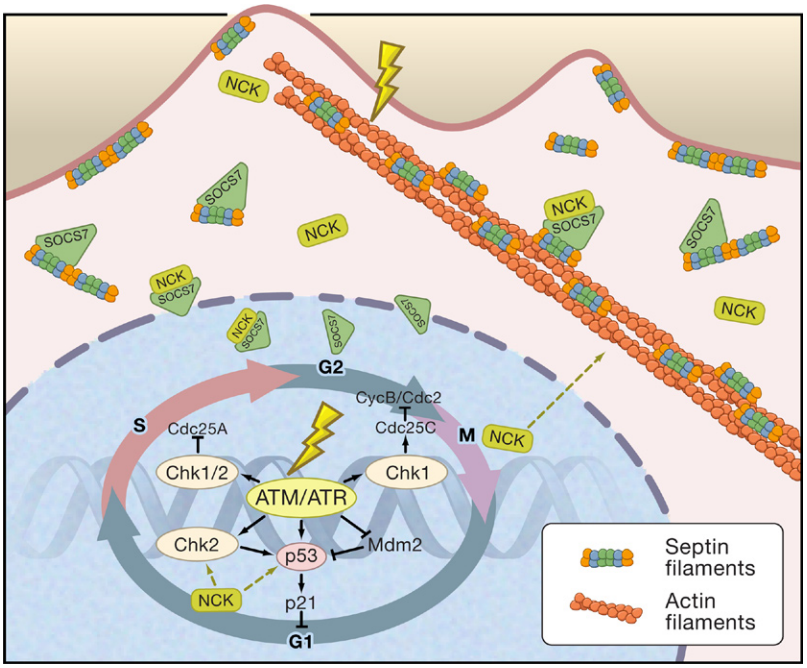

Figure 1. Septins and the DNA Damage Checkpoint

The figure depicts the septin cytoskeleton and the cell-cycle checkpoint regulators mediated by a new septin-NCK-SOCS7 signaling pathway (Kremer et al., 2007). Septin heteropolymers serve as cytoplasmic sinks for the adaptor protein SOCS7. SOCS7 autonomously shuttles to the nucleus, accompanying NCK, another multifunctional adaptor protein involved in actin organization. Perturbation of septin filaments—as well as genotoxic stress such as UV irradiation—induces nuclear translocation of NCK, which disorganizes actin stress fibers and modifies the cell-cycle/DNA damage checkpoint machinery.

mulate in the nucleus. The resulting nuclear localization of NCK leads to disorganization of actin stress fibers and a change in cell shape by an as yet unknown mechanism. Kremer et al. show that the nuclear accumulation of NCK causes the reorganization of actin that occurs in response to septin depletion.

Kremer et al. previously reported that septin-mediated sequestration of MAP4 (a microtubule-associated protein) negatively regulates the stability of microtubules, which also contributes to the cell shape changes observed after septin depletion (Kremer et al., 2005). A common view is that septin polymers dispersed throughout the cytoplasm without forming a continuous polymer network serve as depots or sinks that sequester key signaling molecules that have remote functions (Kinoshita, 2006).

Kremer et al. (2007) also show an unexpected association of NCK-mediated signals with the DNA damage checkpoint, which senses DNA damage and halts the cell cycle to enable repair of the damage or, if the damage is irreparable, triggers apoptosis. The authors demonstrate that NCK and SOCS7 accumulate in the nucleus upon DNA damage. In fact, the effects of UV radiation damage in mammalian cells mimicked those of septin depletion, including loss of cell polarity and disassembly of actin filaments. Importantly, nuclear accumulation of NCK was necessary for activation of the tumor suppressor p53. The transcriptional activity of p53 is enhanced by checkpoint kinases such as ATM and CHK2 (*S. cerevisiae* Rad53p) in response to DNA damage. The result is the upregulation of inhibitors of cyclin-dependent kinases and subsequently of components of the apoptotic pathway. Thus, the subcellular localization of NCK affects both actin organization and the DNA damage checkpoint (Figure 1).

The proposed link between cytoskeletal organization and the DNA damage checkpoint pathway provides insight into a classic question in the field of radiation biology: How does p53-dependent apoptosis suppress radiation-induced teratogenesis in embryos (Norimura et al., 1996)? To prevent teratogenesis, the p53-mediated signaling pathway has to recognize abnormal cell-cell interactions. Thus, unlike unicellular organisms, metazoan cells need to monitor not only the status of genomic DNA but also signals from neighboring cells. The cell-cell interactions may affect the damage checkpoint through the newly described interplay between the DNA damage checkpoint and the septin-SOCS7-NCK pathway, because this pathway can sense a variety of extracellular signals. The damage checkpoint of mammalian cells thereby accomplishes an important mission in vivo: the prevention of malformations in embryonic tissues or tumor formation in adult tissues.

It remains to be seen whether other DNA insults, such as ionizing radiation, require NCK for stimulating checkpoint signaling. In the present study, Kremer et al. studied UV irradiation, which not only promotes the nuclear accumulation of NCK but also affects c-Jun N-terminal kinase (JNK) signaling (Jaeschke et al., 2006), leading to disruption of actin stress fibers. It will therefore be crucial to test whether the observed phenomenon is specific to UV or is a general feature of the DNA damage response.

The Kremer et al. (2007) study has begun to uncover an intricate molecular scheme for the coordination of remote events, that is, cytoskeletal organization and cell-cycle regulation. Future studies will address the many questions this study raises: What is the physiological role of the septin-SOCS7-NCK pathway in the DNA damage checkpoint? Could the pathway represent a part of the putative morphogenesis checkpoint in mammals? How does this pathway mediate organization and remodeling of the actin network? Addressing these and other questions should provide clues to how dysregulation of the septin cytoskeleton is involved in neoplastic and neurodegenerative disorders.

ACKNOWLEDGMENTS

The authors thank H. Kondoh and N. Watanabe for valuable comments.

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How Hair Gets Its Pigment

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DOI 10.1016/j.cell. 2007.08.032

Mutations in the transcription factor *Foxn1* cause the *nude* phenotype in mice, which is characterized by a lack of visible hair. New work by Weiner et al. (2007) in this issue of *Cell* now shows that *Foxn1* also contributes to hair color by marking which cells are to receive pigment from melanocytes.

"If you build it, they will come." The phrase from the movie "Field of Dreams" refers to a situation in which the mere presence of a structure catalyzes recruitment of its occupants. In this context, consider the development of hair follicles in the skin. Hair follicle formation is initiated by a series of epithelial-mesenchymal interactions and built and maintained by programs of differentiation and self-renewal. Yet a hair follicle and the surrounding epidermis are not truly complete until colonized by pigment cells that come from the neural crest. Is building a hair follicle sufficient to guarantee its pigmentation, or are additional instructions necessary? The prevailing view supports a permissive role for the epithelium in determining pigmentation, but new work from Weiner et al. (2007) suggests that certain epithelial components can determine their own pigmentation in an instructive manner that depends on the gene *Foxn1*.

In adult animals, both hair and skin color depend on pigment-producing melanocytes that remain stationary at the base of the epithelium and transfer melanin-containing organelles to adjacent keratinocytes that are pushed upward as they proliferate. During embryogenesis, however, the nonpigmentary components of the follicle are built first, and melanocyte movement is a secondary and stepwise process that proceeds from the dermis to the epidermis and then into developing follicles (Figure 1). These stages of pigment cell movement depend on a series of paracrine interactions, most of which have been recognized through mutations that cause white spotting. For example, activation of the *Edn3* gene (originally known as *lethal spotting*) or its downstream effectors cause melanocytes to accumulate in the dermis, whereas activation of the *Kit ligand* (*Kitl)* gene (originally known as *Steel*) causes melanocytes to accumulate in the epidermis (Van Raamsdonk et al., 2004; Garcia et al., 2007).

In fact, a large body of previous work from Nishikawa and colleagues (Kunisada et al., 1998; Mak et al., 2006; Yoshida et al., 1996) suggests that it is the precise site and timing of *Kitl* expression by different types of keratinocytes that determines if melanocytes ultimately reside in the skin, the hair, or both (Figure 1A). Thus, in newborn mice, *Kitl* is transiently expressed in the interfollicular epidermis, but as hair follicles develop, expression becomes restricted mainly to hair bulbs, helping to explain why melanocytes move from the interfollicular epidermis to the hair follicles after birth (Mak et al., 2006). Furthermore, using a *Kitl* transgene expressed specifically in the basal epidermis, together with antibodies against the Kit receptor, it was possible to recruit pigment cells to the hair but not the skin, to the skin but not the hair, or to both hair and skin, all depending on the combination and timing of transgene expression and administration of antibodies