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Putting SUMO and SoxE into context

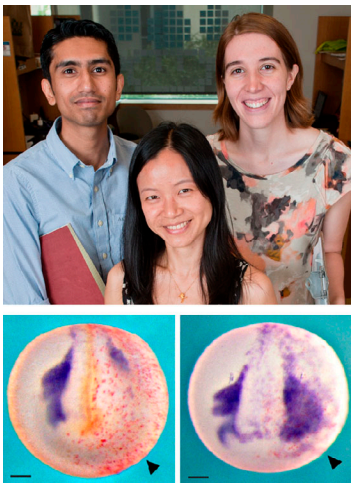
Study reveals how SUMOylation converts a transcriptional activator into a repressor.

Nature makes impressive use of a relatively small number of proteins. The same signaling pathways and transcription factors are often reused in different contexts to direct diverse developmental processes, and understanding how proteins show the right activity at the right time and place is a fundamental question for developmental biologists. Lee et al. reveal how the small ubiquitin-like modifier SUMO changes the function of the SoxE family of transcription factors during neural crest development (1).

Neural crest cells are stem cell–like progenitors that arise from the embryonic ectoderm, undergo an epithelial–mesenchymal transition, and disperse throughout the embryo before they differentiate into a variety of different lineages (2). "They're a unique and fascinating cell population," says Carole LaBonne from Northwestern University in Evanston, Illinois. "There are a handful of key factors that play multiple roles in neural crest development. For example, SoxE transcription factors are critical for the initial formation of the stem cell population, but then, counterintuitively, they direct the stem cells' differentiation into a subset of neural crest derivatives, namely glial cells, melanocytes, and cartilage cells."

SoxE transcription factors are best known as transcriptional activators (3). In 2005, LaBonne and graduate student Kimberly Taylor-Jaffe found that SoxE's function in the neural crest of *Xenopus* embryos was regulated by SUMOylation (4). Non-SUMOylatable forms of SoxE induced the formation of neural crest stem cells, whereas constitutively SUMOylated SoxE blocked neural crest development and promoted ear formation instead. "So we knew that SUMO had a profound influence, but we didn't understand the mechanism," recalls LaBonne, who says that *Xenopus* embryos are ideal for these studies because of their amenability to both cell biological and biochemical approaches.

Focal Point



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(Top, left to right) Maneeshi Prasad, Pei-Chih Lee, Kara Nordin, and colleagues (not pictured) Kimberly Taylor-Jaffe, Rachel Lander, and Carole LaBonne investigate how modification by the small ubiquitin-like molecule SUMO changes the function of SoxE transcription factors during neural crest development. SUMOylation prevents SoxE from recruiting the transcriptional coactivators CBP and p300 and instead promotes SoxE's association with the corepressor Grg4. *Xenopus* embryos injected (arrowheads) with Grg4 mRNA (bottom left) show reduced expression of a neural crest marker (purple). This repression is reversed by the coinjection of mRNA encoding a non-SUMOylatable form of SoxE (bottom right). Because SoxE performs several different functions during neural crest development, SUMOylation might help these transcription factors display the right activity at the right time and place.

> "SUMOylation changes the context in which SoxE factors are functioning."

To investigate how SUMOylation affects SoxE function, LaBonne and colleagues, led by Taylor-Jaffe and Pei-Chih Lee, focused on SoxE's role during melanocyte differentiation, when it works with another transcription factor, Mitf, to induce an enzyme required for melanin production called dopachrome tautomerase (Dct). Lee et al. found that SUMOylating Mitf or SoxE inhibited their ability to activate the *Dct* promoter in *Xenopus* embryos, whereas non-SUMOylatable forms of the transcription factors strongly induced *Dct* expression (1).

SUMO didn't affect the localization of Mitf or SoxE, nor did it inhibit their cooperative binding to the *Dct* promoter. "However, we did see effects on SoxE's ability to recruit coregulatory molecules," LaBonne says. SUMOylation prevented SoxE from binding to the transcriptional coactivators CBP and p300 and instead promoted its association with Grg4, a member of the Groucho family of corepressor proteins.

Misexpressing Grg4 in *Xenopus* embryos had similar effects to SUMOylating SoxE: shutting down the *Dct* promoter and inhibiting the formation of neural crest progenitors. Grg4 had no effect on embryos coexpressing non-SUMOylatable SoxE, however, indicating that Grg4-mediated repression was dependent on SoxE SUMOylation.

"So SUMOylation changes the context in which SoxE factors are functioning and switches them from being activators to repressors of transcription," LaBonne explains. "This probably contributes to their ability to rapidly and reversibly change their function so that they can carry out different roles in time and space."

Moreover, SoxE SUMOylation provides context to Grg4, which lacks a sequence motif typically found in SUMO-interacting proteins. "Grg4 interacts with part of SoxE and part of SUMO that together allow a physiologically significant interaction," LaBonne says. This explains why Grg4 doesn't interact with every SUMOylated molecule, and it suggests that, just like phosphorylation, the downstream effects of SUMOylation depend on the modified protein.

LaBonne and colleagues now want to investigate when and where SoxE is SUMOylated. "We're trying to understand what recruits the SUMOylation machinery to chromatin and to determine whether this is directed by signaling pathways," LaBonne says.

1. Lee, P.-C., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201204161.
2. Prasad, M.S., et al. 2012. *Dev. Biol.* 366:10–21.
3. Bowles, J., et al. 2000. *Dev. Biol.* 227:239–255.
4. Taylor, K.M., and C. LaBonne. 2005. *Dev. Cell.* 9:593–603.