

## The healing power of Ron

**A** blood-localized growth factor hastens wound healing by pulling an integrin switcharoo on skin cells. The exchange, shown by Massimo Santoro (University of Piemonte Orientale, Novara, Italy) and colleagues, both releases adhered cells and promotes migration.

Skin cells stick to the basement membrane through hemidesmosome (HD)-localized integrin  $\alpha_6\beta_4$ . Santoro et al. show that the MSP growth factor releases  $\alpha_6\beta_4$  from HDs and activates a migratory integrin,  $\alpha_3\beta_1$ , instead. Binding of MSP to its tyrosine kinase receptor, Ron, led to phosphorylation of both Ron and  $\alpha_6\beta_4$ , which introduced binding sites for 14-3-3

scaffolding proteins into both proteins. Through typical 14-3-3 dimerization, the phosphorylation thus creates a complex containing Ron and  $\alpha_6\beta_4$ .

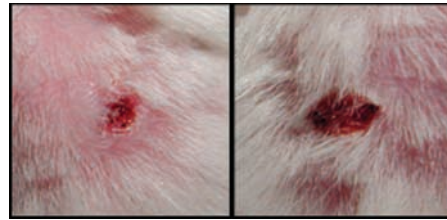
MSP-induced Ron/integrin complexes were seen at the leading edge of migrating cells and corresponded with loss of  $\alpha_6\beta_4$  from HDs. At the lamellipodia, phosphorylated  $\alpha_6\beta_4$  switched to a signaling role. Along with Ron,  $\alpha_6\beta_4$  activated transcription pathways that promote migration via production of

matrix metalloproteases and additional MSP.

The venue change for  $\alpha_6\beta_4$  had a ripple effect on another integrin. Before MSP stimulation,  $\alpha_3\beta_1$  was stuck at cell-cell contacts, apparently in an inactive complex with Ron. But Ron exchanged partners upon phosphorylation, thus allowing  $\alpha_3\beta_1$  to move to focal contacts, where it interacts with actin fibers to promote migration. This may explain

why application of MSP to open wounds shortened the healing time for mice. ■

Reference: Santoro, M., et al. 2003. *Dev. Cell.* 5:257–271.



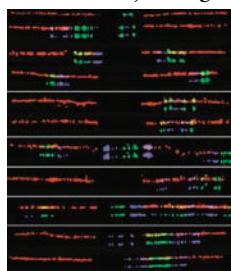
Santoro/Elsevier

Wounds heal more quickly with MSP (left).

## Nucleotides choose origins

**I**n vertebrate cells, not all potential DNA replication origins fire in each S phase, but it is unclear what parameters control that decision. Mauro Anglana, Michelle Debatisse (Institut Curie, Paris, France), and colleagues find that nucleotide availability can determine which origins are activated.

Under normal conditions (when nucleotides were readily available), initiation occurred predominantly at one site within the AMPD2 locus. Only in a few cases did minor sites fire instead. Firing of the dominant origin seems to prevent other nearby origins from initiating replication, as only an origin spaced far from the major origin was used simultaneously.



Debatisse/Elsevier

**Nucleotide levels can alter replication initiation site selection.**

Cells with limited nucleotide availability, however, replicated from a wider variety of origins. Although the predominant origin was not used as often, simultaneous activation from multiple minor sites was more common. Firing efficiency of competent origins has been attributed mainly to epigenetic controls, including nuclear organization. But Debatisse says “things that are far simpler can also determine the choice of origin, including nucleotide pools. And it’s

completely reversible from one cell cycle to another.”

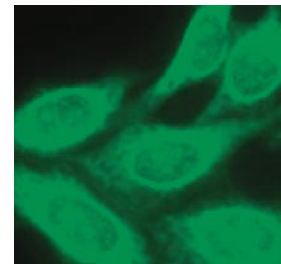
A change in origin selection strategy probably equalizes genome replication times. Low nucleotide levels slowed replication fork progression, but the increased number of actively firing origins compensated for this difference, thus resulting in equally long S phases. Now, Debatisse hopes to identify proteins that localize to an origin in a nucleotide-dependent manner. ■

Reference: Anglana, M., et al. 2003. *Cell.* 114:385–394.

## Losing self-awareness

**W**aste is rife in the immune system, based on a report from Hedda Wardemann, Michel Nussenzweig (Rockefeller University, New York, NY), and colleagues. The group has determined that more than half of the human B cell antibody population is removed before maturation.

The removal is a consequence of antibody gene rearrangement—a random process that is certain to generate some autoreactive antibodies. Nussenzweig’s group now shows just how often autoreactivity occurs by identifying autoreactive B cells at different stages of development. Between 55% and 75% of the antibodies made by early immature B cells react against self antigens. These potentially dangerous antibodies are removed from the repertoire at two checkpoints: the number of self-reactive antibody-producing B cells were halved from within the bone marrow and then halved again after entering the blood stream. Also, nearly 90% of developing B cells producing polyreactive antibodies, whose promiscuity is probably a risk to the host, were removed at the marrow checkpoint.



Nussenzweig/AAAS

**Most self-reactive antibodies (green) are filtered from the developing immune system.**

These studies will help determine how autoimmune diseases arise. “Any problem in the checkpoints that would allow self-reactive B cells to get through might be dangerous,” says Wardemann. “We determined the numbers in normal, healthy donors. If we compare this to autoimmune patients, we should get an idea of where the problem lies.” ■

Reference: Wardemann, H., et al. 2003. *Science.* 10.1126/science.1086907.