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CELL MIGRATION

Healing aid

Growth factors and integrins often join forces to regulate biological processes, but in the process of keratinocyte migration, a third protein — 14-3-3 — puts in an appearance. The growth factor macrophage-stimulating protein (MSP) induces its receptor, Ron, to complex, through 14-3-3, with the $\alpha_6\beta_4$ integrin. This removes $\alpha_6\beta_4$ from cell-adhesion structures and relocalizes it at lamellipodia. In conjunction with increased migration, this implicates Ron and 14-3-3 in wound healing, as reported by Santoro and colleagues.

Serine 1394 in the Ron carboxyl terminus is a potential phosphorylation site for many kinases, but only Akt, through phosphatidylinositol 3-kinase, phosphorylated Ron *in vivo* in response to MSP. Ron's carboxyl terminus also matches consensus motifs for several protein-protein interaction domains — and the phosphorylation-dependent scaffold protein 14-3-3 did, in fact, bind to MSP-mediated, Akt-phosphorylated Ron. 14-3-3 co-immunoprecipitated with Ser1394-phosphorylated Ron, and both proteins colocalized at the leading edge of migrating cells in lamellipodia.

In primary keratinocytes, 14-3-3 associated with Ron in response to MSP. MSP induced keratinocytes to spread and migrate faster on the extracellular-matrix component laminin-5 compared with cells in which Ser1394 was mutated, or in which the carboxyl terminus of 14-3-3 was deleted (both these constructs

interfere with the Ron–14-3-3 complex). These effects pointed to a potential involvement of integrins, and Santoro and colleagues found β_4 to interact with 14-3-3. Protein kinase C (PKC) has been shown to phosphorylate β_4 , and the authors found that MSP induced the phosphorylation, by PKC α , of $\alpha_6\beta_4$ at the 14-3-3 binding site — thereby causing subsequent $\alpha_6\beta_4$ –14-3-3 complex formation.

So, if 14-3-3 binds to Ron and to $\alpha_6\beta_4$, can it mediate a complex between the two proteins? Indeed it can. And as $\alpha_6\beta_4$ is usually found in hemidesmosomes — structures that support cell adhesion — and Ron–14-3-3 in lamellipodia, the authors then assessed the effect of MSP on $\alpha_6\beta_4$ localization. MSP was found to induce $\alpha_6\beta_4$ relocalization from hemidesmosomes to lamellipodia. Concurrent with this, cells adhered to laminin-5 through $\alpha_3\beta_1$ instead of $\alpha_6\beta_4$. As this occurs during wound healing, Santoro and colleagues looked at MSP's role in this process. MSP promoted keratinocyte migration in wounds in mice and in *in vitro* wound-healing assays. This required the formation of a Ron–14-3-3– $\alpha_6\beta_4$ complex and $\alpha_3\beta_1$ -dependent cell migration.

When they studied downstream signalling, the authors found that $\alpha_6\beta_4$ was phosphorylated only when a Ron– $\alpha_6\beta_4$ complex was formed, and that this complex activated p38 and nuclear factor κ B signalling. Both pathways were required for the transcriptional upregulation, not only of MSP itself, but also of matrix metalloproteinases, which are normally induced during keratinocyte wound healing. So, $\alpha_6\beta_4$ seems to change from being an adhesive molecule to a signalling component during wound re-epithelialization.

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References and links

ORIGINAL RESEARCH PAPER Santoro, M. M., Gaudino, G. & Marchisio, P. C. The MSP receptor regulates $\alpha_6\beta_4$ and $\alpha_3\beta_1$ integrins via 14-3-3 proteins in keratinocyte migration. *Dev. Cell* **5**, 257–271 (2003)

