HIGHLIGHTS

ADHESION AND MIGRATION

Going places

Until a few years ago, netrins were thought to work exclusively in neural tissues as guidance cues. But recent work has shown that netrins are found in several epithelial tissues too. Now, Vincenzo Cirulli's team, in collaboration with Marc Tessier-Lavigne, reports that netrin-1 functions as an efficient guidance cue for the navigation of epithelial cells. In their report in *Developmental Cell*, Cirulli and co-workers indeed show that netrin-1 can interact with integrins in epithelial cells to mediate adhesion and migration.

First, the authors pinpointed netrin-1 expression in the developing human pancreas to a discrete population of epithelial cells — more specifically, to their basal membranes. This prompted them to look for interactions with integrins, which they indeed saw. As components of the extracellular matrix, integrins regulate adhesion and migration, so an obvious next step was to investigate netrin-1's potential role in these processes.

Primary and stable pancreatic cells adhered efficiently to netrin through a highly basic 25-residue sequence in its carboxyl terminus. This region of netrin-1 doesn't overlap with the binding sites for the netrin receptors DCC and neogenin, which indicated that there was another receptor — this turned out to be integrin $\alpha_6\beta_4$. Pancreatic epithelial cells also adhered to soluble netrin-1; this is a noteworthy point, as netrin-1 is a diffusible chemoattractant.

While verifying the binding specificity of $\alpha_6\beta_4$ to netrin-1 using affinity chromatography with pancreatic cell lysates, Cirulli and his team also found that $\alpha_3\beta_1$ interacted with netrin-1, again through netrin-1's carboxyl terminus. The reason that $\alpha_3\beta_1$ hadn't been found to mediate the short-term adhesion of pancreatic cells to netrin-1 — as $\alpha_6\beta_4$ had — later became clear. The authors found that this integrin instead facilitated hepatocyte growth factor/scatter factor (HGF/SF)-induced migration of PDX1$^+$ putative pancreatic progenitor cells on netrin-1. $\alpha_6\beta_4$, it seems, could mediate migration on, as well as stable adhesion to, netrin-1. Both integrins were also necessary for migration of pancreatic progenitors towards an increasing concentration of immobilized netrin-1. Soluble netrin-1, however, had no effect. The β_4 subunit reportedly interacts with the HGF/SF receptor, Met, so the authors tested whether the two components interacted in this system. The finding that they did, together with previous reports of a role for β_4 in signalling events that regulate cell migration, indicates that netrin-1–$\alpha_6\beta_4$ interactions might mediate HGF/SF-induced cell migration.

The authors wrapped up their study by showing that α_3, α_6, β_1 and β_4 all colocalize with netrin-1 in the developing pancreatic epithelium. So, as a neural chemoattractant that now mediates the adhesion and migration of pancreatic epithelial cells through integrins, netrin is really going places.

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References and links

ORIGINAL RESEARCH PAPER Yebra, M. *et al.* Recognition of the neural chemoattractant netrin-1 by integrins α6β4 and α3β1 regulates epithelial adhesion and migration. *Dev. Cell* **5**, 695–707 (2003)