ImmunoTools special Award 2013

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Cell-microenvironment interactions during collective cell migration

Our lab investigates how chemotactic cues influence collective cell migration using chick and Xenopus Neural Crest cells. Cells are monitored using time-lapse cinematography in 2D/3D cultures and in vivo. External source of purified candidate chemoattractants will be used to generate local gradients. We have set up an experimental system allowing us to control gradient formation in vitro. Cell behaviour will then be analyzed under various conditions (control vs gain/loss-of-function). We focus mainly on how cell-cell and cell-environment interactions affect the ability of cells to respond to a given molecule. By doing so, we have previously unravelled unexpected mechanisms of cooperation between migratory cells and between cells and their surrounding tissues[1-3]. One aspect that we will analyze further is how guidance cues interact with the environment, in particular the extracellular matrix. We are interested in the ability of specific extracellular matrix components to trap or present guidance cues to migratory cells.

ImmunoTools products will be tested on various substrates (Fibronectin, Laminin or Collagen). We are also looking into how migratory cells modify the matrix and how they change the properties of the matrix in terms of regulating diffusion or presentation of guidance cues. Cell's response to a given molecule will be tested in control conditions or after inhibiting matrix remodelling factors such as ADAMs and MMPs.

We have clearly established that SDF1 is a strong chemoattracatnt for Neural Crest cells in vitro and in vivo. Therefore, purified SDF1 from ImmunoTools will be used as a gold standard for chemotaxis response. Other factors have been proposed as attractants such as VEGF, PDGFAA, PDGFBB and FGF8, they will be tested and their ability to redirect migratory cells will be assessed in vitro and in vivo and compared with that of SDF1. Their ability to influence cell directionality will be tested in the context of purified 2D matrices (as mentioned above), 3D gels and in vivo in order to see if their action is context/environment dependent. BDNF, NGF, Neuregulin, EGF, TGF-beta, FGF1/2 are candidate upstream regulators of SDF1 expression and their ability to induce local expression of SDF1 will be tested in vivo.

Neural crest cells are very similar to metastatic cancer cells in that they undergo epithelial-mesenchymal transition controlled by Snail/Twist/Ets genes, invade local

tissues and are guided by similar signals such as the ones mentioned above. Therefore we plan on using the data generated using the ImmunoTools purified proteins with Neural Crest cells to design experiment using melanoma and neuroblastoma cells lines (two cancer cell lines directly derived from Neural Crest cells) but also with breast carcinoma cells which are known to be responding to SDF1. We hope that these approaches using Chick, Xenopus and Mouse cells in 2D/3D in vitro cultures and in vivo will give new insights into how individual factors influence cell behaviour in the context of their local environment, in particular the surrounding extracellular matrix.

1. Theveneau E, Steventon B, Scarpa E, Garcia S, Trepat X, Streit A, et al. Chase-and-run between adjacent cell populations promotes directional collective migration. Nat Cell Biol 2013; 15.
2. Theveneau E, Mayor R. Collective cell migration of epithelial and mesenchymal cells. Cell Mol Life Sci 2013.
3. Theveneau E, Marchant L, Kuriyama S, Gull M, Moepps B, Parsons M, et al. Collective chemotaxis requires contact-dependent cell polarity. Dev Cell 2010; 19:39-53.