Research Highlight

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Stem cells: Self-help in the niche

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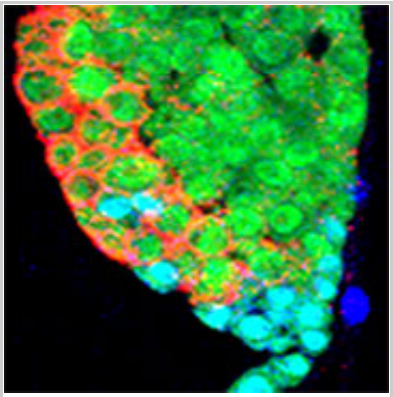

Niche-derived (blue) and differentiating cell-derived (red) signals collaborate in the maintenance of blood progenitors (green) during *Drosophila melanogaster* haematopoiesis. Image courtesy of J. A. Martinez-Agosto, University of California, Los Angeles, USA.

Stem cells and progenitor cells reside in a microenvironment, or niche, that regulates their activity. Mondal *et al.* show that, in *Drosophila melanogaster*, differentiating blood cells themselves produce signals that, together with cues from the surrounding niche, contribute to the maintenance of their haematopoietic progenitors.

All *D. melanogaster* blood lineages arise from a group of undifferentiated progenitor cells located within the lymph gland. Progenitor cells are maintained by a small group of cells that form a haematopoietic niche. The authors observed that the time when the first blood cells start differentiating coincides with the onset of quiescence among the precursor population (which is required for their maintenance). This suggested that differentiating cells might provide feedback to regulate progenitor cell proliferation and maintenance. Indeed, if cell death was induced in differentiating blood cells, their adjacent progenitors, which would normally be quiescent, started proliferating.

But what are the signals that regulate this quiescence? Using RNA interference (RNAi), the authors identified the growth factor PVF1 as a signalling molecule necessary for the maintenance of progenitor cell quiescence. However, they found that quiescence was affected only when PVF1 was specifically knocked down in the niche and when its receptor, PVR, was knocked down in differentiating cells. This indicates that PVF1 is synthesized in the niche and activates PVR in maturing blood cells, and that this signalling pathway maintains progenitor cell quiescence.

Mondal *et al.* next asked how maturing cells signal back to their progenitors. The secreted protein Adenosine deaminase-related growth factor A (ADGFA) functions to inactivate and reduce extracellular levels of adenosine, which is sensed by Adenosine receptor (ADOR), and generates a mitogenic signal through a G protein and cyclic AMP-dependent protein kinase A (PKA) pathway. The authors saw that RNAi-driven downregulation of ADGFA in differentiating cells induced loss of progenitor quiescence, similarly to that seen upon loss of PVR. Furthermore, overexpression of ADGFA suppressed progenitor proliferation induced by PVR knockdown; this suggests that ADGFA acts as a signal originating from differentiating cells, downstream of PVR, to maintain progenitor quiescence. VEGFR-like receptors, such as PVR, have multiple downstream effectors, and the authors found that inactivation of STAT92E in differentiating cells caused loss of progenitor cells, indicating that STAT functions downstream of PVR. Thus, ADGFA functions downstream of PVR and STAT to promote progenitor maintenance.

To further investigate the role of adenosine, the authors knocked down ENT3,

which mediates adenosine uptake, in progenitor cells. Loss of ENT3 induced progenitor cell differentiation, presumably by causing local accumulation of extracellular adenosine, which signals through ADOR to promote proliferation and differentiation. This shows that PVR and ADGFA counteract adenosine signalling through ADOR in progenitor cells to promote quiescence.

niche cells and differentiating cells collaborate to maintain an undifferentiated and quiescent progenitor population.

Finally, how does signalling from differentiating cells interact with signals arising from the niche? Niche cells express Hedgehog as a signal for the maintenance of progenitor cells. The transcription factor Cubitus interruptus (CI) is a downstream effector of Hedgehog signalling. It is maintained in an active form (which promotes quiescence) in blood progenitors in the presence of Hedgehog, and is converted to a repressor form in the absence of Hedgehog. CI acts as a central integrator of both signals, as its conversion from an active to repressed form is mediated by PKA, which is inhibited by Hedgehog and activated by adenosine, the levels of which are lowered by ADGFA originating from differentiating cells. Therefore, niche cells and differentiating cells collaborate to maintain an undifferentiated and quiescent progenitor population.

Progenitor and differentiating cells are found in close proximity in other systems, such as those driving bone morphogenesis, haematopoiesis and skin cell renewal in vertebrates; so, a similar interaction between signals derived from niche and differentiating cells could occur, as was recently

demonstrated for skin cells. Furthermore, the role of adenosine or other small molecules in the maintenance of vertebrate progenitors remains to be addressed.

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References and links

ORIGINAL RESEARCH PAPER

Mondal, B. C. *et al.* Interaction between differentiating cell- and niche-derived signals in hematopoietic progenitor maintenance. *Cell* **147**, 1589–1600 (2011) **Article**

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