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Review

Tip cells: Master regulators of tubulogenesis?

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ABSTRACT

The normal development of an organ depends on the coordinated regulation of multiple cell activities. Focusing on tubulogenesis, we review the role of specialised cells or groups of cells that are selected from within tissue primordia and differentiate at the outgrowing tips or leading edge of developing tubules. Tip or leading cells develop distinctive patterns of gene expression that enable them to act both as sensors and transmitters of intercellular signalling. This enables them to explore the environment, respond to both tissue intrinsic signals and extrinsic cues from surrounding tissues and to regulate the behaviour of their neighbours, including the setting of cell fate, patterning cell division, inducing polarity and promoting cell movement and cell rearrangements by neighbour exchange. Tip cells are also able to transmit mechanical tension to promote tissue remodelling and, by interacting with the extracellular matrix, they can dictate migratory pathways and organ shape. Where separate tubular structures fuse to form networks, as in the airways of insects or the vascular system of vertebrates, specialised fusion tip cells act to interconnect disparate elements of the developing network. Finally, we consider their importance in the maturation of mature physiological function and in the development of disease.

Contents

1. Introduction

The construction of an organ involves the regulation of many different cell activities including cell specification, proliferation, growth, recruitment, movement, shape change and finally differentiation. Failure to regulate any one of these in time and space has disastrous effects and all need to occur in coordination with the others to produce the final patterned and fully functional structure. While many aspects of developmental control result from reciprocal signalling involving all or the majority of constituent cells, a special class of distinctively placed cells at the tips of tubes or the leading front of migrating cell groups have been found in a wide variety of systems to regulate the activity of their neighbours at key stages of organ development. In this review we discuss the

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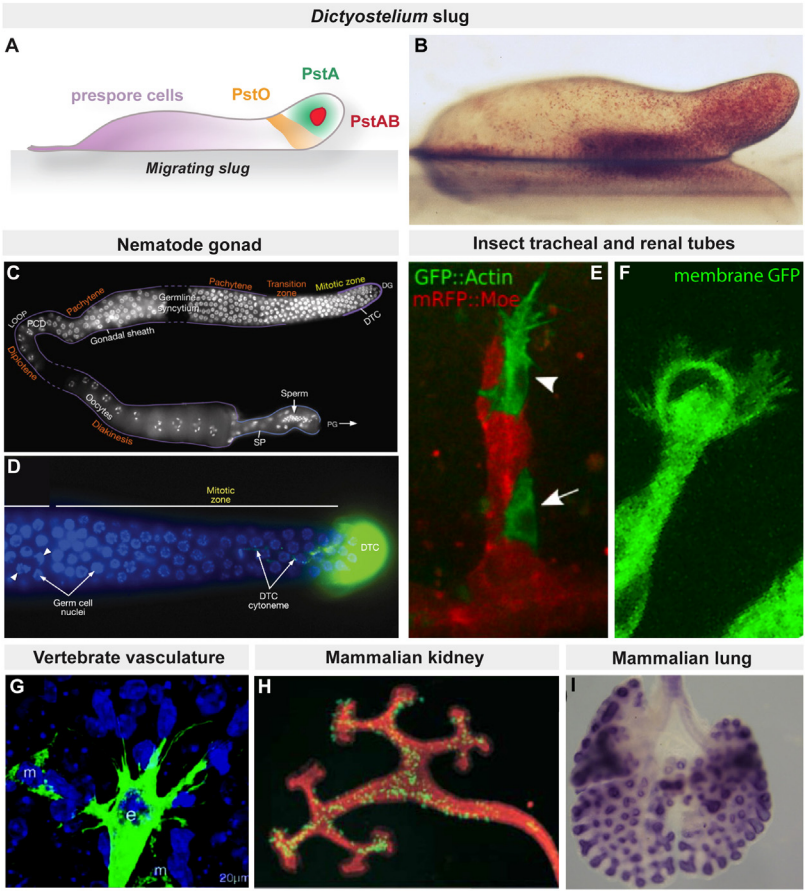

Fig. 1. Examples of tip cells. Specialised cells located at the tips of developing organs are found in diverse tissues from primitive *Dictyostelium* slugs (A) to the mammalian kidney and lung (H and I). In the migrating slug (A,B), prestalk A (pstA) cells populate the apical tip and guide slug migration; the remainder of the slug is composed of prestalk cells, pstO cells and pstAB cells. In the *C. elegans* gonad, a single distal tip cell (DTC, green in D) is located at each end of the U-shaped gonad arms at the tip of the mitotic region (C,D). In the insect tracheal (E) and renal systems (F), dynamic tip cells (E, arrowhead) with prominent filopodia are found at the distal-most ends of the developing tubes. Tip cells are also observed in the vertebrate vasculature during sprouting angiogenesis (G). Groups of cells located at the growing bud tips regulate branching morphogenesis in the mammalian kidney (H) and lung (I). Figure credits: images reproduced with permission from (B), D Dormann University College London; (C) and (D), J Maciejowski & E Hubbard NYU from http://www.wormatlas.org; (E), M Affolter University of Basel originally published in Curr Biol doi: http://dx.doi.org/10.1016/j.cub.2008.10.062; (G), C Betsholtz, Karolinska Institute ©Betsholtz et al., 2003. Originally published in JCB doi:10.1083/jcb.200302047; (H), F Costantini Columbia originally published in Dev Cell doi; http://dx.doi.org/10.1016/j.devcel.2004.11.008; (I) V. Papaioannou Columbia from PLOS Genetics 2012 doi:10.1371/journal.pgen.1002866.

selection and distinctive characteristics of these so-called tip cells and chart their activities and, where known, the mechanisms by which they exert their influence.

Tip cells can only be loosely defined because they occur as a distinctive and more or less permanent cell type at the tip of a wide variety of developing tissues, often a tube or branched structure within an organ. However, they are also found as a collection of cells marked out by their position at the leading edge of a moving group of cells, where they exert an influence over their neighbours. A common feature of tip cells is that they have specialised patterns of gene expression and exhibit specific cell behaviours. They feature from the simplest multicellular organisms (in the migrating slug of *Dictyostelium*) to the most complex (the vascular and renal systems of mammals) and in tubular systems (insect and mammalian airways or renal tubules) as well as in groups of migrating cells (insect border cells, zebra fish lateral line) (see Fig. 1 for examples).

Whilst there are many striking parallels in the molecular mechanisms governing the selection, behaviour and function of cells at the tips of what initially appear to be physiologically and morphologically diverse tissues, there are also crucial differences, which ensure that an organ's structure is tailored for its specific physiological function.

Our aim in this review is to highlight major roles played by tip cells during tubulogenesis and in the mature tissue, taking examples from diverse systems. We do not aim to provide a comprehensive description of tip cell activity in every organ.

2. Tip cell specification and selection

In many tissues tip cells are selected by a regulatory network, in which high levels of a facilitating signal confer on a group of cells the potential to develop tip cell fate. This potential is then restricted by competitive and mutual inhibition through Delta-Notch signalling to refine patterning, determining which cell or cells actually adopt the tip cell fate. However the levels of initial signal bias the outcome of lateral inhibition as more highly activated cells inhibit their neighbours more effectively. For example, during angiogenesis in mammalian systems high levels of activating Vascular endothelial growth factor receptor (VEGFR) signalling (VEGFR2/3) and low levels of inhibitory VEGFR1 signalling lead to enhanced expression of the Notch ligand, Dll4, enabling these cells to outcompete their neighbours for the tip cell fate (reviewed in [1,2]). This network appears to be conserved in zebrafish [3–5].

In a very similar way tip cells in the developing tubes of both the tracheal and renal system in *Drosophila* are selected by signals promoting tip cell fate (high levels of Fibroblast Growth Factor (FGF) signalling in trachea and of Wingless and JAK/STAT in Malpighian tubules ([6,7]; Denholm, Brown et al., unpublished)), followed by

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