Chapter 3. Cytokinesis and epithelial growth.

In addition to controlling cell shape and mitotic spindle assembly, cytoskeletal filaments regulate the active cargo-trafficking of proteins, RNAs, and other cellular components. In yeast cells, cytoskeletal remodelling is tied to the cell-cycle progression [1]. As multicellular organisms evolved from single free-living cells, the mechanisms that regulated cellular polarity and the cell-cycle oscillation were adapted to allocate differential cell fates. To form an undifferentiated epithelium demands only that the proliferating daughter cells fail to separate and remain attached to each other. This requirement implies the involvement of specialised junctional complexes. Given such junctions, a sheet of cells could grow with the limited complexity of the yeast genome. A primitive raft of cells would tend to absorb nutrients through its top and bottom surfaces and share them through lateral cell interfaces. Nutrient flux, and membrane export, would be roughly balanced between neighbouring cells, while any minor imbalances would modify local growth rate. However, the proliferation of epithelial sheets with precise topographical boundaries would require the polarised redistribution of nutrients and metabolic products. Polarised cargo trafficking could also generate patterns of differentiated cell types, but this would require more complex regulatory mechanisms. Notably, dividing epithelial cells distort the shape of their neighbouring cells as they intercalate. The resultant mechanical stresses are transmitted through the cortical actin cytoskeleton and extracellular matrix [2 3]. In such a system, the lack of stress along the apico-basal (Ap/Ba) epithelial axis would influence spindle orientation, and indeed spindle asters tend to be normal to the Ap/Ba axis of epithelial sheets. Given this initial Ap/Ba alignment, the preferred spindle orientations should control both clonal growth and the topographical shape of epithelial fields. Spindle-polarity need not be coupled between all proliferating cells, provided that morphogenetic field boundaries are constrained. Indeed, the precise coupling of mitotic spindle orientations between adjacent cells may require that they divide in synchrony (Gubb 1998). Spindle coupling is characteristic of the first embryonic divisions in multicellular organisms, and again during terminal differentiation, but is not evident during the proliferative growth of epithelial sheets. What is the experimental evidence that morphogenesis is keyed to the cell-cycle?

The cell-cycle oscillation in yeasts is regulated by a set of Cdc (cell division cycle) genes [1]. Among this set, Cdc42 controls actin microfilament assembly and the establishment of budding sites [5]. Microfilament assembly is also regulated by Cdc42 in multicellular organisms, together with cellular polarity and the cell cycle progression [6 7 8]. Notably, Cdc42 acts through intracellular tight-junctions, affecting apical cell tension, endocytic transport, actin stress-fibre formation, lamellipodial growth, macrophage chemotaxis, axon guidance, spindle polarity and hair orientation [9 10 11 12 13 14 15]. Strikingly, the human Cdc42 gene may complement yeast Cdc42 mutant phenotypes [16]. The Cdc42 protein has been strongly conserved and Cdc42 mutations generate multiple pleiotropic phenotypes in multicellular organisms.

Summary:

The cell-cycle progression and cytoskeletal remodelling of eukaryotic cells is regulated by Cdc genes. In multicellular organisms, neighbouring cells are coupled by junctional complexes, which may act as foci for the transmission of mechanical stress and regulatory interactions. In consequence, the cell-cycle progression of higher organisms regulates complex morphogenetic interactions.

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