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VII. POLARIZED CELL DIFFERENTIATIONS

The internal polarizing processes involved in the orderly phenomenon of cell differentiation require the concourse of the counter-forces of *antichaos* to polarly reorganize the systems disordered by the randomizing, nonlinear forces of deterministic *chaos*. Preeminent among these antichaos forces would then be the polarizing ones. In this antichaos struggle toward polarly ordered self-organization, differentiation of the cells is assisted by the coordinated behaviour of their genomic system which "acts like a complex parallel-processing computer, or network, in which genes regulate one another's activity either directly or through their products" (Kauffman, 1991). Computer models based on the algebric systems of random Boolean networks have first been proposed by Kauffman in attempts to understand the complexification features of cells differentiating into their dissimilar patterns of genetic activity. In these mathematical models, the behaviour of each gene is considered as a simple binary - on or off - variable and each combination of binary element activities constitutes one network "state" in which it will respond to combinations of signals. It is a transient flipping of a binary element to its opposite state of activity which may push the network into a different basin of attraction and therefore a new state cycle of network behaviour (Kauffman, 1991).

Mechanisms by which cell differentiation is initiated are both asymmetric cell division and cell interactions. The problem of asymmetric division concerns many types of differentiating cells (see VIII.A.2.b., *Volvox* patterns, B.2.i., mouse epithelia) and spatial aspects of cytokinesis beginning with the establishment of division polarity have been reviewed by Wick (1991). The previously described examples of asymmetric cell division in invertebrate embryo development (Davidson, 1986 in **I**) have now been completed by Gurdon (1992) and, concerning their mechanisms, Horvitz and Herskowitz (1992) have attempted to answer the following questions: "what causes a mother cell to be polar? How do initially identical sister cells become different? And in each case, how do initial differences in sister cells lead to their ultimately distinct fates?" The *asymmetry* during embryogenesis is established as a response to signals which are transformed into different positional fates under the controls of the complex genetic system of homeotic selector genes (reviewed by McGinnis and Krumlauf, 1992; St Johnston and Nüsslein-Volhard, 1992). However, their understanding "does not itself account for *how* cells adopt the correct spatial relationship to each other" (Gurdon, 1992).

Molecular probes have allowed to follow the establishment of "fields" and the emergence of properties such as boundaries, gradients, polarity and generation of cell diversity in terms of molecules and mechanisms. However, the concepts these words convey still elude explanations in terms of molecular mechanisms (Ingham and Martinez Arias, 1992).

The fundamental polarizing role of the cytoskeleton in cell differentiation has been emphasized by Pollard and Goldman (1992). In this respect, we have now found that actin microfilaments and dots are selectively accumulated in the differentiating female gametangia of the aquatic fungi *Allomyces*, whichever their positioning - apical-subapical - on the reproductive hyphae (Turian *et al.*, 1992). Suggestion that such high actin content of female organs might be related to their richness in RNA (Turian, 1963 in **I**) rejoins Singer's (1992) speculation of an actin involvement in the setting of apical-basal polarity by an asymmetric exit of mRNA through the nuclear pores.

C. Apico-basal differentiations

3a) *Algal eggs (rhizoid-thallic poles)*

Endogenously-produced ionic currents and gradients are thought to be fundamental to polarity (Nuccitelli, 1983 in **I**, 1988). Around germinating zygotes of *Pelvetia*, Gibbon and Kropf (1991) have measured extracellular pH gradients which contrarily to ATP-produced ionic currents (Harold, 1986, Gow, 1989 in **I** and **III**, respectively), would be generated from polarly distributed mitochondria and thus might play a subtle role in polarized growth.

In developing zygotes of *Fucus*, the process of polar axis stabilization (or fixation) following that of its formation involves both components of the cytoskeleton and the extracellular matrix, a structural complex postulated to stabilize membrane asymmetries generated as a result of axis-forming vectors (Quatrano *et al.*, 1991). It is the polar axis which is labile and can be easily and repeatedly reoriented by imposing a unilateral light gradient from a different direction (Quatrano, 1978 in **I**).

6. *Higher animal cells*

a) *Eggs (animal-vegetal poles)*

The importance of the cytoskeleton for embryo polarity has been reviewed by Elinson (1990). It has been considered how a polarized network is constructed and how useful are the activation steps for contraction of actin in developing eggs.

a^3 *Insects*

As reviewed by Gurdon (1992), the polarity of the egg of *Drosophila* is determined by the relative position of the oocyte to its nurse cells within the ovary; the nurse cells contribute gene products coded by *bicoid* which controls monopolar anterior development, *nanos* which controls posterior development, *torso* which controls bipolar, terminal developments of the egg, and other genes. Such developments rely on prelocalized positional determinants present within the cytoplasm of the newly laid egg (Frohnhöfer and Nüsslein-Volhard, 1986 in **I**). These maternal materials are localized to

the anterior and posterior poles of the egg, and St Johnston and Nüsslein-Volhard (1992) have further described how, on the molecular level, the four maternal signals concour to establish positional information in this embryo.

Oskar has been found to organize the germ plasm of the *Drosophila* oocyte and to be colocalized with *nanos*, suggesting that *oskar* directs localization of the posterior determinant *nanos* (Ephrussi *et al.*, 1991). *Oskar* mRNA has been localized to the posterior pole of the *Drosophila* oocyte (Kim-Ha et al., 1991). The posterior group gene *staufen* also codes for a protein which is one of the first molecules to localize to the posterior pole of the oocyte, in the polar granules, perhaps in association with *oskar* RNA (St Johnston *et al.*, 1991).

a5 *Amphibians*

The animal-vegetal, future anterior-posterior bipolar axis of their egg is determined by the relative position of the nucleus and an asymmetric creating accumulation of mitochondria in the oocyte (Heasman *et al.*, 1984 in Gurdon, 1992). A nucleotide localization signal would direct RNA localization to the vegetal pole (Mowry and Melton, 1992).

b) *Epithelia (apical-basolateral poles)*

The polarity of epithelial cells is manifested at many levels of organization and mechanisms by which they generate and maintain cell surface asymmetry are still largely unknown (Gumbiner, 1990). An important role in the sorting process of the two - apical versus basolateral - domains is suggested by differential blocking of the apical delivery of secretion enzymes by the microtubule-active drug nocodazole (Eilers *et al.*, 1989). A role had also been ascribed by Achler et al. (1989) to microtubules (MTs) in polarized delivery of apical membrane proteins to the brush border of the intestinal epithelium using colchicine- and vinblastine-induced depolymerization of MTs. Microtubule disruption by colchicine or nocodazole impairs the transport of proteins to the apical pole of rat hepatocytes (Durand-Schneider *et al.*, 1991). A role for the uniformly aligned microtubules has also been ascribed in maintenance and generation of polarity in enterocytes (Drenckhahn, 1992).

How proteins finally residing on the apical or basolateral surfaces are sorted from each other? Polarity trafficking signals are effective in that process (Hopkins, 1991). Contrary to current models, basolateral transport in MDCK cells (see **I**) has now been found to occur not only by "default" but to depend on one or more cytoplasmic domain determinants (Hunziker *et al.*, 1991). Nevertheless, many membrane proteins can reach the apical surface in the absence of this determinant.

A 14-residue sequence of the cytoplasmic domain proximal to the membrane-spanning segment has been found (Casanova *et al.*, 1991) to contain an autonomous signal, which specifies sorting from the trans-Golgi network to the basolateral surface, a process previously postulated to occur by "default" (see above).

Development and maintenance of cell surface polarity is fundamental for proper epithelial cell function and proteins are asymmetrically distributed in such polarized cells (Simons and Wandinger-Ness, 1990). The basolateral *versus* apical sorting of plasma membrane proteins has been studied by polarized Caco-2 monolayers and a model proposed for the sorting of apical and basolateral membrane proteins and their transcytotic pathway in intestinal epithelial cells (Matter *et al.*, 1990). Interesting "molecular cross talks" between epithelial cells and pathogenic microorganisms have been further discussed in a recent meeting summarized by Wick *et al.* (1991).

Epithelial cells often display - perpendicular to their apico-basal polarity - a second polarity axis within the plane of the cell sheet. This planar cell polarity expresses itself as scales, hairs or bristles whith point tangentially with respect to the epithelium. A supracellular tangential tissue polarity is thus produced by the uniform orientation of cell structures (Nübler-Jung and Eschbach, 1992).

GPI (glycosyl phosphatidylinositol)-anchored isoforms of N-CAM (calcium-independent neural cell adhesion molecule) are targeted to different surfaces of polarized epithelial cells (Powell *et al.*, 1991). Several signals have recently been identified that control the sorting of plasma membrane proteins among which the GPI anchor for their apical targeting (Bomsel and Mostov, 1991). Many additional references about polarized sorting are provided by this last review.

Preferential retention of active Na^+, K^+-ATPase in the basal-lateral membrane domain and selective inactivation and loss from the apical membrane domain would be the mechanism by which cell surface distributions of membrane proteins are regulated in polarized MDCK cells (Hammerton *et al.*, 1991). These last cells lack membrane-cytoskeletal complexes contrarily to other polarized epithelial cells with different distributions of the ATPase in which the same subunits are localized in the apical membrane (see Gundersen *et al.*, 1991). The normal renal tubule polarized location of Na^+-K^+-ATPase in basolateral membranes has been shown by immunolocalization studies (Wilson *et al.*, 1991) to be completely reversed to apical, luminal plasma membranes of autosomal dominant polycystic kidney disease (ADPKD). Such a polarity mislocation is due to an intracellular sorting defect specific for the ATPase pump.

Field potentials across the lingual epithelium modulate taste reception, the functional unit of which includes receptor cells that contain apical Na^+ channels and basolateral sodium pumps connected functionally in series. Chloride provides a shunting that compensates the electropositive field potential due to the transcellular and paracellular transport of Na^+ (Ye *et al.*, 1991). The electropositive potential created could act as a hyperpolarizing field potential depressing the receptor potential of the taste cells (Harper, 1987 and Elliott and Simon, 1990 in Ye *et al.*, 1991).