Plasticity, Nuclear Diapause, and a Requiem for the Terminal Differentiation of Epithelia

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Once in a while, we should compulse over well-established paradigms, and I have been thinking about the terminality of differentiated epithelial cells. There are many believers in terminal differentiation, but if the concept encourages a sense of immutability, then does it cripple new ideas regarding the plasticity of transitions among mature epithelia? I think so, and my apostasy is this: Although epithelial cells differentiate to expected levels of function, they are not necessarily terminal. Mature epithelia occasionally morph into other phenotypes depending on the availability of somatic cues that engage new molecular programs.

If this argument is defensible, what are the merits? Some brief outline of epithelial maturation may be a good starting point. Early patterning of epithelial tissues requires specification and expansion of new cell lineages. Under temporal exposure to biochemical drivers and inductive signals, a developmental periodicity shapes the forward differentiation of epithelial cells forming functional units as tissue structures. Periodicity in biologic systems is called diapause. Nuclear diapause in cells, as I define it, denotes a modulated period of chromatin stability surrounding intervals of developmental change. Polycomb/trithorax group proteins and methylation domains in clusters of non-coding elements near coding sequence for lineage-appropriate transcription factors may orchestrate such diapause epigenetically. Hypothetically, these control elements gradually limit access to more chromatin and eventually stabilize maturation. Under such conditions, epithelia remain diapausal in the nucleus and function appropriate for the cell.

Mature epithelial cells that reach this stage of development have a centriole-derived primary cilium and stop proliferating, join neighbors by intercellular attachment, and regionally polarize, as needed, through the asymmetrical assignment of surface proteins. In this relative state of mature cell life, what is popularly called terminal differentiation is really just an evolutionary pause maintained by signaling events, transcription factors, and genomic setting. Normally, little else really befalls these epithelia except to divide, hypertrophy, die apoptotically, or undergo dysplasia. Does referring to this diapause as terminal really know what these tests might be.

Another facet to consider is the diapora of epithelia are really quite diverse. The descriptive features of various epithelial cells belong to the storied lexicon of histopathology, and the notion of terminal differentiation is particularly entrenched in this discipline. Such morphologic determinism springs in part from a necessity to contrast normal epithelial tissues from those arrested in development or to distinguish normal differentiated cells from those that are dysplastic. In both instances, the underlying assumptions are understandable but increasingly difficult to square with recent observations of other epithelial behaviors. A growing number of studies now suggest mature epithelia can change phenotype without risk of apoptosis; that is, they revise their diapause and epigenetic memory. Two forms of plasticity occasionally alter mature cells to make this point.

The first is the process of epithelial transdifferentiation. Transdifferentiation describes the conversion of one mature epithelium into another with or without intervening cell divisions—pathologists call this metaplasia. Such plasticity has been documented both in culture systems and in vivo. The definition of transdifferentiation requires interconverting cells to derive from the same ancestral lineage without producing heterokaryons expected from cell fusion. Implied in this notion is mature epithelia, although not multipotent, have some degrees of freedom in reprogramming their chromatin and changing their phenotype in response to new somatic cues (Figure 1A). Interconversions, for example, have been observed above the gastroesophageal junction, where stratified squamous epithelial cells become columnar, like the intestine, to form Barrett’s esophagus; in type B intercalated cells from the renal collecting duct that change into type A intercalated cells; in type 2 pneumocytes that transdifferentiate into type 1 pneumocytes in the lung; in neural retinal cells that morph into pigmented epithelia; in retinal pigmented cells that become lens epithelia; in lactotrophs that interconvert to somatotrophs in the pituitary gland; in pancreatic exocrine cells that become hepatocytes; and in hepatocytes that transdifferentiate into insulin producing cells. All of the drivers underlying these conversions are not understood, but a couple of examples are illustrative.

The peripheral retina is the source of several nonpigmented and pigmented ocular layers that sheath the eye around its lens.
In the peripheral eye, cells from the neural retina transdifferentiate into pigmented epithelia under the control of the homeodomain gene $\text{Chx10}$ or morph in the other direction under the control of $\text{Mitf}$. The products of these genes and their targets establish molecular boundaries in the peripheral retina, determining the interconversion of ocular cells that alters the phenotype of a mature lineage. In vertebrate uroceles (newts and salamanders), pigmented epithelial cells also transdifferentiate into lens cells. Newts can do this throughout their life, but it is not easily demonstrated in higher vertebrates outside of cell culture.

Transdifferentiation also occurs in cells formed out of anterior foregut endoderm by the interconversion of pancreatic epithelia and hepatocytes. Partial pancreatic duct obstruction in primates produces ductal hyperplasia and new endocrine tissue with a scattering of unexpected hepatocytes. Pancreatic exocrine cells in mice that overexpress keratinocyte growth factor or a transcription factor called C/EBPβ also switch into hepatocytes. Conversely, overexpression of the transgenes encoding Pdx1 or Pax4 in hepatocytes converts some of them into insulin-producing pancreatic cells that rescue hyperglycemia in diabetic mice.

A more physiologic example of transdifferentiation is suggested in the kidney. The renal collecting duct is home to intercalated tubular cells, which secrete $\text{H}^+$ ions (type A cells), $\text{HCO}_3^-$ ions (type B cells), or $\text{H}^+$ and $\text{HCO}_3^-$ ions (type non-A, non-B cells) into tubular fluid. These highly differentiated epithelia change phenotype by re-addressing $\text{H}^+$-ATPases and $\text{Cl}^-/\text{HCO}_3^-$ exchangers to either the basolateral or the apical cell membrane and by modifying their apical surfaces. Interconversions forming these two mature phenotypes are occasioned by the acid-base demands of the host. Although there is some debate as to how many intercalated cells have intermediate phenotypes and whether type A or type B cells along the nephron derive only from the intermediate form, it is clear from cell culture studies that mature type B cells can become type A. An extracellular protein called hensin modulates this transdifferentiation, and type A cells emerge columnar with microvilli, whereas type B cells are neither. This conversion has been considered a terminal event, but
Consequently, fibroblasts formed by EMT may differ graphically by epithelial somites, perhaps based on a “Hox” transcriptional modulators such as CBF-A, Snail, Sip1, Twist, HMGA2, dependent on outside-inside signaling that engages transcriptional programs induced by hepatocyte growth factor and bone morphogenetic protein-7. The dynamic tension between EMT and MET normally encourages the preservation of nuclear diapause and a mature epithelial phenotype providing expected physiology.

The somatic cues that favor transdifferentiation over EMT still need clarification. The popular perception of terminal differentiation, however, is a problem for the field of epithelial biology and ripe for retirement. Terminal differentiation is at odds with cellular plasticity and cannot persist as a rarified cul-de-sac if cells are to respond adaptively to new environmental cues. While epithelial lineages mature and maintain to ensure unique functions, they also are dynamically poised to change. I suggest the notion of nuclear diapause better reflects what the less attractive concept of terminal differentiation cannot.

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