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Waddington's Valleys and Captain Cook's Islands

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Somatic reprogramming has relied heavily on theoretical models that view differentiation in terms of developmental branch point decisions. Recent studies in *Cell* now reveal a dominant role of the microenvironment in shaping epigenetic identity of macrophages, thus providing support for alternative models of cell fate acquisition.

During development of a multicellular organism, a single totipotent zygote ultimately gives rise to multiple differentiated cell types with unique gene expression programs. A pioneer of epigenetics, the developmental biologist Conrad H. Waddington has likened this process to a ball rolling downhill through branching valleys that successively restrict developmental options until a stable state of terminal differentiation is reached at the bottom of the valley (Waddington, 1957). The model thus classifies cells according to their previous developmental decisions. In line with this, much work has focused on the mechanisms (particular transcription factors) that drive cell fate in a specific direction at the branch points of development (Graf and Enver, 2009).

Two recent studies have now used modern epigenetic analysis in macrophages to take a fresh look at the old question about the relative contributions that developmental history and the microenvironment make on determining cellular identity (Lavin et al., 2014; Gosselin et al., 2014). Macrophages are particularly well-suited to address this question. They are present in essentially every tissue of the body and provide important homeostatic functions specific to the tissue of residence, such as axon pruning in the nervous system, clearance of surfactant in the lung, or regulation of B cells in the peritoneum. These tissue resident macrophages develop from early progenitors in the embryo (Perdiguero et al., 2014) and can be maintained within their tissue of residence by local proliferation (Sieweke and Allen, 2013). Under inflammatory conditions, with age, or after bone marrow transplantation, however, blood monocytes can replace embryo-derived macrophages and acquire similar tissue-specific functions (Gentek et al., 2014). Two studies in *Cell* now provide a detailed genome-wide map of open chromatin and enhancer-associated histone modifications for different tissue macrophages. They show that the environment dictates tissue-specific epigenetic enhancer signatures independently of cellular origin and thus plays a dominant role in specifying cellular identity (Lavin et al., 2014; Gosselin et al., 2014). Most strikingly, upon transfer of differentiated macrophages from one tissue to another (Lavin et al., 2014) or upon tissue culture with factors specific for a different tissue (Gosselin et al., 2014), macrophages can acquire to a large extent the newly induced identity. The ability of the environment to impose tissue specialization on macrophages of diverse developmental origins suggests that the precise binary developmental decisions during cellular differentiation might be less critical than previously assumed, and it suggests that a highly similar cellular identity can be reached from different origins.

These observations recall findings from experimental reprogramming between two differentiated mature cell types by defined transcription factor cocktails (Graf and Enver, 2009). Such direct lineage conversions have now been reported between developmentally very distant cell types of different germ layer origin, such as fibroblasts, neurons, and hepatocytes. This outcome is difficult to reconcile with Waddington's model (Figure 1A) because the energy required for a push over multiple ridges appears prohibitive. Furthermore, conversion can be achieved without passage through common developmental progenitors (stages 1, 2, and 3). This is indicated, for example, by genome-wide gene expression analysis during reprogramming of B cells into macrophages (Di Tullio et al., 2011) or by lineage tracing techniques in the conversion of fibroblasts into motor neurons (Son et al., 2011). How can transitions between developmentally distant cells (a and c) be explained if they are many mountain ridges apart and if backtracking up the valley does not occur?

Perhaps Waddington's rolling hills are not the only landscape to model epigenetic identity. When visiting Melbourne it is hard to evade the legacy of the great explorer Captain James Cook. On his voyages through the Pacific islands he encountered a fundamentally different landscape without valleys and mountains, but rather, one of small and distant islands in a vast ocean. Could this scenario serve as an alternative model of cellular identity? When explaining cell identity we have to come to terms with the relatively limited number of a few hundred stable cell fates observed for the enormous number of possible combinations of over 20,000 coding genes. If we imagine each landmass on the surface of the Pacific Ocean to represent a theoretical possible combination of gene activities, the rare and widely dispersed geographical positions of small islands serve as a good analogy of the few stable cell fates. Indeed, mathematical modeling of antagonistic and self-enforcing gene activities, particularly transcriptional regulators, has identified rare but highly robust self-stabilizing states of defined gene activity (Huang, 2009).

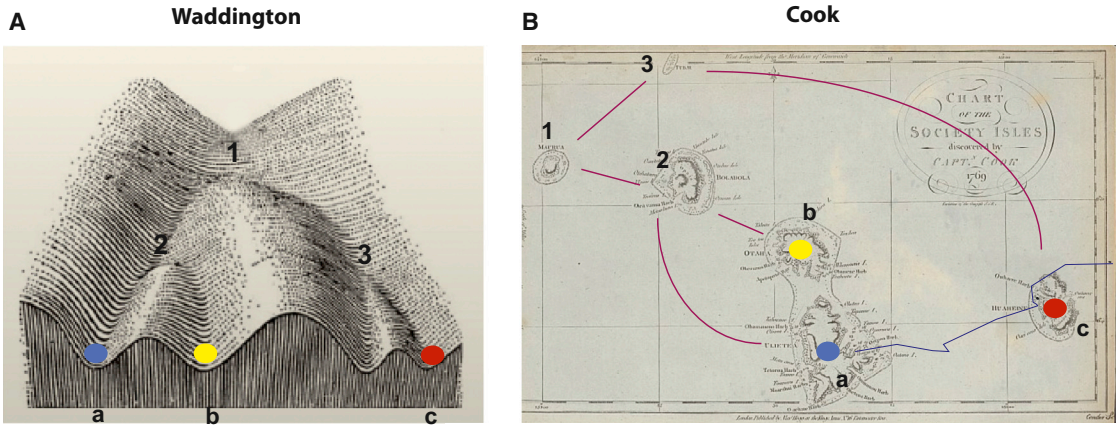

Figure 1. Waddington's and Cook's Reprogramming Landscapes
Alternative models of Waddington's (A) and Cook's (B) reprogramming landscapes showing mature cell types (a, b, and c) and intermediate states (1, 2, 3) of cellular development. Lines in (B) retrace a hypothetical Polynesian settlement of French Polynesia from west to east (red) and Captain Cook's route from east to west (blue) as models of development and reprograming, respectively.

In Waddington's model cell identity depends on a sequence of correct branch point decisions. This is a navigation system we typically employ on land, where taking the right turn at each cross road indeed works well to get from one location to another. At sea, there are no roads or intersections. Routes are highly flexible but if the precise coordinates are known, a small island can be reached from many directions. In this model (Figure 1B) there is no conceptual hurdle to move between developmentally distant cell identities (c and a), as observed in direct lineage reprogramming or by placing macrophages in a new environment.

Since Cook's epigenetic landscape has no defined branch points, successful navigation would require a global positioning system to localize islands of stability. The genomic analyses of Lavin et al. and Gosselin et al. are providing such precise molecular coordinates of cellular identity. Using chromatin accessibility assays (ATAC sequencing) and ChiP-seq analysis of Histone 3 lysine 4 mono- or bi-methylation (H3K4me1/2) and promoter distal binding of the macrophage transcription factor PU.1, they reveal a detailed map of genomic enhancer positions in macrophages from different tissues. Consistent with previous studies, they show that genomic enhancer positions are highly cell type specific. They not only reveal enhancers shared by all macrophages but also positions that are specific to the tissue of residence. Confirming dominance of the microenvironment, highly similar enhancer landscapes were observed in endogenous or bone-marrow-transplant derived macrophages (Lavin et al., 2014). Interestingly, binding site analysis identified specific motif enrichment for transcription factors that cooperate with PU.1 to establish tissue-specific enhancers (Lavin et al., 2014; Gosselin et al., 2014). In an ingenuous approach Gosselin et al. establish the functional importance of these binding sites by comparing enhancer marks and expression of associated genes in natural variants of these binding sites in different mouse strains (Gosselin et al., 2014). Together such approaches could be useful to identify new transcription factor combinations for precisely tailored reprogramming efforts. Future genome-wide mapping of enhancer repertoires and characteristic transcription factor binding sites of different cell types in their natural microenvironment might enable understanding and manipulation of cellular identity without prior knowledge of developmental origin. This might be particularly important for applications wherein rather than a generic cell type a highly specific subtype would be required for tailored screening or therapeutic benefit. Our tools may still be in their infancy but just as the newly developed sextant and chronometer enabled Captain Cook to determine his position in the vast Pacific Ocean, the new genomic technologies might put us in the position to undertake bold new voyages to desired islands of stable cellular identities.

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