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Current Opinion in Cell Biology

Cellular plasticity: 1712 to the present day

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Cell identity is a fundamental feature of cells. Tissues are often organized into cellular hierarchies characterized by progressive differentiation and developmental commitment. However, it is been historically evident that the cells of many organisms of various phyla, especially in the context of injury, exhibit remarkable plasticity in terms of their ability to convert into other cell types. Recent modern studies, using genetic lineage tracing, have demonstrated that many mature functional cells retain a potential to undergo lineage reversion (dedifferentiation) or to convert into cells of other more distant lineages (transdifferentiation) following injury. Similarly, mimicking progenitor cell transdetermination, stem cells can interconvert. These forms of plasticity may be essential for organismal survival, and are likely part and parcel of regeneration.

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Current Opinion in Cell Biology 2016, **43**:46–54

This review comes from a themed issue on **Differentiation and disease**

Edited by **Cedric Blanpain** and **Erwin Wagner**

http://dx.doi.org/10.1016/j.ceb.2016.07.005

0955-0674/© 2016 Published by Elsevier Ltd.

Introduction to plasticity

Multicellular organisms often need to maintain their form and function by continuously generating new cells to replace older cells that have been lost in the process of normal wear and tear. When the equilibrium of new cell generation and steady state cell loss is perturbed by tissue injury, homeostatic mechanisms are invoked to allow regeneration of damaged tissue. Until recently, it was thought that this equilibrium was, in the main, restored through the replication of adult stem/progenitor cells and their subsequent differentiation or through the replication of mature differentiated cells. These homeostatic cellular mechanisms were thought to obey defined lineage hierarchies, but it is becoming increasingly clear that classical directional lineage hierarchies do not define all the physiologically relevant paths a regenerating cell can tread.

During development, from egg to embryo, embryonic progenitor cells differentiate into progressively more diverse cell types. These events are thought to occur in such a way that several distinct cell intermediates are generated, with increasingly restricted lineage potential, until the final mature specialized cell types are generated and functionally integrated into their respective tissues. This general schema has been indelibly imprinted in our thinking by Konrad Waddington through his use of cartoons to depict the so-called epigenetic landscape of the embryo [1]. An implicit corollary to these notions is that progressively mature cells irretrievably lose the potential to give rise to progeny outside of their given lineage. That said, much earlier in the history of embryology, as far back as the late 1800s, August Weismann's and Wilhelm Roux's notion that embryonic cell fate was 'determined' with each subsequent cell division of the embryo, stood in contrast to the results of Han Driesch's experiments that suggested that early embryonic cells were plastic or 'regulative' and could respond to external injury [2]. More specifically, when Roux used thermal injury to kill one of the cells of a 2 cell frog embryo, the resulting larva possessed only a right or left half, suggesting that even early embryonic cells were 'determined' [2]. In contrast, Driesch's isolation of a single blastomere from an early multicellular sea urchin embryo, suggested that a single isolated blastomere could produce an entire larva, suggesting that sea urchins possessed 'regulative' development where multiple embryonic cells retain a potency to form an entire organism [2].

Harkening back to these very early seemingly discrepant findings, later studies challenged the notion that adult differentiated cells are irreversibly committed to a particular fate, both in experimentally-induced and physiological conditions. In a remarkable example of experimentally induced reprogramming, Briggs and King in 1952 managed to generate frog tadpoles by transplanting the nuclei of cells from the blastula into *Xenopus* oocytes [3]. John Gurdon then showed that this reprogramming could be accomplished with even more differentiated cells [4–6] and this body of work eventually culminated with the cloning of a mammal [7]. Less well known work from the laboratory of Ernest Hadorn revealed that fly imaginal disc progenitors from one imaginal disc could 'transdetermine' and acquire the characteristics of different imaginal disc progenitor cells when transplanted from one larva to a

heterologous site in a second larva (Figure 1a). In 1987, it was then shown that ectopic expression of the *Antennapedia* homeotic gene led to changes in the body plan of flies, such that leg appendages appeared where antennae should have formed [8]. Similarly, studies revealed that ectopic expression of the *eyeless* gene could lead to the formation of ectopic eyes where normal legs should have formed [9]. Subsequently, the remarkable capacity of *MyoD* to reprogram disparate cells into muscle cells set the stage for modern iPSC and direct cell reprogramming strategies, therein completing an arc of experiments concerned with 'artificially' induced cell plasticity [10,11]. Herein we would like to give an overview of the historical and modern experimental basis for thinking about cell plasticity *as a* normal physiologic agency following injury-induced regeneration. Stated otherwise, we endeavor to show that cell plasticity is not 'unnatural'.

Historical perspectives on adult cell plasticity in regeneration

Some of the first descriptions of regeneration date back to 1712, when Swiss scientist Abraham Trembley noted that the freshwater polyp *hydra* regenerates after being cut in half. In his descriptions from his treatise '*Mémoires, Pour Servir à l'Histoire d'un Genre de Polypes d'Eau Douce, à Bras en Forme de Cornes*', he noted that when polyps were cut into two vertical halves, each part gave rise to two smaller, but fully intact, normally re-patterned organisms [12]. In 1769, Spallanzani described how tadpoles could regenerate their tails and how salamanders could regrow amputated limbs, tails and jaws (*An assay on animal reproductions, Spallanzani, 1769*) [13]. In 1895, Wolff used a model of lens extirpation in the newt to show that missing lens tissue was, in fact, regenerated from developmentally distinct iris pigment epithelial cells. The pigment cells first dedifferentiated into non-descript cells without pigment, and then transdifferentiated into lens cells (Figure 1b) [14,15]. Thus, tissue-level observations from long ago set the stage for our current modern exploration of cell plasticity [13].

Terminology and definitions

Cellular plasticity during regeneration has now been scrutinized in many model organisms and tissues using inducible cell type-specific lineage tracing and in some cases by direct visualization. In this review, we refer to dedifferentiation as a process of lineage reversion in which differentiated cells acquire the properties of more immature cells within the same lineage hierarchy. Transdetermination classically refers to the conversion of one progenitor/stem cell population into another, thereby potentially forming a basis for a metaplastic tissue transformation [16–19]. Transdifferentiation, in contrast, refers to the conversion of one differentiated cell type into another, thereby affording another possible mechanism for tissue level metaplasia. Indeed, all 3 of these processes may occur in different contexts, and with further studies we may find that they all occur within the same tissues in various differing degrees based upon the extent and specific nature of the tissue injury. We would like suggest that each case of injury in each tissue must be examined individually before any general conclusions about the nature of plasticity can be drawn. Below we present an incomplete synopsis of some of the first such experiments that may be illustrative of more general principles of plasticity, focusing on vertebrate cell plasticity.

Cellular plasticity in invertebrates

In the fly germarium, when female or male germ stem cells are lost either via genetically forced differentiation or by laser ablation, differentiating gonialblasts and spermatogonia were shown to restore the missing germ cell population via dedifferentiation [20•]. In male flies, interconnected spermatogonia lose their ring canals and separate into single cells to form functional germ stem cells [21•,22,23]. Similar plasticity has been noted in the mouse testis where interconnected spermatogonial clusters fragment into single cells and act as stem cells [24,25]. Of note, in both male and female fly germaria, no terminally differentiated oocytes or spermatocytes have been shown to possess the capacity to dedifferentiate into stem cells. The remarkable regenerative capacity of planarians may further teach us about fundamental mechanisms of cell plasticity, but it remains unclear how insights into the biology of neoblasts will apply to vertebrates [26].

Cellular plasticity in vertebrates

When newt limb is amputated, a cluster of seemingly dedifferentiated progenitor cells, referred to as the blastema, appear and these cells then give rise to the tissues of the newly regenerated limb. Interestingly, even in the case of newt limb regeneration, it appears that the axolotl regenerates differentiated limb cells in a lineage-restricted form of dedifferentiation [27]. Remarkably in another newt, *Notophthalmus viridescens*, following limb amputation Pax7+ stem cells regenerate myocytes without large scale dedifferentiation. Thus, in seemingly closely related organisms, dedifferentiation and more conventional stem cell differentiation can be deployed to differing degrees to effect a superficially similar form of regeneration [28,29•]. This again points to the need to study cell plasticity within particular defined contexts, and the need to be cautious about generalizing experimental findings.

Zebrafish can regenerate their hearts following partial amputation. During this process, cardiomyocytes dedifferentiate and proliferate to regenerate missing ventricular tissue. Specifically, the sarcomere contractile apparatus and myosin heavy chain proteins are lost prior to myocyte replication, indicating that these dedifferentiated cells have undergone a complex structural, molecular and morphological change during this process (Figure 2a)

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