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Review

Tumoral reprogramming: Plasticity takes a walk on the wild side ☆

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ABSTRACT

Cellular plasticity is the capacity that cells have to change their fate and adopt a new identity. Plasticity is essential for normal development and for tissue regeneration and, in an experimental setting, for the induction of pluripotency. All these processes involve a reprogramming of the cellular identity, mediated by signals from the environment and/or by internal changes at the transcriptional and epigenetic levels. Tumorigenesis is a process in which normal cells acquire a new malignant identity and give rise to a clonal aberrant population. This is only possible if the initiating cell has the necessary plasticity to undergo such changes, and if the oncogenic event(s) initiating cancer has the essential reprogramming capacity so as to be able to lead a change in cellular identity. The molecular mechanisms underlying tumoral reprogramming are the pathological counterparts of the normal processes regulating developmental plasticity or experimentally-induced reprogramming. In this review we will first revise the main features of non-pathological examples of reprogramming, and then we will describe the parallelisms with tumoral reprogramming, and we will also delineate how the precise knowledge of the reprogramming mechanisms offers the potential for the development of new therapeutical interventions. This article is part of a Special Issue entitled: Stress as a fundamental theme in cell plasticity.

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1. Introduction

A tight homeostatic control of both cellular proliferation and differentiation is an essential need for all multicellular organisms. This control depends on intrinsic factors (transcriptional and epigenetic) and extrinsic signals received from the cellular environment. Any deregulation of the normal, developmentally programmed, transcriptional and epigenetic profiles or an abnormal signaling from the environment will likely lead to an aberrant phenotype/function. This is what happens in cancer, where oncogenic alterations reprogram normal cellular identity and originate a new pathologic lineage. However, this anomalous deviation from the normal differentiation programs can only occur if the initial cell in which the oncogenic event(s) takes place has enough plasticity so as to allow their reprogramming activity to take place. In this review, we will first describe physiological plasticity and how it is a property that is required for normal development. Then, we will revise this characteristic under the light of what we currently know about tumor biology, development and experimentally-induced cellular reprogramming. In order to do this, we need first to define the terminology and to understand the origin and the meaning of the different terms under the light of the developmental biology discipline that gave rise to them.

2. Definitions

We will use the term *physiological plasticity* to define the capacity that cells (stem or differentiated) have to adopt the biological properties (gene expression profile, epigenetic profile, phenotype, etc.) of other types of cells (that may be stem of differentiated, and may belong to the same or different lineages). *Competence* (or *potency*) would therefore be a specific form of plasticity, defined as the ability of undifferentiated cells (stem cells and progenitors) to give rise to their different descendant lineages during normal development (i.e. not pathologically- or experimentally-induced) (Fig. 1A). We will use the general term *plasticity* to cover both concepts, since it is nowadays demonstrated that the same mechanisms involved in stem cell competence during normal development are also involved in the plasticity of differentiated cells, and not only in pathological conditions like tumorigenesis, but also in normal development and in experimentally-induced fate changes. In the last 10 years, enormous advances have been made in our understanding of the biology of developmental plasticity [1–5]. However, the molecular bases of the specification and maintenance of cellular identity (or plasticity) are still not fully understood.

Stem cells are defined by two main biological properties: one of them is competence, as we have defined it; the other is self-renewal, supported by their capacity to divide in an asymmetric manner. This allows stem cells to generate, at every division cycle, a daughter cell poised for differentiation/proliferation, and another daughter retaining stem cell properties. Symmetrical division cycles are also possible, either replenishing the stem cell pool, or giving two daughter cells poised

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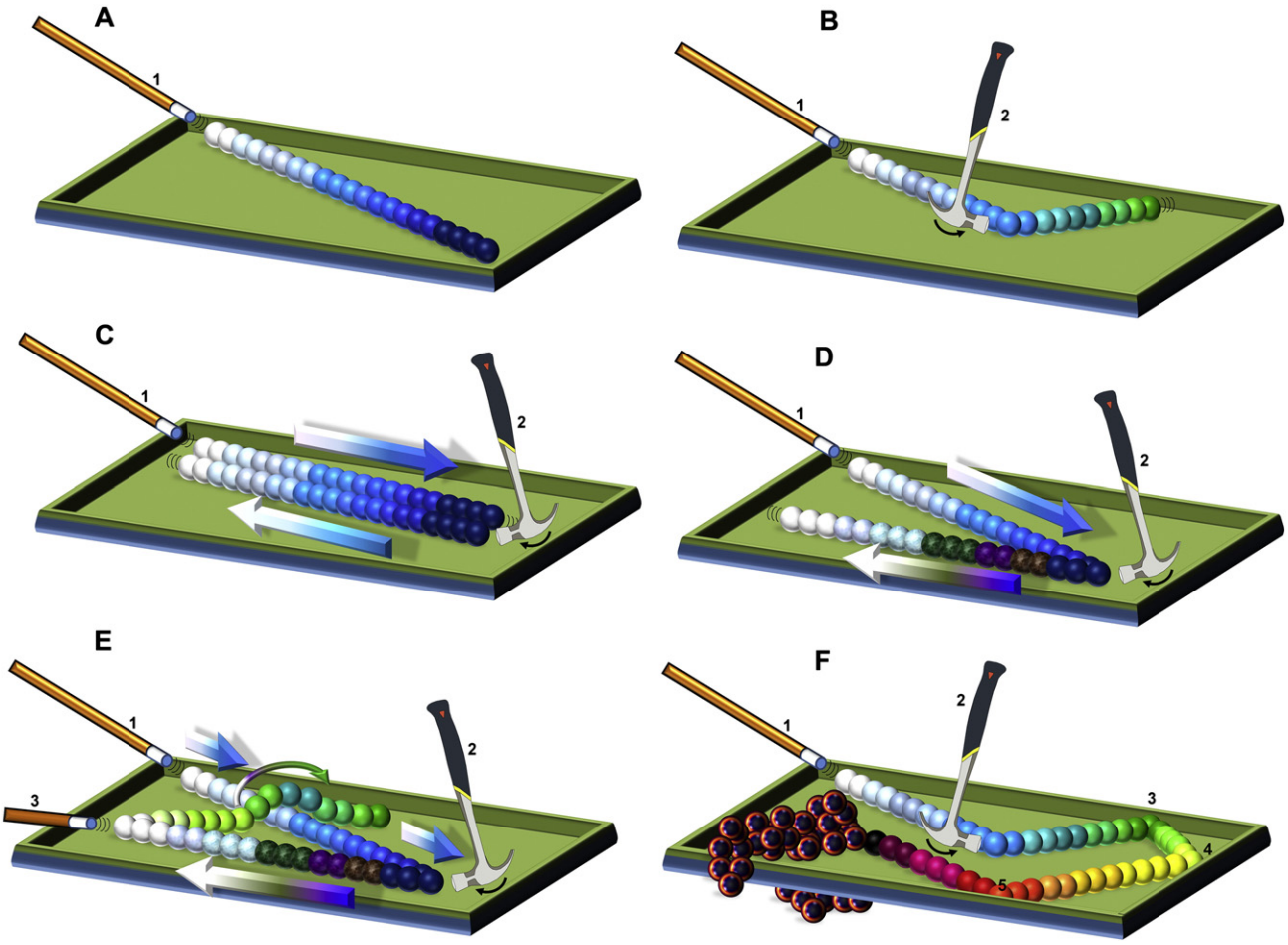

Fig. 1. The many faces of plasticity. In this series of figures we represent development as a pool ball rolling towards different directions (fates) depending on the strokes (stimuli) it has received. A) Normal development: the fate of an undifferentiated progenitor (white ball) is established once the initial impulse has been provided by the combined actions of internal transcription factors and external signals, and then the cell develops "lineally" towards this fate. B) Transdifferentiation: the action of a new force (the hammer, for example a master regulator transcription factor) redirects the cell towards a new fate, pushing it out of its initially determined physiological route. C) Dedifferentiation: this is an inversion of the normal process of development, through the same developmental intermediate forms that were followed in the first instance, but in a reversed order. In this figure, we have pictured an opposite driving force (the hammer) but the reversion could also be due to the lack of an initial impulse (for example, the lack of an essential driving transcription factor). D) Reprogramming to pluripotency: an external force (the Yamanaka factors, for example, here represented by the hammer) counteracts the normal developmental program and sends the cell back to a progenitor condition (in this case going through non-physiological cellular intermediates). E) Re-differentiation: after pluripotency has been induced, the cells can be re-differentiated into new cell types with the help of external of internal stimuli (billiards cue no. 3). F) Tumorigenic reprogramming: an oncogenic hit (represented by the hammer), hitting at the right cellular stage, with the right angle and strength, will send the cell into a new developmental program that will end up in cancer generation. As it is schematized here, the second hits in tumorigenesis (nos. 3, 4, 5) are already implicit given the first hit and the nature of the target cell.

for differentiation. These are the normal features of stem cell-based tissue generation and replenishing under physiological conditions. However, this normal functioning can be altered in several ways, either experimentally or in different pathologies, like cancer or developmental abnormalities. In all these cases, the final consequences of reprogramming are largely divergent, depending on the plasticity of the target cell, and on the initiating stimulus that triggers the reprogramming. Since there are nowadays many types of processes described involving fate changes in different experimental settings and in different organisms, this has created some confusion in the scientific literature in terms of nomenclature. We will speak of *transdifferentiation* to talk about the direct conversion of a differentiated cell type into another type of mature cell, without the need of dedifferentiating to earlier developmental stages; this process frequently implicates going through cellular intermediates that are non-physiological since they share markers that are normally mutually exclusive, corresponding to the initiating and the final cell (Fig. 1B). On the contrary, *dedifferentiation* is the process by which normal development is reverted in such a way that differentiated cells give rise to more plastic, earlier progenitors, usually going backwards through the same developmental stages they followed before (Fig. 1C). *Commitment* designates the point of no return in a process of normal development, at which the cell irreversibly enters a particular differentiation program. In the case of stem cells, it implies the loss of self-renewal. *Epigenetic* refers to the inheritance of specific patterns of gene expression, without altering the genetic code itself. This means that it is a type of inheritance that is not codified in the DNA sequence. From a molecular perspective, it encompasses all the different DNA and chromatin modifications that establish and allow the inheritance of all the different possible patterns of gene expression (that determine the cellular phenotypes) of a given, unique organisms' genome. *Reprogramming*, when considered from the cellular point of view, refers to the natural or experimentally-induced alteration of the differentiation program of a given cell (Fig. 1D–E). From the point of view of the molecular mechanisms, it refers to the entire molecular changes (mainly epigenetic) taking place in a cell that changes its identity. Therefore, both dedifferentiation and transdifferentiation are specific forms of reprogramming, usually experimentally-induced, but not always. Oncogenesis is equally a form of reprogramming, but in this case one that spontaneously happens in nature (Fig. 1F). *Cancer stem cells* (*CSCs*) are the cells responsible for the maintenance, propagation, metastasis and relapse of tumors. As stem cells, they have self-renewal and differentiation capabilities, and can therefore give rise to all the tumoral cellular types that form part of the tumor mass. They can also be named

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