Biochimica et Biophysica Acta 1849 (2015) 371–377

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagrm

Review

Stress as a fundamental theme in cell plasticity ☆

Ofer Shoshani [a], Dov Zipori [b,*]

[a] Department of Cellular and Molecular Medicine, Ludwig Institute for Cancer Research, University of California, San Diego, La Jolla, CA, USA
[b] Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel

ARTICLE INFO

Article history:
Received 13 May 2014
Received in revised form 8 July 2014
Accepted 9 July 2014
Available online 16 July 2014

Keywords:
Reprogramming
Stress
Dedifferentiation
Transdifferentiation
Stem cell
Cell plasticity

ABSTRACT

Over a decade of intensive investigation of the possible plasticity of mammalian cells has eventually substantiated that mammalian species are endowed with a remarkable capacity to change mature cell fates. We review below the evidence for the occurrence of processes such as dedifferentiation and transdifferentiation within mammalian tissues in vivo, and in cells removed from their protective microenvironment and seeded in culture under conditions poorly resembling their physiological state in situ. Overall, these studies point to one major conclusion: stressful conditions, whether due to in vivo tissue damage or otherwise to isolation of cells from their in vivo restrictive niches, lead to extreme fate changes. Some examples of dedifferentiation are discussed in detail showing that rare cells within the population tend to turn back into less mature ones due to severe cell damage. It is proposed that cell stress, mechanistically sensed by isolation from neighboring cells, leads to dedifferentiation, in an attempt to build a new stem cell reservoir for subsequent regeneration of the damaged tissue. This article is part of a Special Issue entitled: Stress as a fundamental theme in cell plasticity.

1. Introduction

1.1. Mammalian cell plasticity

It has been traditionally accepted as common knowledge among cell biologists that mature cell phenotypes are rigid, and tend to maintain unchanged the cells' properties attained through the process of differentiation. However, a growing body of evidence refutes this notion. Indeed, several processes including dedifferentiation and transdifferentiation, portray the dramatic capacity of mammalian cells to change their fate. These phenomena are often referred to as "plasticity". One outstanding example is that of α pancreatic cells which turn into β cells, due to extreme depletion of the latter [89]. Experimental evidence for the plastic nature of mammalian cells has been repeatedly scrutinized as being either an artifact of imperfect experimental analyses or otherwise an extreme result of unrealistic and non-physiological conditions. However, as discussed below, recent studies demonstrate that both moderate culture conditions [76], and in vivo circumstances [81,86], bring about plastic behavior of normal mammalian tissue cells.

Reversibility of cell differentiation, i.e., dedifferentiation, has been assumed until recently to occur in plants [93] and in insects, such as in *Drosophila*, where it was shown that maturing cells forced into the gonadal stem cell niche dedifferentiate into gonadal stem cells [39]. Such processes are also part of blastema formation in amphibians [32]. Apparently, dedifferentiation is not restricted to non-mammalian organisms as demonstrated by the study of mouse spermatogenesis; when stem cell niches were emptied, cells downstream in the differentiation cascade assume stemness [58]. In fact, an ample amount of published data supports the notion that dedifferentiation also occurs in mammalians: Primary human skeletal myoblasts dedifferentiated and acquired the capacity to differentiate into neurons, glial cells, smooth muscle cells and adipocytes [11]. Such events have also been documented in nervous tissue derived cells; mature mouse astrocytes turned in vitro into neural progenitors, due to a short term treatment with transforming growth factor α [72] and oligodendrocyte precursors, stimulated with bone morphogenic protein (BMP) and fibroblast growth factor (FGF)-2, reverted into neuronal stem-like cells [44]. Also mammalian melanocytes [30] and adipocytes [53,71] and pancreatic cells [25,31,51] were reported to assume a dedifferentiation process. Such transitions from differentiated cells into immature tissue specific cells may also occur during development of the skin, gut and hemopoietic system [15,87], wherein relatively mature cells become early stem cells [6].

These few examples, among a multitude of other reported, demonstrate the possibility that cell commitment may be reversible in mammalians, as proposed early on, by the "Stem State" theory. The latter assumes that upon demand, mature cells may revert to their differentiated state and move backwards into less differentiated stages, and even make all the way into pluripotency [99,100].

A different expression of cell plasticity is found in the process termed transdifferentiation, in which cells of one tissue, with well-defined functions, assume a new phenotype and acquire properties of a distinctly different cell type. One such example comes from the work of Eva

☆ This article is part of a Special Issue entitled: Stress as a fundamental theme in cell plasticity.

* Corresponding author at: Department of Molecular Cell Biology, Weizmann Institute of Science, Herzl St. 234, Rehovot 76100, Israel.

http://dx.doi.org/10.1016/j.bbagrm.2014.07.006
1874-9399/

Mezey, in which it was demonstrated that transplanted bone marrow cells are capable of turning into neuronal-like cells in vivo [57]. In fact, such processes were documented repeatedly in mammalian cell systems. Bone marrow cells integrated into the muscle [23,28,74], brain neuronal compartment [5], liver [64], wound [2], retina [18] and pancreas [33,37]. Human neurospheres gave rise to human hemopoietic cells [73] and muscle [24], and hepatic cells were shown to transdifferentiate into pancreatic hormone producing cells [96]. Endothelial cells are also amenable to fate changes, as one study demonstrated their transdifferentiation into cardiac muscle [13], and another provided evidence for endothelial–mesenchymal transition, in an activin-like kinase-2 (ALK2) receptor-dependent mechanism [56,78]. When mammary epithelium is removed from the glands and the empty mammary space is infused with cells obtained from mature testis, redirection of the testis cells, into a mammary epithelial fate occurred [8]. Furthermore, upon implantation onto mammary fat pad, labeled neural stem cells transdifferentiated into functional mammary epithelium producing the milk protein, β-casein [7]. Evidence for transdifferentiation of mouse splenocytes into functional β-cells came from a pioneering study [42]. In their work, it was shown that diabetic mice can regenerate β-cells and ameliorate disease by using a combination of Freund's adjuvant and fresh splenocytes. It was suggested that although the adjuvant by itself can lead to elimination of autoimmunity and rescue diabetic mice, the splenocytes injected hasten the process, possibly by transdifferentiating into β-cells. This study was later criticized by other groups which failed to detect such transdifferentiating events, although they did find that Freund's adjuvant treatment indeed cures some of the mice [12,60,84]. It appears that the three studies trying to confirm Kodama's work did not use Y chromosome FISH, as done in the original paper, which might explain why the results were not confirmed [22]. However, Y chromosome FISH, although a powerful tool, still has limitations such as possible high background levels. This example raises the question whether dedifferentiation or transdifferentiation are at all technically detectible. By performing lineage tracing experiments such technical difficulties were circumvented. A striking example for such lineage tracing approach is the transition of α pancreatic cells into β cells upon extreme depletion of the latter [89]. Some of the so-called transdifferentiation processes were found to be due to cell fusion leading to genome reprogramming. Green fluorescence protein (GFP) tagged bone marrow cells regenerated defective liver functions of transplanted animals. This occurred by fusion of the hemopoietic cells with liver cells [90]. Since cell fusion is common to many physiological processes and occurs in a variety of disease states, such a process may contribute significantly to cell plasticity. The possibility that some or all of the transdifferentiation processes occur through an intermediate stage of dedifferentiation should be further investigated.

The above-described phenomena of dedifferentiation and transdifferentiation, suggest that cell maturation is not a final state. The genomic information seems to be unaffected following cell maturation with the exception of immune cells in which the T cell receptor (TCR) or B cell receptor (BCR) genes undergo rearrangement. The isolation of a frog somatic cell nucleus and its transfer into an unfertilized egg, resulted in the formation of a normal embryo [27]. The demonstration of possible dedifferentiation processes in mammalians suggested that nuclear transfer may equally work in animals of this class. Indeed, the cloning of Dolly the sheep, using a nucleus from an adult mammalian cell [94] and the use of nuclear transfer that results in reprogramming of mature B and T cells [34], further proved the integrity of the genome following differentiation and showed that it is possible to reverse the differentiation state. In this context it is important to note that some studies did report variation in the genetic and epigenetic layers in cloned animals [35,36,54] (This aspect of genomic instability is covered in this issue by Ben-David U.). A further development in this field of research was the discovery that forced expression of transcription factors caused reversal of somatic cells into cells resembling embryonic stem cells (ESCs). Initially, mouse embryo fibroblasts (MEFs) and adult mouse fibroblasts, transfected with cDNAs of c-Myc, Sox-2, Oct-4 and Klf-4, turned into pluripotent ESC-like cells [85]. The resulting cells were designated induced pluripotent stem cells (iPSCs). Such cells were then found to be obtainable from gut epithelium and from adult functional liver cells [1]. These studies thus showed that overexpression of four exogenously introduced genes, is sufficient to recreate stemness.

The modes described above, by which reprogramming and transition of cells from maturity to stemness was achieved, required harsh and artificial conditions. The question raised is whether the phenomena of dedifferentiation in mammalians occur only under such experimental conditions. In fact this does not seem to be the case since reprogramming has been documented following treatment of perforated cells by protein extracts [9,29,50]. Testis derived cells from mouse [26] or human [14,45] origin acquired differentiation potencies similar to ESCs without the need for harsh manipulations, such as those required for obtaining iPSCs. Spermatogonia become pluripotent simply due to their isolation from the normal in vivo niche and their subsequent propagation in vitro.

On the basis of these observations and the prior suggested stem state notion it was proposed that each mammalian cell harbors certain molecular machinery, termed the “return to the stem state” (RtSS). Such molecular machinery is designed to sense stimuli generated by the cells' environment and if these stimuli predict cell damage the RtSS will turn on and would pull the cell backwards in the differentiation cascade, either partially or all the way to pluripotency [101]. The major prediction of this theory is that RtSS is a normal, physiological cell function, rather than an artifact of laboratory manipulation. Recent studies showed indeed that dedifferentiation and the return to stemness occur in vivo; airway epithelial cells were shown to revert into functional stem cells in vivo. The investigators showed by lineage tracing that differentiated luminal secretory cells are reverting into basal stem cells. The dedifferentiated cells were indistinguishable from stem cells both morphologically and functionally [86]. An independent study used the gastric cell marker Troy expressed by a small subpopulation of differentiated chief cells. Lineage tracing indicated that single chief cells are capable of generating complete gastric units. The investigators thus challenge the notion of unidirectional stem cell hierarchies (Stange et al. [81]). Another example comes from the kidney, where by using a proximal tubule injury model it was shown that mature kidney epithelial cells take part in regeneration, possibly by undergoing dedifferentiation as they re-expressed several stem cell markers [49]. Two papers dated January 2014 claimed that a short exposure of newborn mouse hematopoietic cells to low pH is sufficient to cause reprogramming. The papers were recently retracted [61,62] and the validity of the phenomenon remains unclear.

In light of the above evidence it is concluded that dedifferentiation does occur in mammalian tissues, and as predicted [99,101] the process occurs physiologically. It seems though that in order for plastic cell behavior to be manifested, cells should encounter stressful conditions that endanger cell integrity and longevity. Going back into a stem state is apparently a mode by which cells attempt to escape from damage and contribute to regeneration as soon as the risk situation is lifted.

One additional implication that emerges from the occurrence of dedifferentiation in mammalians is an alternative to what is called “stem cell self-renewal”. For most stem cells, including the HSC, it has never been conclusively shown that these cells are generated through a process of self-renewal. It is nevertheless generally accepted and advertised in a multitude of publications that new stem cells arise from the symmetrical division of other stem cells. If however, stem cells may also arise due to dedifferentiation of their progeny, the importance of self-renewal becomes almost negligible: the number of progeny is exceedingly greater than that of the stem cells themselves. Therefore very rare dedifferentiation process would be more than sufficient to maintain the stem cell pool throughout an entire life span of a mammalian. Thus, the observed reduction in blood stem cells during aging might not only be a result of impaired self-renewal [68], but also due to