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Review

Microenvironment-evoked cell lineage conversion: Shifting the focus from internal reprogramming to external forcing

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ABSTRACT

Seeking possible ways to create replacement cells for the faded ones with deficits in functionality or quantity inspires comprehensive needs for cell lineage conversion. To fulfill this promise, reprogramming and microenvironment direction have been used to manipulate abundant cell fates. We briefly describe the evolution and fundamental insights of these two major strategies applied for lineage specification, comment generally on their current limitations, and analyze the orchestral interplay between them. We also present several future directions and discuss the potential clinical uses. Based on the relatively slight safety and technical issues, we conclude that microenvironment-evoked cell lineage conversion, instead of reprogramming, will be the shifting focus in regenerative medicine.

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1. Introduction

Various diseases such as aging, diabetes, hematopoietic impairment, multiple organ dysfunction, neurodegenerative disorders, several cardiovascular or hepatic diseases and even tumors are triggered by deficits in either the functionality or quantity of particular cell types (Lengner, 2010). Therefore, seeking possible ways to create replacement cells for the faded ones may ameliorate or even cure the above deficits. Moreover, renewable sources of cell types that cannot be readily isolated from humans or animal models may also serve as tools for drug discovery and toxicology testing (Laustriat et al., 2010). To realize these probabilities, novel strategies are required to convert necessary cell lineages into the ones needed for research and therapeutic purposes.

Currently, two major strategies used to direct the fates of abundant cell types into desired lineages have been described in detail, as shown in Fig. 1. They are not separate processes, and both are needed to produce transplantable target cell types. One strategy is termed reprogramming (also referred to as transdifferentiation), in which one fully differentiated cell type is converted directly, or indirectly through induced pluripotency, into another type, usually by induction/ablation of defined transcription factors (Davis et al., 1987; Graf and Enver, 2009; Kulessa et al., 1995; Zhou and Melton, 2008), cell fusion (Blau, 1989), nuclear transfer (Gurdon and Byrne, 2003; Gurdon and Melton, 2008; Hochedlinger and Jaenisch, 2002; Wilmut et al., 1997) or epigenetic modulation (Enver et al., 2009; Kauffman, 1969). In such strategy, fibroblasts or some other readily available healthy/patient cell types are selected as the starting material, theoretically permitting the generation of large quantities of origin-specific cells. The other strategy is termed directed differentiation (or named microenvironment-evoked lineage conversion in our preference), in which cultured healthy/patient pluripotent stem cells are exposed under a series of steps that are usually designed to mimic those producing the desired cell types in vivo (Cohen and Melton, 2011; Kiskinis and Eggan, 2010); hereby, it possesses the superiority to produce cells suitable to transfer back without immune rejection.

Nevertheless, plenteous challenges have emerged since the use of reprogramming strategy. For instance, most currently available reprogramming techniques have been developed in mouse cells, which may be either inappropriate or insufficient for the reprogramming of human cells. Meanwhile, cells reprogrammed using viruses are unlikely to gain safety acceptance for transplantation into humans, and the other methods not using viral integration are generally more technically demanding and less efficient (Huangfu et al., 2008a; Kim et al., 2009; Nishimura et al., 2010; Okita et al., 2008; Si-Tayeb et al., 2010; Stadtfeld et al., 2008; Warren et al., 2010; Woltjen et al., 2009; Yu et al., 2009; Zhou and Freed, 2009). In contrast, microenvironment-evoked lineage conversion faces slight safety or technical issues, and its challenges are limited to the lower efficiency of produced desired cells (often 30% or less), as well as contamination of immature cells with embryonic or early postnatal phenotypes (D'Amour et al., 2006; Oldershaw et al., 2010; Oshima et al., 2010).

In this review, we briefly describe the evolution of reprogramming and extrinsic microenvironment-evoked lineage conversion

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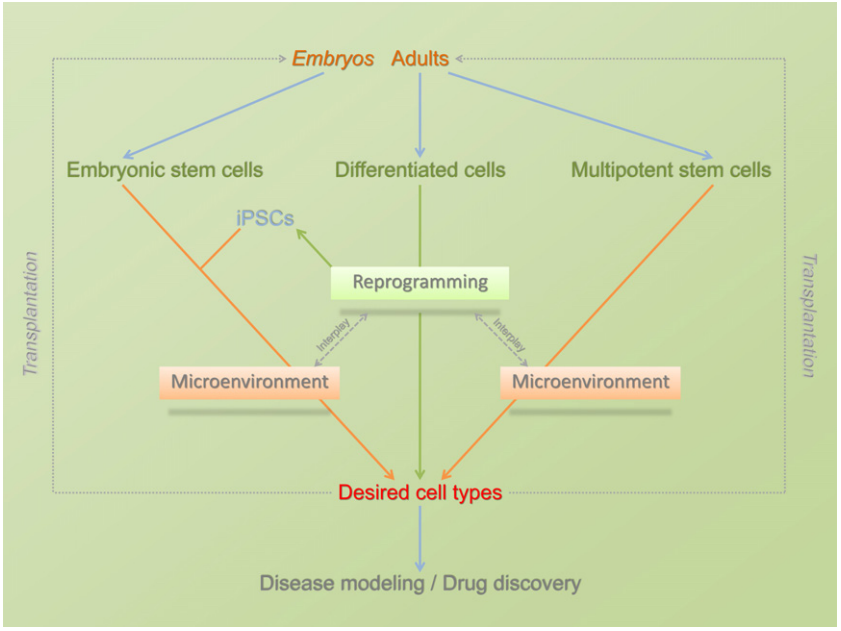

Fig. 1. Two major strategies for cell lineage conversion in regenerative medicine. Primary differentiated cells derived from healthy/patient adults can be used to generate desired cell types, or induced pluripotent stem cells (iPSCs), directly by reprogramming. Alternatively, embryos-derived embryonic stem cells (ESCs), adults-derived multipotent stem cells and iPSCs can be directed into desired cell types under given microenvironment. An orchestral interplay between internal reprogramming and external microenvironment also functions in this process. The desired cells obtained by either strategy may be further applied in disease modeling, drug discovery or transplantation into the origins.

and discuss how they have provided fundamental insights into the process of lineage specification. We also comment more generally on the current limitations and challenges that must be overcome in both strategies and analyze the orchestral interplay between them. Finally, we present several future directions for lineage conversion and discuss the potential clinical uses. We conclude that microenvironment-evoked lineage conversion will be the shifting focus for regenerative medicine, instead of reprogramming. Due to the uncertainty and uncontrollability, this review does not emphasize the intrinsic microenvironment which may also arouse remarkable cell lineage conversion.

2. Reprogramming

Direct conversion of one cell type into another was first demonstrated in 1987, when it was proved that overexpression of MyoD in mouse fibroblasts could convert them into myoblasts (Davis et al., 1987). Since then, various lineage conversion events have been reported. More recently, adult somatic cells have been found able to be reprogrammed to a pluripotent state, demonstrating that drastic alterations in cell fates can be realized with a combination of factors (Takahashi and Yamanaka, 2006). Furthermore, reprogramming can be achieved by cell fusion (Blau, 1989), nuclear transfer (Gurdon and Byrne, 2003; Gurdon and Melton, 2008; Hochedlinger and Jaenisch, 2002; Wilmut et al., 1997) or epigenetic modulation (Enver et al., 2009; Kauffman, 1969). These results open a bright window to search for factors that can drive the transdifferentiation of readily differentiated yet available cells, such as fibroblasts, to the desired cells (e.g. neurons or cardiomyocytes) for therapeutic use, as summarized in Table 1.

2.1. General reprogramming strategy

According to the approach taken by Shinya Yamanaka and his co-workers (Takahashi and Yamanaka, 2006) to generate induced pluripotent stem cells (iPSCs), the first step in most reprogramming studies is to identify suitable transcription factors and test their ability to contribute to the desired reprogramming. As transcription factors are vital mediators of cellular identity, a series of them are generally compiled, or more rarely chromatin-remodeling factors (Ieda et al., 2010) are applied in addition. Usually, those transcription factors which are highly expressed and participate in the development of target cell types are selected. Overexpression of defined receptors to sensitize the starting cells to certain signaling pathways (Kondo et al., 2000) or ablation of those transcription factors necessary for maintaining the identity of the starting cells (Cobaleda et al., 2007) may also be considered.

Selection of a starting cell is also a crucial decision, for not all cell types are equally amenable to a given reprogramming (Schafer et al., 1990). It is widely accepted that reprogramming may be easier if the starting cell shares a common developmental history with the desired cell type. Once the candidate reprogramming factors and the starting cell type have been confirmed, the viruses encoding the reprogramming factors are typically applied to the starting cells as a fishnet. The reprogramming factors are often expressed at the down-stream of a ubiquitous promoter to ensure their robust expression in various cell types. Reducing the number of factors in the reprogramming pool often increases the efficiency of the reprogramming procedure, due to a higher multiplicity of infection for each of the active reprogramming factors (Ieda et al., 2010). Then, transduced cells are evaluated to identify reprogramming events, and a subset of factors may be selected for retesting. Finally, reprogrammed cells must be evaluated to determine their functional similarity to the starting cells (Cohen and Melton, 2011).

2.2. Direct reprogramming and indirect induced pluripotency

Since the ultimate goal for lineage conversion is to produce differentiated yet usable cell types on demand, it seems more convenient to take direct reprogramming of cells from one lineage to another without first inducing them to a pluripotent state. Following the evidence that a single transcription factor, MyoD, is sufficient to directly reprogram fibroblasts and various other cell types into muscle phenotype (Weintraub et al., 1989),

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